Caring Ambassadors Lung Cancer Program
Literature Review, October 2022

SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

Lung Cancer Screening in Individuals With and Without Lung-Related Comorbidities JAMA Netw Open. 2022 Sep 1;5(9):e2230146. doi: 10.1001/jamanetworkopen.2022.30146. Eman M Metwally, et al. **IMPORTANCE:** Comorbidities characterize the underlying health status of individuals. In the context of lung cancer screening (LCS), lung-related comorbidities may influence the observed benefits and harms. **OBJECTIVE:** To compare the characteristics of individuals undergoing LCS, the LCS examination result, the cancer detection rate (CDR), and the false-positive rate (FPR) in those with and without lung-related comorbidities. **DESIGN, SETTING, AND PARTICIPANTS:** A prospective cohort study was conducted in 5 academic and community screening sites across North Carolina from January 1, 2014, to November 7, 2020. Participants included 611 individuals screened for lung cancer who completed a 1-page health history questionnaire. **EXPOSURES:** Presence of at least 1 self-reported lung-related comorbidity, including chronic obstructive pulmonary disease, chronic bronchitis, emphysema, asthma, bronchiectasis, pulmonary fibrosis, silicosis, asbestosis, sarcoidosis, and tuberculosis. **MAIN OUTCOMES AND MEASURES:** The LCS examination result was determined from the radiologist's Lung Imaging Reporting and Data System assessment (negative, 1 or 2; positive, 3 or 4). The age-adjusted CDR and FPR were calculated per 100 LCS examinations, using binary logistic regression. **RESULTS:** Among the 611 individuals screened for lung cancer (308 men [50.4%]; mean [SD] age, 64 [6.2] years), 335 (54.8%) had at least 1 lung-related comorbidity. Individuals with vs without lung-related comorbidities were more likely to be female than male (180 of 335 [53.7%] vs 123 of 276 [44.6%]; P = .02), White vs non-White race (275 of 326 [84.4%] vs 193 of 272 [71.0%]; P < .001), and have high school or less education vs greater than a high school education (108 of 231 [46.7%] vs 64 of 208 [30.8%]; P = .001). There were no significant differences in the proportion of positive LCS examinations in those with vs without a lung-related comorbidity at baseline (37 [16.0%] vs 22 [11.1%]; P = .14) or subsequent (40 [12.3%] vs 23 [10.6%]; P = .54) LCS examination. Comparing individuals with vs without lung-related comorbidities, there was no statistically significant difference in the CDR (1.6 vs 1.9 per 100; P = .73) or FPR (13.0 vs 9.3 per 100; P = .16). Of the 17 individuals with lung cancer, 13 patients (76.5%) were diagnosed with stage I lung cancer. **CONCLUSIONS AND RELEVANCE:** The findings of this study suggest that individuals with self-reported lung-related comorbidities undergoing LCS were more

likely to be female, of White race, and have less education than those without lung-related comorbidity. Although no statistically significant differences in the proportion of positive examinations, CDR, or FPR by self-reported lung comorbidities were noted, additional studies with larger numbers of individuals undergoing screening are needed to understand LCS outcomes in those with lung-related comorbidities.

COVID-19 and lung cancer: update on the latest screening, diagnosis, management and challenges
J Int Med Res. 2022 Sep;50(9):3000605221125047. doi: 10.1177/03000605221125047. Simon Moubarak, et al.
Lung cancer, considered one of the most common causes of cancer deaths worldwide, is a complex disease with its own challenges. The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), compounded these challenges and forced the medical healthcare system to alter its approach to lung cancer. This narrative review aims to identify the effect of the COVID-19 pandemic on lung cancer screening, diagnosis and management. During this public health crisis, various medical societies have worked on developing guidelines to protect patients with lung cancer from the deleterious effects of SARS-CoV-2 infection, as well as from the complications imposed by treatment delays. The different therapeutic approaches, such as surgery, radiation oncology and immune checkpoint inhibitor therapy, along with the latest international recommendations, will be discussed. Protecting patients with lung cancer from COVID-19 complications, while avoiding barriers in treatment delays, has brought unique challenges to healthcare facilities. Prompt modifications to guidelines, and constant evaluation of their efficacy, are thus needed.

Use and Outcomes of Low-Dose CT Scan Lung Cancer Screening in the Medicare Population
Chest. 2022 Sep;162(3):721-729. doi: 10.1016/j.chest.2022.03.031. Epub 2022 Mar 29. Paul F Pinsky 1 , Eric Miller 2.
BACKGROUND: Relatively little is known about various aspects of low-dose CT (LDCT) scan lung cancer screening in US clinical practice, including characteristics of cases diagnosed after screening. We assessed this using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. **RESEARCH QUESTION:** What were the characteristics of patients with lung cancer, including stage and survival, whose disease was diagnosed after LDCT scan screenings? **STUDY DESIGN AND METHODS:** We created an LDCT scan use cohort consisting of everyone in the 5% SEER-Medicare sample with ≥ 12 months of non-health maintenance organization (HMO) Part A and B coverage while 65 to 77 years of age from 2015 through 2019. LDCT scan use and lung cancer diagnosis rates were assessed in this cohort. Additionally, we created a lung cancer cohort consisting of patients who received a diagnosis between 2015 and 2017 at 65 to 78 years of age with complete (non-HMO Part A and B) coverage the year before diagnosis. The cases cohort comprised those screened or unscreened based on undergoing screening during that period; lung cancer characteristics and survival were compared between these groups. **RESULTS:** In the LDCT scan use cohort (n = 414,358), use rates increased from 0.10 (per 100 person-years) in 2015 to 1.3 in 2019. Among those with first screenings, 39.2% underwent a subsequent screen within 18 months. The 1-year cumulative lung cancer diagnosis rate after initial screenings was 2.4%. Claims for prescreen counseling were infrequent (about 10%). Of 48,891 patients in the lung cancer cohort, 1,150 (2.4%) underwent screening. Among screened patients, 52.3%, 11.0%, 20.7%, and 16.0% received diagnoses of stages I, II, III, and IV disease, respectively. Lung cancer-specific survival through 3 years was significantly greater in screened versus unscreened patients overall and for all stages except stage II; 3-year lung cancer-specific survival was 89.0% in screened patients with stage I disease. **INTERPRETATION:** LDCT scan use was low but increased over time. The lung cancer yield was substantial; cases among those who underwent screening primarily were in the early stage with high survival rates. Although screening rates were unacceptably low, screening outcomes in those Medicare recipients undergoing screening were favorable.

Utility of Single-Gene Testing in Cancer Specimens Clin Lab Med. 2022 Sep;42(3):385-394. doi: 10.1016/j.cll.2022.05.001. Epub 2022 Aug 22. Mehenaz Hanbazazh 1, et al.
Molecular testing is now considered the standard of care to screen for disease, confirm the diagnosis, guide management, and use target therapy. Currently, several testing strategies are being used. One of the most common strategies is single-gene testing, which is often conducted for known mutations, such as BRAF in melanoma and EGFR in lung cancer. Subsequently, next-generation sequencing (NGS), which tests many genes simultaneously, was developed using targeted gene panels, whole-exome, or whole-genome sequencing. Ordering the best diagnostic tool and choosing between single-gene testing and NGS depends on several factors. In this review, we discuss different single-gene testing methodologies and the impact of using them in comparison to NGS/multigene panel.

The evolving role of liquid biopsy in lung cancer Lung Cancer. 2022 Oct;172:53-64. doi: 10.1016/j.lungcan.2022.08.004. Epub 2022 Aug 10. Umberto Malapelle, et al.
Liquid biopsy has revolutionized the management of cancer patients. In particular, liquid biopsy-based testing has proven to be highly beneficial for identifying actionable cancer markers, especially when solid tissue biopsies are insufficient or unattainable. Beyond the predictive role, liquid biopsy may be a useful tool for comprehensive tumor genotyping, identification of emergent resistance mechanisms, monitoring of minimal residual disease, early detection, and cancer interception. The application of next generation sequencing to liquid biopsy has led to the "quantum leap" of predictive molecular pathology. Here, we review the evolving role of liquid biopsy in lung cancer.

Liquid biopsies based on DNA methylation as biomarkers for the detection and prognosis of lung cancer Clin Epigenetics. 2022 Sep 24;14(1):118. doi: 10.1186/s13148-022-01337-0. Peilong Li, et al.
Lung cancer (LC) is the main cause of cancer-related mortality. Most LC patients are diagnosed in an advanced stage when the symptoms are obvious, and the prognosis is quite poor. Although low-dose computed tomography (LDCT) is a routine clinical examination for early detection of LC, the false-positive rate is over 90%. As one of the intensely studied epigenetic modifications, DNA methylation plays a key role in various diseases, including cancer and other diseases. Hypermethylation in tumor suppressor genes or hypomethylation in oncogenes is an important event in tumorigenesis. Remarkably, DNA methylation usually occurs in the very early stage of malignant tumors. Thus, DNA methylation analysis may provide some useful information about the early detection of LC. In recent years, liquid biopsy has developed rapidly. Liquid biopsy can detect and monitor both primary and metastatic malignant tumors and can reflect tumor heterogeneity. Moreover, it is a minimally invasive procedure, and it causes less pain for patients. This review summarized various liquid biopsies based on DNA methylation for LC. At first, we briefly discussed some emerging technologies for DNA methylation analysis. Subsequently, we outlined cell-free DNA (cfDNA), sputum, bronchoalveolar lavage fluid, bronchial aspirates, and bronchial washings DNA methylation-based liquid biopsy for the early detection of LC. Finally, the prognostic value of DNA methylation in cfDNA and sputum and the diagnostic value of other DNA methylation-based liquid biopsies for LC were also analyzed.

Use of Preoperative FDG PET/CT and Survival of Patients with Resectable Non-Small Cell Lung Cancer Radiology. 2022 Oct;305(1):219-227. doi: 10.1148/radiol.212798. Epub 2022 Jun 21. Wan-Ming Chen, et al.
BACKGROUND The added value of preoperative PET/CT for the overall survival of patients with resectable non-small cell lung cancer (NSCLC) is unknown. **PURPOSE** To investigate the association of the use of preoperative PET/CT on survival of patients with resectable stage I-IIIB NSCLC.
MATERIALS AND METHODS In this retrospective study, patients with resectable stage I-IIIB

NSCLC who underwent thoracic surgery from January 1, 2009, to December 31, 2018, from the Taiwan Cancer Registry were included. The last follow-up date was December 31, 2019. Patients were categorized into two groups according to whether they underwent preoperative metabolic imaging with fluorine 18 fluorodeoxyglucose PET/CT. Patients who did not undergo preoperative imaging were used as the control group. The primary outcome of interest was all-cause mortality. Patients in both groups were propensity score matched at a ratio of 1:1. Matching variables used were sex, age, histologic findings, American Joint Committee on Cancer clinical stage, cT stage, cN stage, current and past smoker history, adjuvant chemotherapy, adjuvant chemoradiation, Charlson comorbidity index, and hospital type. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. **RESULTS** In the matched cohort, 6754 patients (3349 men, mean age ± SD: 64 years ± 11) underwent PET/CT and 6754 did not (3362 men, mean age: 64 years ± 11). In adjusted analysis, patients with stage IIIA or IIIB NSCLC and preoperative PET/CT had a lower risk of death versus those without PET/CT (for stage IIIA: hazard ratio [HR] = 0.90 [95% CI: 0.79, 0.94], P = .02; for stage IIIB: HR = 0.80 [95% CI: 0.71, 0.90], P < .01). There was no improvement in a lower risk of death for patients with stage I-II NSCLC (after multivariable adjustment, the HR was 1.19 [95% CI: 0.89, 1.30], P = .65). **CONCLUSION** Use of preoperative PET/CT was associated with lower risk of death in patients with stage IIIA-IIIB non-small cell lung cancer compared with those without preoperative PET/CT. © RSNA, 2022 Online supplemental material is available for this article.

Parameters of Dual-layer Spectral Detector CT Could be Used to Differentiate Non-Small Cell Lung Cancer from Small Cell Lung Cancer Curr Med Imaging. 2022;18(10):1070-1078. doi: 10.2174/1573405618666220308105359. Ronghua Mu, et al.

BACKGROUND AND OBJECTIVE: Differentiating non-small cell lung cancer (NSCLC) from small cell lung cancer (SCLC) remains a substantial challenge. This study aimed at evaluating the performance of dual-layer spectral detector CT (DLCT) in differentiating NSCLC from SCLC. **METHODS:** Spectral images of 247 cancer patients confirmed by pathology were retrospectively analyzed in both the arterial phase (AP) and the venous phase (VP), including 197 cases of NSCLC and 50 cases of SCLC. Effective atomic number (Z-eff), Spectral CT-Mono Energetic (MonoE [40keV~90keV]), iodine density (ID) and thoracic aorta iodine density (IDaorta) in contrast-enhanced images were measured and compared between the SCLC and NSCLC subgroups of tumors. The slope of the spectral curve (λ, interval of 10 keV) and normalized iodine density (NID) were also calculated between the SCLC and NSCLC. Through the statistical analysis, the diagnostic efficiency of each spectral parameter was calculated, and the difference in their efficiency was analyzed. **RESULTS:** Both in NSCLS and SCLC, all parameters in VP were significantly higher than those in AP ($p<0.001$), except for λ90. There were significant differences in all spectral parameters between NSCLS and SCLC, both in AP and VP ($p < 0.001$). Except for VP-λ90, there was no significant difference in ROC curves of all spectral parameters. VP-NID exhibited the best diagnostic performance with an AUC value of 0.917 (95%[CI]: 0.870~0.965), sensitivity and specificity of 92.9% and 80%, and a diagnostic threshold of 0.217. **CONCLUSION:** All parameters of DLCT have high diagnostic efficiency in differentiating NSCLC from SCLC except for VP-λ90, and VP-NID has the highest diagnostic efficiency.

Personalized mid-course FDG-PET based adaptive treatment planning for non-small cell lung cancer using machine learning and optimization Phys Med Biol. 2022 Sep 13;67(18). doi: 10.1088/1361-6560/ac88b3. Ali Ajdari, et al.

OBJECTIVE. Traditional radiotherapy (RT) treatment planning of non-small cell lung cancer (NSCLC) relies on population-wide estimates of organ tolerance to minimize excess toxicity. The goal of this study is to develop a personalized treatment planning based on patient-specific lung radiosensitivity, by combining machine learning and optimization. **APPROACH.** Sixty-nine non-small cell lung cancer

patients with baseline and mid-treatment [18]F-fluorodeoxyglucose (FDG)-PET images were retrospectively analyzed. A probabilistic Bayesian networks (BN) model was developed to predict the risk of radiation pneumonitis (RP) at three months post-RT using pre- and mid-treatment FDG information. A patient-specific dose modifying factor (DMF), as a surrogate for lung radiosensitivity, was estimated to personalize the normal tissue toxicity probability (NTCP) model. This personalized NTCP was then integrated into a NTCP-based optimization model for RT adaptation, ensuring tumor coverage and respecting patient-specific lung radiosensitivity. The methodology was employed to adapt the treatment planning of fifteen NSCLC patients. **MAIN RESULTS.** The magnitude of the BN predicted risks corresponded with the RP severity. Average predicted risk for grade 1-4 RP were 0.18, 0.42, 0.63, and 0.76, respectively ($p < 0.001$). The proposed model yielded an average area under the receiver-operating characteristic curve (AUROC) of 0.84, outperforming the AUROCs of LKB-NTCP (0.77), and pre-treatment BN (0.79). Average DMF for the radio-tolerant (RP grade = 1) and radiosensitive (RP grade ≥ 2) groups were 0.8 and 1.63,$p < 0.01$. RT personalization resulted in five dose escalation strategies (average mean tumor dose increase = 6.47 Gy, range = [2.67-17.5]), and ten dose de-escalation (average mean lung dose reduction = 2.98 Gy [0.8-5.4]), corresponding to average NTCP reduction of 15% [4-27]. **SIGNIFICANCE.** Personalized FDG-PET-based mid-treatment adaptation of NSCLC RT could significantly lower the RP risk without compromising tumor control. The proposed methodology could help the design of personalized clinical trials for NSCLC patients.

Automated extraction of information of lung cancer staging from unstructured reports of PET-CT interpretation: natural language processing with deep-learning BMC Med Inform Decis Mak. 2022 Sep 1;22(1):229. doi: 10.1186/s12911-022-01975-7. Hyung Jun Park # 1 2, et al.
BACKGROUND: Extracting metastatic information from previous radiologic-text reports is important, however, laborious annotations have limited the usability of these texts. We developed a deep-learning model for extracting primary lung cancer sites and metastatic lymph nodes and distant metastasis information from PET-CT reports for determining lung cancer stages. **METHODS:** PET-CT reports, fully written in English, were acquired from two cohorts of patients with lung cancer who were diagnosed at a tertiary hospital between January 2004 and March 2020. One cohort of 20,466 PET-CT reports was used for training and the validation set, and the other cohort of 4190 PET-CT reports was used for an additional-test set. A pre-processing model (Lung Cancer Spell Checker) was applied to correct the typographical errors, and pseudo-labelling was used for training the model. The deep-learning model was constructed using the Convolutional-Recurrent Neural Network. The performance metrics for the prediction model were accuracy, precision, sensitivity, micro-AUROC, and AUPRC. **RESULTS:** For the extraction of primary lung cancer location, the model showed a micro-AUROC of 0.913 and 0.946 in the validation set and the additional-test set, respectively. For metastatic lymph nodes, the model showed a sensitivity of 0.827 and a specificity of 0.960. In predicting distant metastasis, the model showed a micro-AUROC of 0.944 and 0.950 in the validation and the additional-test set, respectively. **CONCLUSION:** Our deep-learning method could be used for extracting lung cancer stage information from PET-CT reports and may facilitate lung cancer studies by alleviating laborious annotation by clinicians.

Analysis of Eligibility for Lung Cancer Screening by Race After 2021 Changes to US Preventive Services Task Force Screening Guidelines JAMA Netw Open. 2022 Sep 1;5(9):e2229741. doi: 10.1001/jamanetworkopen.2022.29741. Laura C Pinheiro 1 2 3 , et al.
IMPORTANCE: Lung cancer incidence and mortality have disproportionate consequences for racial and ethnic minority populations. The extent to which the 2021 changes to the US Preventive Services Task Force (USPSTF) screening guidelines have reduced the racial disparity gap in lung cancer screening eligibility is not known. **OBJECTIVE:** To assess the consequences of the changes in USPSTF low-dose computed tomography eligibility criteria for lung cancer screening between 2013 and 2021 among Black

and White community-dwelling adults. **DESIGN, SETTING, AND PARTICIPANTS:** This cohort study analyzed data from the Reasons for Geographic and Racial Differences in Stroke study, a prospective longitudinal cohort study of community-dwelling Black and White adults 45 years and older who were initially recruited across the US between January 2003 and October 2007, with ongoing follow-up. All participants who would have been potentially eligible for lung cancer screening based on the 2021 USPSTF guidelines (N = 14 285) were included. Follow-up data for the current cohort study were collected and analyzed between January 2013 and December 2017, with final analysis performed in 2021. **EXPOSURES:** Self-reported Black vs White race. **PRIMARY OUTCOMES AND MEASURES:** Differences in the proportion of Black vs White participants eligible for lung cancer screening according to 2013 and 2021 guidelines were assessed using modified Poisson models with robust SEs. Associations between important covariates (demographic characteristics and social factors associated with health), including interaction and dissimilarity indices (2 measures of residential segregation), and differences in screening eligibility were also examined. **RESULTS:** Among 14 285 participants (mean [SD] age, 64.7 [7.5] years; 7675 men [53.7%]), 5787 (40.5%) self-identified as Black and 8498 (59.5%) as White. Based on the 2013 USPSTF guidelines, 1109 of 5787 Black participants (19.2%) and 2313 of 8498 White participants (27.2%) were eligible for lung cancer screening (difference, -8.06 percentage points; 95% CI, -9.44 to -6.67 percentage points). Based on the 2021 guidelines, 1667 of 5787 Black participants (28.8%) and 2940 of 8498 White participants (34.6%) were eligible for screening (difference, -5.73 percentage points; 95% CI, -7.28 to -4.19 percentage points). After adjustment for differences in individual characteristics and residential segregation, the 2013 difference in screening eligibility among Black vs White participants was -12.66 percentage points (95% CI, -14.71 to -10.61 percentage points), and the 2021 difference was -12.15 percentage points (95% CI, -14.37 to -9.93 percentage points). **CONCLUSIONS AND RELEVANCE:** In this study, 2021 changes to the USPSTF lung cancer screening guidelines were associated with reductions in but not elimination of existing eligibility disparities in lung cancer screening among Black and White adults. These findings suggest that accounting for factors beyond age and pack-years of smoking is needed when tailoring guidelines to improve screening eligibility among groups at high risk of lung cancer.

The Effect of CT Imaging Technology in the Diagnosis of Thoracic and Cardiac Surgery Diseases
Scanning. 2022 Aug 24;2022:9385451. doi: 10.1155/2022/9385451. eCollection 2022. Min Yang 1 , Hongbo Qian 1 , Dafa Zhang 1 , Yingjing Gui 1.
In order to increase doctors' cognition of the three-dimensional anatomical structure of cardiothoracic and cardiothoracic surgery and increase the diagnosis rate and cure rate of cardiothoracic surgery diseases, the authors propose a method of CT imaging technology for diagnosing cardiothoracic surgery diseases. Through the joint Hookwire positioning of 3D-CTBA, application in thoracoscopic segmentectomy and CT energy spectrum curve, retrospective analysis of diagnosis of intrathoracic lymph node metastasis in non-small-cell lung cancer, 3D-CTBA and CT-guided Hookwire localization, and preoperative CT-enhanced scanning were performed using two methods. The experimental results showed that the chest tube placement time, postoperative thoracic drainage volume, and postoperative hospital stay after the first operation all showed a good trend. The diagnostic sensitivity was 87.1%. The specificity was 92.6%. The correct index was 79.7%. The accuracy was 91.3%. The positive predictive value was 79.4%. And the negative predictive value was 95.7%. These data prove that CT imaging technology has high diagnostic value for thoracic and cardiac surgery diseases and can effectively help the formulation and implementation of thoracic and cardiac surgery diseases.

A feature selection-based framework to identify biomarkers for cancer diagnosis: A focus on lung adenocarcinoma PLoS One. 2022 Sep 6;17(9):e0269126. doi: 10.1371/journal.pone.0269126.

eCollection 2022. Omar Abdelwahab 1 , Nourelislam Awad 1 2 , Menattallah Elserafy 1 3 , Eman Badr 1 4

Lung cancer (LC) represents most of the cancer incidences in the world. There are many types of LC, but Lung Adenocarcinoma (LUAD) is the most common type. Although RNA-seq and microarray data provide a vast amount of gene expression data, most of the genes are insignificant to clinical diagnosis. Feature selection (FS) techniques overcome the high dimensionality and sparsity issues of the large-scale data. We propose a framework that applies an ensemble of feature selection techniques to identify genes highly correlated to LUAD. Utilizing LUAD RNA-seq data from the Cancer Genome Atlas (TCGA), we employed mutual information (MI) and recursive feature elimination (RFE) feature selection techniques along with support vector machine (SVM) classification model. We have also utilized Random Forest (RF) as an embedded FS technique. The results were integrated and candidate biomarker genes across all techniques were identified. The proposed framework has identified 12 potential biomarkers that are highly correlated with different LC types, especially LUAD. A predictive model has been trained utilizing the identified biomarker expression profiling and performance of 97.99% was achieved. In addition, upon performing differential gene expression analysis, we could find that all 12 genes were significantly differentially expressed between normal and LUAD tissues, and strongly correlated with LUAD according to previous reports. We here propose that using multiple feature selection methods effectively reduces the number of identified biomarkers and directly affects their biological relevance.

Liquid Biopsy Analysis as a Tool for TKI-Based Treatment in Non-Small Cell Lung Cancer Cells. 2022 Sep 14;11(18):2871. doi: 10.3390/cells11182871. Karolina Buszka 1 2 , et al.

The treatment of non-small cell lung cancer (NSCLC) has recently evolved with the introduction of targeted therapy based on the use of tyrosine kinase inhibitors (TKIs) in patients with certain gene alterations, including EGFR, ALK, ROS1, BRAF, and MET genes. Molecular targeted therapy based on TKIs has improved clinical outcomes in a large number of NSCLC patients with advanced disease, enabling significantly longer progression-free survival (PFS). Liquid biopsy is an increasingly popular diagnostic tool for treating TKI-based NSCLC. The studies presented in this article show that detection and analysis based on liquid biopsy elements such as circulating tumor cells (CTCs), cell-free DNA (cfDNA), exosomes, and/or tumor-educated platelets (TEPs) can contribute to the appropriate selection and monitoring of targeted therapy in NSCLC patients as complementary to invasive tissue biopsy. The detection of these elements, combined with their molecular analysis (using, e.g., digital PCR (dPCR), next generation sequencing (NGS), shallow whole genome sequencing (sWGS)), enables the detection of mutations, which are required for the TKI treatment. Despite such promising results obtained by many research teams, it is still necessary to carry out prospective studies on a larger group of patients in order to validate these methods before their application in clinical practice.

Racial Disparities in Adherence to Annual Lung Cancer Screening and Recommended Follow-Up Care: A Multicenter Cohort Study Ann Am Thorac Soc. 2022 Sep;19(9):1561-1569. doi: 10.1513/AnnalsATS.202111-1253OC. Roger Y Kim 1, et al.

RATIONALE: Black patients receive recommended lung cancer screening (LCS) follow-up care less frequently than White patients, but it is unknown if this racial disparity persists across both decentralized and centralized LCS programs. **OBJECTIVES:** To determine adherence to American College of Radiology Lung Imaging Reporting and Data System (Lung-RADS) recommendations among individuals undergoing LCS at either decentralized or centralized programs and to evaluate the association of race with LCS adherence. **METHODS:** We performed a multicenter retrospective cohort study of patients receiving LCS at five heterogeneous U.S. healthcare systems. We calculated adherence to annual LCS among patients with a negative baseline screen (Lung-RADS 1 or 2) and recommended follow-up care among those with a positive baseline screen (Lung-RADS 3, 4A, 4B, or 4X) stratified by type of LCS

program and evaluated the association between race and adherence using multivariable modified Poisson regression. **RESULTS:** Of the 6,134 total individuals receiving LCS, 5,142 (83.8%) had negative baseline screens, and 992 (16.2%) had positive baseline screens. Adherence to both annual LCS (34.8% vs. 76.1%; P < 0.001) and recommended follow-up care (63.9% vs. 74.6%; P < 0.001) was lower at decentralized compared with centralized programs. Among individuals with negative baseline screens, a racial disparity in adherence was observed only at decentralized screening programs (interaction term, P < 0.001). At decentralized programs, Black race was associated with 27% reduced adherence to annual LCS (adjusted relative risk [aRR], 0.73; 95% confidence interval [CI], 0.63-0.84), whereas at centralized programs, no effect by race was observed (aRR, 0.98; 95% CI, 0.91-1.05). In contrast, among those with positive baseline screens, there was no significant difference by race for adherence to recommended follow-up care by type of LCS program (decentralized aRR, 0.95; 95% CI, 0.81-1.11; centralized aRR, 0.81; 95% CI, 0.71-0.93; interaction term, P = 0.176). **CONCLUSIONS:** In this large multicenter study of individuals screened for lung cancer, adherence to both annual LCS and recommended follow-up care was greater at centralized screening programs. Black patients were less likely to receive annual LCS than White patients at decentralized compared with centralized LCS programs. Our results highlight the need for further study of healthcare system-level mechanisms to optimize longitudinal LCS care.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Video-assisted thoracoscopic versus open sleeve lobectomy for non-small cell lung cancer: A systematic review and meta-analysis from six comparative studies Asian Cardiovasc Thorac Ann. 2022 Oct;30(8):881-893. doi: 10.1177/02184923221115970. Epub 2022 Sep 10. Georgios Geropoulos, et al.

BACKGROUND: Lung sleeve resection is indicated for centrally located lung tumors, especially for patients who cannot tolerate pneumonectomy. With video-assisted thoracoscopic surgery (VATS) being increasingly implemented for a wide variety of thoracic pathologies, this study aims to compare the intraoperative, postoperative, and long-term outcomes of VATS and open bronchial sleeve lobectomy for non-small cell lung cancer (NSCLC). **METHODS:** The MEDLINE (via PubMed), Cochrane Library, and Scopus databases were searched. Original clinical studies, comparing VATS and open sleeve lobectomy for NSCLC were included. Evidence was synthesized as odds ratios for categorical and weighted mean difference (WMD) for continuous variables. **RESULTS:** Our analysis included six studies with non-overlapping populations reporting on 655 patients undergoing bronchial sleeve lobectomy for NSCLC (229 VATS and 426 open). VATS sleeve lobectomy was associated with significantly longer operative time ((WMD): 45.85 min, 95% confidence interval (CI): 12.06 to 79.65, $p = 0.01$) but less intraoperative blood loss ((WMD): -34.57 mL, 95%CI: -58.35 to -10.78, $p < 0.001$). No significant difference was found between VATS and open bronchial sleeve lobectomy in margin-negative resection rate, number of lymph nodes resected, postoperative outcomes (drainage duration, length of hospital stay, 30-day mortality), postoperative complications (pneumonia, bronchopleural fistula/empyema, prolonged air leakage, chylothorax, pulmonary embolism, and arrhythmia), and long-term outcomes (overall survival, recurrence-free survival). **CONCLUSIONS:** The limitation of our study arises mainly due to the heterogeneity of the included studies. Nevertheless, VATS bronchial sleeve lung resection constitutes a feasible and safe alternative to the open sleeve lung resection surgery for the management of centrally located lung tumors.

Robotic-assisted thoracoscopic surgery demonstrates a lower rate of conversion to thoracotomy than video-assisted thoracoscopic surgery for complex lobectomies Eur J Cardiothorac Surg. 2022 Aug 3;62(3):ezac281. doi: 10.1093/ejcts/ezac281. Mirza Zain Baig 1, et al.

OBJECTIVES: Locally advanced lung cancers present a significant challenge to minimally invasive thoracic surgeons. An increasing number of centres have adopted robotic-assisted thoracoscopic surgeries for these complex operations. In this study, we compare surgical margins achieved, conversion rates to thoracotomy, perioperative mortality and 30-day readmission rates for robotic and video-assisted thoracoscopic surgery (VATS) lobectomy for locally advanced lung cancers. **METHODS:** Using the National Cancer Database, we identified patients with non-small-cell lung cancer who received neoadjuvant chemotherapy/radiotherapy, had clinical N1/N2 disease or in the absence of these 2 features had a tumour >5 cm treated with either robotic or VATS lobectomy between 2010 and 2016. Perioperative outcomes and conversion rates were compared between robotic and VATS lobectomy. **RESULTS:** A total of 9512 patients met our inclusion criteria with 2123 (22.3%) treated with robotic lobectomy and 7389 (77.7%) treated with VATS lobectomy. Comparable R0 resections, 30- and 90-day mortality and 30-day readmission rates were observed for robotic and VATS lobectomy while a higher rate of conversion to thoracotomy was observed for VATS (aOR = 1.99, 95% confidence interval = 1.65, 2.39, P < 0.001). **CONCLUSIONS:** Our analysis of the National Cancer Database suggests that robotic lobectomy for complex lung resections achieves similar perioperative outcomes and R0 resections as VATS lobectomy with the exception of a lower rate of conversion to thoracotomy.

Segmentectomy versus lobectomy for inner-located small-sized early non-small-cell lung cancer Interact Cardiovasc Thorac Surg. 2022 Sep 9;35(4):ivac218. doi: 10.1093/icvts/ivac218. Shinya Tane 1 2 , et al.

OBJECTIVES: Although segmentectomy is an acceptable alternative to lobectomy for peripheral small-sized non-small-cell lung cancer, the effectiveness of segmentectomy for inner lesions remains unknown. The aim of this study was to examine the feasibility of segmentectomy in comparison with lobectomy for inner lesions. **METHODS:** We retrospectively analysed 570 patients with small (≤2 cm) cN0 non-small-cell lung cancer who underwent segmentectomy or lobectomy between January 2007 and March 2021. We focused on patients with lesions located in the inner two-thirds, which were determined using three-dimensional computed tomography (n = 227). After propensity score matching analysis based on sex, age, pulmonary function, serum carcinoembryonic antigen level, radiographic tumour findings and tumour location, we compared the surgical and oncological outcomes in patients who underwent segmentectomy (n = 66) and lobectomy (n = 66). **RESULTS:** Postoperative mortality or morbidity did not differ significantly between the 2 groups. The 5-year recurrence-free and overall survival rates in the segmentectomy and lobectomy groups were 93.6% vs 84.1% and 95.8% vs 87.9%, respectively. The differences between 2 groups were not significant (P = 0.62 and P = 0.23, respectively). The 2 groups also showed no differences in loco-regional recurrence. Multivariable Cox regression analysis revealed that segmentectomy had a comparable impact on recurrence-free survival (hazard ratio, 0.61; 95% confidence interval, 0.17-2.03; P = 0.43). **CONCLUSIONS:** Segmentectomy for inner-located small-sized non-small-cell lung tumours could be an acceptable treatment in comparison with lobectomy.

Efficacy and safety of intraoperative cone-beam CT-guided localization of small pulmonary nodules Interact Cardiovasc Thorac Surg. 2022 Sep 9;35(4):ivac236. doi: 10.1093/icvts/ivac236. Taisuke Kaiho 1 et al.

OBJECTIVES: This study aimed to evaluate the efficacy and safety of intraoperative cone-beam computed tomography-guided video-assisted thoracoscopic surgery wedge resection of impalpable small pulmonary nodules. **METHODS:** This was a single-centre phase 2 trial conducted between April 2018 and March 2019. Peripheral small pulmonary nodules, defined as either ground-glass opacity-dominant

(>50%) nodules measuring ≤3 cm in diameter (ground-glass opacity-dominant type) or nodules measuring ≤2 cm in diameter located deeper than the nodule diameter from the visceral pleura (deep solid type), were eligible for resection using a cone-beam computed tomography-guided thoracoscopic manner. The primary end-point was macroscopic complete resection, and secondary end-points were: nodule extraction rate, operation time, localization time, marking accuracy, microscopic complete resection and safety. **RESULTS:** Twenty-two nodules, in 9 men and 11 women with a mean age of 64.3 years, were visualized and resected. The nodules were located in the right upper, middle and lower lobes in 3, 1 and 5 patients, respectively, and in the left upper and lower lobes in 5 and 8 patients, respectively. Seven nodules were ground-glass opacity-dominant types, and 15 were deep solid types. Cone-beam computed tomography could clearly image all nodules. The mean time for localization was 17.4 min. The mean operation time was 110.7 min. Macroscopic complete resection was accomplished in 21 nodules (95.5%). Microscopic complete resection was achieved in all nodules (100%). Postoperative air leakage and bleeding were observed in 1 patient (5%). **CONCLUSIONS:** Cone-beam computed tomography might be a safe and useful guide for video-assisted thoracoscopic surgery wedge resection of impalpable peripheral pulmonary nodules.

Minimally invasive lobectomy versus stereotactic ablative radiotherapy for stage I non-small cell lung cancer Eur J Cardiothorac Surg. 2022 Aug 3;62(3):ezac118. doi: 10.1093/ejcts/ezac118. Julianne Cynthia de Ruiter 1 , et al.
OBJECTIVES: A minimally invasive lobectomy (MIL) is the standard treatment for stage I non-small cell lung cancer (NSCLC) in medically operable patients. Stereotactic ablative radiotherapy (SABR) is recommended for inoperable patients and has been proposed as a potential alternative for operable patients as well. Here, we present the results of a feasibility study in preparation for a nationwide retrospective cohort study, comparing outcomes between both treatment modalities. **METHODS:** In this retrospective cohort study, data from patients with clinical stage I NSCLC treated with MIL or SABR in 2014-2015 were retrieved from databases from 12 Dutch hospitals. Progression-free survival (PFS), overall survival (OS) and lung cancer-specific survival (LCSS) were compared between MIL and SABR. **RESULTS:** A total of 597 patients with clinical stage I NSCLC treated with MIL (n = 356) or SABR (n = 241) were included. In total, 106 (30%) patients had died in the MIL group and 142 (59%) in the SABR group. After MIL and SABR, unadjusted 5-year PFS was 63% and 30%, OS was 72% and 38% and LCSS was 81% and 76%, respectively. Propensity score-weighted analyses did not show significant differences between MIL and SABR in OS [hazard ratios (HR) 0.74 (95% confidence interval (CI) 0.43-1.29)], PFS [HR 0.74 (95% CI 0.42-1.32)] or LCSS [HR 0.81 (95% CI 0.42-1.59)]. **CONCLUSIONS:** Unadjusted analyses revealed superior OS and PFS for MIL and similar LCSS, but this feasibility study was not sufficiently powered to demonstrate significant differences using propensity score methodology. Therefore, this study is currently being extended to include more than half of Dutch hospitals in order to enlarge the population to ≥1880 patients, not only to determine the best treatment for patients with stage I NSCLC overall, but also to assess the preferred treatment for patient groups with specific characteristics.

Five decades of progress in surgical oncology: Tumors of the lung and esophagus J Surg Oncol. 2022 Oct;126(5):921-925. doi: 10.1002/jso.27033. Valerie W Rusch 1
During the past 50 years, there has been a remarkable transformation in the management of lung and esophageal cancers. Improved methods of diagnosis, better staging and patient selection for surgery, the advent of minimally invasive approaches to resection, decreasing operative mortality, greater insights into tumor biology, and the development of effective multimodality therapies and precision medicine have contributed to this transformation. Progress has been most notable in lung cancer.

Robotic-assisted pulmonary lobectomy with lung cancer in a patient with situs inversus totalis

J Cardiothorac Surg. 2022 Sep 1;17(1):221. doi: 10.1186/s13019-022-01983-8. Chen Yang # 1 , et al.
BACKGROUND: Situs inversus totalis (SIT) is a relatively rare congenital abnormality in which the major thoracic and abdominal visceral organs are reversed from their usual positions. In patients with SIT and bronchial carcinoma, surgical difficulty increases sharply. It has been reported that the video-assisted thoracic surgery (VATS) still poses the operator to a challenge situation. The similarity of surgical positions and the flexibility of the mechanical arm in robotic surgery, may be beneficial to SIT patients due to reducing technical difficulties. Here, we present a first case of SIT patient with lung cancer, in which Da Vinci robot-assisted thoracic surgery (RATS) was performed successfully. **CASE PRESENTATION:** A 66-year old patient, previously diagnosed with SIT since childhood, came to our hospital with two pulmonary nodules in his left lung field. The bigger one had increased somewhat for the last 2 years of follow-up. Software Mimics was preoperatively carried out to analyze anatomical variations. RATS was conducted to complete left upper lobectomy and left middle wedge resection. The patient had no intraoperative complications and was discharged day 5 after the operation.
CONCLUSIONS: This is the first report of a successful robot-assisted lung cancer resection in a patient with SIT. In such challenging cases as lung cancer and rare anomaly as SIT, RATS is more advantageous and suitable than VATS with the help of software Mimics utilized for 3D reconstruction, which can identify the anatomical abnormalities and facilitate the surgical procedures.

Relationship of smoking cessation period with the incidence of complications in lung cancer surgery
Eur J Cardiothorac Surg. 2022 Aug 3;62(3):ezac163. doi: 10.1093/ejcts/ezac163. Yuka Kadomatsu 1 , et al.
OBJECTIVES: The incidence of postoperative complications is relatively high in smokers. Although 4-week smoking cessation before surgery is generally recommended, it has not been sufficiently studied in lung cancer surgery. This study investigated whether smoking cessation for a short period of time significantly reduced complications after lung cancer surgery. **METHODS:** This was a retrospective, observational study that investigated the relationship between the smoking cessation period and the incidence of complications in lung cancer surgery. Patients who underwent curative-intent surgery for lung cancer at our institution between January 2014 and December 2017 were included. The smokers were classified into the following 4 categories of smoking cessation period before surgery: current (<4 weeks), recent (4 weeks to 12 months), distant (12 months to 5 years) and ex-smokers (>5 years).
RESULTS: A total of 911 patients were included in this study. The incidence of pulmonary complications was 5 times higher in the smoker group than in the never smoker group (12.9% vs 2.5%, P < 0.001). On multivariable analysis in both models, the odds ratio for complications was significantly higher in distant smokers than in recent smokers and never smokers. Across all models, low lung function significantly predicted the development of postoperative complications.
CONCLUSIONS: The evidence-based smoking cessation duration that reduces the incidence of complications after thoracic surgery remains unclear. The incidence of postoperative complications was more strongly affected by low pulmonary function than by the duration of preoperative smoking cessation. For patients with marginal indications for surgery, postponing surgery to accommodate a smoking cessation period seemed unnecessary.

Prognostic Value of Uncertain Resection for Overall Survival in Non-small Cell Lung Cancer
Ann Thorac Surg. 2022 Oct;114(4):1262-1268. doi: 10.1016/j.athoracsur.2021.07.087. Epub 2021 Aug 30. Yuka Kadomatsu 1, et al.
BACKGROUND: In this study we evaluated the R(un) category proposed by the International Association for the Study of Lung Cancer (IASLC) for non-small cell lung cancer (NSCLC).
METHODS: We retrospectively reviewed the medical records of patients with NSCLC who underwent segmentectomy or lobectomy between 2014 and 2015 at our institution. Residual tumor (R) status was

reclassified from the Union for International Cancer Control designation to the IASLC-proposed R classification of R0 and R(un). The underlying reasons for the R(un) reclassification were analyzed according to pathologic stage, lymph node status, and resected lobe. A Cox proportional hazard model was used to evaluate the impacts of R(un) categorization on overall survival. **RESULTS:** Of 355 patients, 44.5% were reclassified as R(un). The most common reason for the reclassification was insufficient number of harvested lymph nodes or no station 7 lymph nodes. When stratified by tumor location, the absence of station 7 lymph nodes was especially prominent in both the right and left upper lung resections. In the multivariate Cox regression model, the IASLC R classification was associated with poor overall survival in node-positive patients (hazard ratio, 2.657; P = .016). **CONCLUSIONS:** Various factors resulted in reclassification to R(un) because the R(un) group was highly heterogeneous. Careful consideration is required to determine whether the R(un) classification can be used as an indicator of lymph node dissection quality. For advanced cases, the R(un) definition may be useful in predicting poor prognosis.

Robot-assisted Thoracoscopic Lobectomy of T4 Lung Cancer Ann Thorac Surg. 2022 Oct;114(4):e265-e267. doi: 10.1016/j.athoracsur.2021.12.021. Epub 2022 Jan 11. Anuj Shah 1 , et al.
A 79-year-old male former smoker presented with a T4 (>7 cm) adenocarcinoma of the right upper lobe. The patient was staged at clinical T4N0M0 and underwent robot-assisted right upper lobectomy and mediastinal lymph node dissection. The patient was discharged home on postoperative day 3. Larger tumors are a relative contraindication for video-assisted thoracoscopic surgical lobectomy. The robot platform overcomes the technical limitations of video-assisted thoracoscopic surgery and allows for the successful resection of large tumors.

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

Molecular lung cancer: How targeted therapies and personalized medicine are re-defining cancer care 2022 Oct;364(4):371-378. doi: 10.1016/j.amjms.2022.04.019. Epub 2022 Apr 22. Zachary L Quinn, Julie A Barta, Jennifer M Johnson
Lung cancer remains the leading cause of cancer death in the United States and is unfortunately still frequently diagnosed in the metastatic setting, where the disease is considered incurable. Nearly 30% of these cancers may be driven by specific mutations that promote tumor growth and proliferation. These mutations are observed more frequently in young patients without significant smoking history and in certain racial and ethnic backgrounds. The past 15 years have marked a revolution for patients with molecularly driven lung cancer as novel, oral, targeted therapies have been developed that demonstrate superior activity with substantially better toxicity profiles in comparison to chemotherapy. Consideration of molecular testing for a driver mutation is imperative for all providers caring for patients with a new suspected lung cancer diagnosis, as discovery of an actionable mutation will have dramatic implications in regards to patient survival and quality of life.

Surgical Perspective on Neoadjuvant Immunotherapy in Non-Small Cell Lung Cancer Ann Thorac Surg. 2022 Oct;114(4):1505-1515. doi: 10.1016/j.athoracsur.2021.06.069. Epub 2021 Jul 30. Jay M Lee, Masahiro Tsuboi, Alessandro Brunelli
BACKGROUND: With a 5% improvement in 5-year overall survival achieved with current neoadjuvant or adjuvant chemotherapy, new treatments for resectable non-small cell lung cancer (NSCLC) are urgently needed. The use of immune checkpoint inhibitors (ICIs) is established in metastatic NSCLC and is being evaluated in resectable NSCLC. **METHODS:** Publications and conference databases and clinicaltrials.gov were searched for reports on clinical studies of neoadjuvant immunotherapy in patients

with early resectable NSCLC. **RESULTS:** Potential advantages of neoadjuvant ICIs include the following: earlier treatment of micrometastatic disease; activation of a broader, potentially durable immune response by the whole tumor and associated lymph nodes; and pathologic assessment of neoadjuvant treatment response, which may guide adjuvant therapy. Surgical considerations include delays to surgery, potential disease progression preventing curative resection, and perioperative morbidity and mortality. Surrogate end points of efficacy (pathologic complete response, major pathologic response) and biomarkers predictive of outcome (programmed death ligand 1 expression, tumor mutational burden, and circulating tumor DNA) can accelerate clinical trial completion and early-stage treatment development; their application in neoadjuvant ICI studies in NSCLC is reviewed. **CONCLUSIONS:** Phase 2 trials of neoadjuvant ICIs alone or in combination with chemotherapy showed encouraging safety and efficacy in patients with resectable NSCLC, thus warranting the ongoing phase 3 studies of neoadjuvant immunotherapy combined with chemotherapy. Preoperative and intraoperative unresectability after neoadjuvant ICIs appears comparable to that observed with neoadjuvant chemotherapy. To help thoracic surgeons and medical oncologists to distinguish among ICIs beyond efficacy as phase 3 data emerge, surgery-related end points for perioperative morbidity, mortality, and complexity should be defined, standardized, incorporated into trial designs, and reported.

Top advances in lung cancer, 2021 Cancer. 2022 Oct 1;128(19):3434-3437. doi: 10.1002/cncr.34406. Epub 2022 Aug 10. Nisha A Mohindra, Jyoti D Patel
Despite a global pandemic that continued to inflict chaos and confusion on the world, resulting in fewer cancer screenings and delayed surgeries, remarkable lung cancer treatment advancements were made in 2021. From immunotherapy in the adjuvant setting to the approval of the first-in-class, highly selective inhibitor of KRAS G12C, these treatment advances have significant clinical impact in patients with lung cancer. LAY SUMMARY: There has been tremendous innovation in the treatment of nonsmall cell lung cancer. The year 2021 was marked by new approaches to adjuvant therapy and the availability of agents to target new subsets of nonsmall cell lung cancer.

Perioperative targeted therapy for oncogene-driven NSCLC Lung Cancer. 2022 Oct;172:160-169. doi: 10.1016/j.lungcan.2022.05.007. Epub 2022 May 21. Si-Yang Liu 1 , Jia-Tao Zhang 1 , Kang-Hui Zeng 2 , Yi-Long Wu 3
Targeted therapy has stepped into the perioperative treatment arena and launched a radical revolution in the treatment of early-stage oncogene-driven non-small-cell lung cancer (NSCLC). A series of practice-changing clinical trials has enriched the therapeutic perspectives of potentially curable NSCLC. While the CTONG1104 trial took the first step in investigating the adjuvant gefitinib - a first-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), for the treatment of resected EGFR-mutated NSCLC - the subsequent ADAURA study marked adjuvant osimertinib as the standard of care for resected EGFR-mutant NSCLC. Other targeted agents matched for ALK, ROS1, NTRK, BRAF V600, and RET molecular alterations are also currently being evaluated in the adjuvant and neoadjuvant settings, and there is an urgent need to study biomarker selection, optimal duration, and paradigm making. All these efforts are intended to hit the same target, which is to treat patients on a more personalized level. We review herein the recent major breakthroughs in perioperative targeted therapy for oncogene-driven NSCLC, focusing especially on data from published clinical trials. We discuss challenges from surgical, pathological, and oncological perspectives, and provide recommended strategies for the clinical management of early-stage NSCLC patients.

Tobacco Use and Response to Immune Checkpoint Inhibitor Therapy in Non-Small Cell Lung Cancer Curr Oncol. 2022 Aug 30;29(9):6260-6276. doi: 10.3390/curroncol29090492. Lucy K Corke 1 2 , Janice J N Li 1 2 , Natasha B Leighl 1 2 , Lawson Eng 1 2

Tobacco is a known risk factor for lung cancer, and continued tobacco use is associated with poorer outcomes across multiple lung cancer treatment modalities including surgery, chemotherapy and radiation therapy. Less is known about the association of tobacco use and outcomes with immune checkpoint inhibitors (ICIs), which are becoming an important part of the treatment landscape in lung cancer, both in metastatic and curative settings. We reviewed the literature on the association of tobacco and tumor biology as it relates to immunotherapy. We also reviewed the association of tobacco use on outcomes among phase III randomized clinical trials involving ICIs in non-small cell lung cancer (NSCLC). We identified that patients with a smoking history may have a greater benefit with ICI treatment compared to never smokers in both treatment-naïve (HR 0.82, 95% CI 0.69-0.97, vs. HR 1.06, 95% CI 0.81-1.38) and pre-treated (HR 0.79, 95% CI 0.70-0.90 vs. 1.03, 95% CI 0.74-1.43) settings. In trials where smoking status was further defined, ex-smokers appear to demonstrate greater benefit with ICI therapy compared to current smokers (HR 0.78, 95% CI 0.59-1.01 vs. 0.91, 95% CI 0.72-1.14). We conclude by offering our perspective on future directions in this area of research, including implementation of standardized collection and analysis of tobacco use in clinical trials involving ICI therapy in lung cancer and other disease sites, and also evaluating how tobacco may affect toxicities related to ICI therapy. Based on our review, we believe that a patient's history of tobacco smoking does have a role to play in guiding treatment decision making in patients with lung cancer.

Therapy for Stage IV Non-Small-Cell Lung Cancer With Driver Alterations: ASCO Living Guideline J Clin Oncol. 2022 Oct 1;40(28):3310-3322. doi: 10.1200/JCO.22.00824. Epub 2022 Jul 11. Navneet Singh 1 , et al.

PURPOSE: To provide evidence-based recommendations updating the 2021 ASCO and Ontario Health (Cancer Care Ontario) guideline on systemic therapy for patients with stage IV non-small-cell lung cancer (NSCLC) with driver alterations. **METHODS:** ASCO updated recommendations on the basis of an ongoing systematic review of randomized control trials from 2020 to 2021. **RESULTS:** This guideline update reflects changes in evidence since the previous update. Two studies provide the evidence base. Outcomes of interest include efficacy and safety. **RECOMMENDATIONS:** For patients with an anaplastic lymphoma kinase rearrangement, a performance status (PS) of 0-2, and previously untreated NSCLC, clinicians should offer alectinib or brigatinib or lorlatinib. For patients with an anaplastic lymphoma kinase rearrangement, a PS of 0-2, and previously untreated NSCLC, if alectinib, brigatinib, or lorlatinib are not available, clinicians should offer ceritinib or crizotinib. For patients with a RET rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer selpercatinib or pralsetinib. In second line, for patients with a RET rearrangement who have not received RET-targeted therapy, clinicians may offer selpercatinib or pralsetinib.Additional information is available at www.asco.org/thoracic-cancer-guidelines.

Combinatorial approaches for mitigating resistance to KRAS-targeted therapies Biochem J. 2022 Sep 30;479(18):1985-1997. doi: 10.1042/BCJ20220440. Hannah R Warren 1 , et al.

Approximately 15% of all cancer patients harbor mutated KRAS. Direct inhibitors of KRAS have now been generated and are beginning to make progress through clinical trials. These include a suite of inhibitors targeting the KRASG12C mutation commonly found in lung cancer. We investigated emergent resistance to representative examples of different classes of Ras targeted therapies. They all exhibited rapid reactivation of Ras signaling within days of exposure and adaptive responses continued to change over long-term treatment schedules. Whilst the gene signatures were distinct for each inhibitor, they commonly involved up-regulation of upstream nodes promoting mutant and wild-type Ras activation. Experiments to reverse resistance unfortunately revealed frequent desensitization to members of a panel of anti-cancer therapeutics, suggesting that salvage approaches are unlikely to be feasible. Instead, we

identified triple inhibitor combinations that resulted in more durable responses to KRAS inhibitors and that may benefit from further pre-clinical evaluation.

Randomized Versus Real-World Evidence on the Efficacy and Toxicity of Checkpoint Inhibitors in Cancer in Patients with Advanced Non-small Cell Lung Cancer or Melanoma: A Meta-analysis
Target Oncol. 2022 Sep;17(5):507-515. doi: 10.1007/s11523-022-00901-1. Epub 2022 Aug 1. Evangelos Digkas # 1, Anthony Jagri Tabiim # 2, Daniel Smith 3, Antonis Valachis 4.
BACKGROUND: Both randomized controlled trials (RCTs) and real-world evidence (RWE) studies provide results regarding the efficacy and toxicity of checkpoint inhibitors in cancer patients. The results from these two sources are considered complementary but whether they are comparable remains unknown. **OBJECTIVE:** The aim of this study was to compare the efficacy and toxicity of checkpoint inhibitors between RCTs and RWE studies in patients with advanced non-small cell lung cancer (NSCLC) or melanoma. **PATIENTS AND METHODS:** Two electronic databases were searched to identify eligible studies, either RCTs or RWE studies, investigating the efficacy or toxicity of checkpoint inhibitors given for indications that were approved by the European Medicines Agency (EMA) at the date of the last search. A meta-analysis was performed and the pooled estimates of objective response rates (ORR), progression-free survival (PFS), overall survival (OS), and toxicity and treatment discontinuation between RCTs and RWE studies were compared. **RESULTS:** In total, 43 RWE studies and 15 RCTs were eligible, with adequate data for pooled estimates for immunotherapy indications regarding NSCLC and melanoma. No statistically significant or clinically meaningful differences in terms of pooled PFS, OS, or rates of treatment discontinuation due to toxicity between RCTs and RWE studies were observed. In some indications, a higher rate of response rates and lower rate of toxicity in favor of RWE was observed. **CONCLUSION:** In patients with melanoma or NSCLC, the clinical value of checkpoint inhibitors is evident in both RCTs and real-world settings. Some differences in response or toxicity rates in favor of RWE mainly reflects the inherent difficulties in evaluating these outcomes in RWE studies.

KRAS-G12D mutation drives immune suppression and the primary resistance of anti-PD-1/PD-L1 immunotherapy in non-small cell lung cancer Cancer Commun (Lond). 2022 Sep;42(9):828-847. doi: 10.1002/cac2.12327. Epub 2022 Jul 11. Chengming Liu, et al.
BACKGROUND: Although immune checkpoint inhibitors (ICIs) against programmed cell death protein 1 (PD-1) and its ligand PD-L1 have demonstrated potency towards treating patients with non-small cell lung carcinoma (NSCLC), the potential association between Kirsten rat sarcoma viral oncogene homolog (KRAS) oncogene substitutions and the efficacy of ICIs remains unclear. In this study, we aimed to find point mutations in the KRAS gene resistant to ICIs and elucidate resistance mechanism. **METHODS:** The association between KRAS variant status and the efficacy of ICIs was explored with a clinical cohort (n = 74), and confirmed with a mouse model. In addition, the tumor immune microenvironment (TIME) of KRAS-mutant NSCLC, such as CD8+ tumor-infiltrating lymphocytes (TILs) and PD-L1 level, was investigated. Cell lines expressing classic KRAS substitutions were used to explore signaling pathway activation involved in the formation of TIME. Furthermore, interventions that improved TIME were developed to increase responsiveness to ICIs. **RESULTS:** We observed the inferior efficacy of ICIs in KRAS-G12D-mutant NSCLC. Based upon transcriptome data and immunostaining results from KRAS-mutant NSCLC, KRAS-G12D point mutation negatively correlated with PD-L1 level and secretion of chemokines CXCL10/CXCL11 that led to a decrease in CD8+ TILs, which in turn yielded an immunosuppressive TIME. The analysis of cell lines overexpressing classic KRAS substitutions further revealed that KRAS-G12D mutation suppressed PD-L1 level via the P70S6K/PI3K/AKT axis and reduced CXCL10/CXCL11 levels by down-regulating high mobility group protein A2 (HMGA2) level. Notably, paclitaxel, a chemotherapeutic agent, upregulated HMGA2 level, and in turn, stimulated the secretion of CXCL10/CXCL11. Moreover, PD-L1 blockade combined with paclitaxel significantly

suppressed tumor growth compared with PD-L1 inhibitor monotherapy in a mouse model with KRAS-G12D-mutant lung adenocarcinoma. Further analyses revealed that the combined treatment significantly enhanced the recruitment of CD8+ TILs via the up-regulation of CXCL10/CXCL11 levels. Results of clinical study also revealed the superior efficacy of chemo-immunotherapy in patients with KRAS-G12D-mutant NSCLC compared with ICI monotherapy. **CONCLUSIONS:** Our study elucidated the molecular mechanism by which KRAS-G12D mutation drives immunosuppression and enhances resistance of ICIs in NSCLC. Importantly, our findings demonstrate that ICIs in combination with chemotherapy may be more effective in patients with KRAS-G12D-mutant NSCLC.

Clinical Development of Anti-TIGIT Antibodies for Immunotherapy of Cancer Curr Oncol Rep. 2022 Sep;24(9):1107-1112. doi: 10.1007/s11912-022-01281-5. Epub 2022 Apr 12. Vaia Florou 1 , Ignacio Garrido-Laguna 1.
PURPOSE OF REVIEW: T-cell immunoglobulin and ITIM domain (TIGIT) is a next-generation inhibitory receptor with multiple antibodies under exploration in cancer therapy. Here, we review the available data from the early trials and overview upcoming clinical trials on anti-TIGIT antibodies. **RECENT FINDINGS:** There is a promising activity of anti-TIGIT, particularly in combination with anti-PD-1/PD-L1 in non-small cell lung cancer (NSCLC) with already phase 3 trials currently ongoing to confirm these early findings. Numerous anti-TIGIT antibodies are in clinical trials currently, and others are in preclinical development. Therefore, more data are expected in the next few years regarding the efficacy of this new checkpoint inhibitor in multiple solid and hematologic malignancies. However, preliminary data are promising, and anti-TIGIT treatment seems to confer more favorable responses when combined with anti-PD-1/anti-PD-L1 compared to either agent alone.

Safety and Efficacy of Epitinib for EGFR-Mutant Non-Small Cell Lung Cancer With Brain Metastases: Open-Label Multicentre Dose-Expansion Phase Ib Study Clin Lung Cancer. 2022 Sep;23(6):e353-e361. doi: 10.1016/j.cllc.2022.03.014. Epub 2022 May 7. Qing Zhou 1 , et al.
BACKGROUND: Non-small-cell lung cancer (NSCLC) had poor prognosis in patients with brain metastasis. The trial evaluated the safety and efficacy of epitinib (HMPL-813), an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), for EGFR-mutant NSCLC with brain metastasis. **PATIENTS AND METHODS:** This open-label, dose-expansion phase Ib study (ClinicalTrials.gov: NCT02590952) was conducted at 7 Chinese centers and enrolled patients with EGFR-mutant advanced NSCLC with brain metastasis. Epitinib was administered at 120 mg or 160 mg, orally QD. The primary endpoint was safety and tolerability. **RESULTS:** Between April 2015 and April 2019, 72 patients were enrolled and received epitinib at 120 mg (n = 30) or 160 mg (n = 42). Treatment-related adverse events (TRAEs) of grade ≥3 occurred in 13 (43.3%) patients in 120 mg group and 21 (50.0%) in 160 mg group. The objective response rate (ORR) was 53.6% (95% CI 33.9%-72.5%) in 120 mg group and 40.5% (25.6%-56.7%) in 160 mg group. The median duration of response in the 120 mg and 160 mg groups were 7.40 months (95% CI 3.70-7.40) and 9.10 months (6.50-12.00), respectively. The median progression-free survival were 7.40 months (95% CI 5.40-9.20) and 7.40 months (5.50-10.00), respectively. **CONCLUSION:** In patients with EGFR-mutant NSCLC with brain metastasis, epitinib was well tolerable with a promising efficacy. According to the comprehensive assessment on safety and efficacy, 160 mg QD could be the recommended phase 2 dose.

Non-small cell lung cancer harboring EGFR G724S mutation and exon 19 deletion responded to afatinib monotherapy after multiple lines of target therapies Anticancer Drugs. 2022 Oct 1;33(9):960-962. doi: 10.1097/CAD.0000000000001321. Epub 2022 Aug 12. Francesco Cortiula 1, et al.
Epidermal growth factor receptor (EGFR) G724S mutation represents a resistance mechanism to first- and third-generation EGFR tyrosine kinase inhibitors. Limited data are available regarding the efficacy of

afatinib in patients with non-small cell lung cancer (NSCLC) harboring G724S mutation, particularly after osimertinib. A patient diagnosed with advanced EGFR-mutated (exon 19 deletion) NSCLC after several lines of treatment - gefitinib, osimertinib, heat shock protein inhibitors and chemotherapy-developed EGFR G724S mutation retaining the exon 19 deletion. She was then treated successfully with afatinib leading to a progression free survival of 9 months (and counting). This is the first report of the emergence of G724S mutation, together with ex19del, after three subsequent lines of therapy following progressive disease to Osimertinib, and we report for the first time the activity of afatinib against EGFR exon 18 G724S mutation in this setting.

Rationale and Design of the Phase III KEYLYNK-012 Study of Pembrolizumab and Concurrent Chemoradiotherapy Followed by Pembrolizumab With or Without Olaparib for Stage III Non-Small-Cell Lung Cancer Clin Lung Cancer. 2022 Sep;23(6):e342-e346. doi: 10.1016/j.cllc.2022.04.003. Epub 2022 Apr 29. Salma K Jabbour 1 , et al.
BACKGROUND: Concurrent chemoradiotherapy is a standard therapy for patients with stage III non-small-cell lung cancer (NSCLC). Durvalumab is an approved treatment option following concurrent chemoradiotherapy in the absence of disease progression. The multicenter, phase III, randomized, placebo- and active-controlled, double-blind KEYLYNK-012 study evaluates whether initiation of immunotherapy with pembrolizumab concurrently with chemoradiotherapy, followed by post-chemoradiotherapy pembrolizumab with or without olaparib improves outcomes for participants with stage III NSCLC. (ClinicalTrials.gov: NCT04380636) METHODS: Eligible participants are aged ≥18 years with previously untreated, pathologically confirmed, stages IIIA-C, squamous or nonsquamous NSCLC not suitable for surgery with curative intent. Participants will be randomized 1:1:1 to platinum-doublet chemotherapy plus radiotherapy with pembrolizumab (Groups A and B) or concurrent chemoradiotherapy alone (Group C) for 3 cycles. In the absence of disease progression, participants will receive pembrolizumab plus olaparib placebo (Group A), pembrolizumab plus olaparib (Group B), or durvalumab monotherapy (Group C). Dual primary endpoints are progression-free survival per RECIST version 1.1 by independent central review and overall survival. **RESULTS:** Enrollment began on July 6, 2020, and is ongoing at approximately 190 sites. **CONCLUSION:** KEYLYNK-012 will provide important information on the efficacy and safety of pembrolizumab combined with concurrent chemoradiotherapy and subsequent pembrolizumab with or without olaparib in participants with unresectable stage III NSCLC.

Real-World Efficacy and Tolerability of Brigatinib in Patients with Non-Small Cell Lung Cancer with Prior ALK-TKIs in the United States Oncologist. 2022 Sep 2;27(9):790-798. doi: 10.1093/oncolo/oyac116. Mohammad Jahanzeb 1, et al. **BACKGROUND:** Real-world evidence for brigatinib, a next-generation anaplastic lymphoma kinase-tyrosine kinase inhibitor (ALK-TKI) used in ALK-rearranged non-small cell lung cancer, is scarce. This retrospective study evaluated real-world brigatinib utilization in the US post other ALK-TKIs. **MATERIALS AND METHODS:** Adults with ≥1 brigatinib claim (index date) between 1 April 2017 and 30 September 2020 in the IQVIA longitudinal pharmacy claims database were followed until dose reduction, discontinuation, or end of follow-up. Patients had ≥12 months pre- and ≥1-month post-index observations. **RESULTS:** A total of 413 patients treated with brigatinib were analyzed. Over 80% received ≥1 prior ALK-TKI; alectinib and crizotinib were the most common (58.8% and 51.3% patients, respectively). The median follow-up was 8.4 months. The median time to treatment discontinuation (TTD) for brigatinib was 10.3 months (95% CI, 8.2-15.0), with 45% remaining on therapy at 12 months. The TTD was shortest (~8 months) in patients receiving both crizotinib and alectinib and longest in patients who received alectinib only prior to brigatinib (11.8 months). Adherence was high, with 92.7% of patients having a medication possession ratio of >80%. The mean dose compliance score was 1.0. Most patients reached the brigatinib dose of 180 mg/day (77%);

13.2% of patients had a dose reduction, with 89.3% and 84.6% continuing 180 mg/day therapy at 3 and 6 months, respectively. **CONCLUSIONS:** Brigatinib appears to be effective and well-tolerated in the real-world ALK+ NSCLC population in the US, showing benefit in patients after a next-generation ALK-TKI. Notably, dose reduction rates appeared markedly less than those seen in trials when most trial-related dose reductions were for asymptomatic laboratory abnormalities

Effect of neoadjuvant therapy on tumor tissue PD-L1 and VISTA expression levels in non-small-cell lung cancer Immunotherapy. 2022 Oct;14(14):1121-1131. doi: 10.2217/imt-2021-0338. Epub 2022 Sep 1. Orhun Akdoğan 1 , et al.
BACKGROUND: PD-L1 and VISTA are important checkpoint control stations and play an immunomodulatory role in patients with non-small-cell lung cancer. **METHOD:** The expression levels of PD-L1 and VISTA between pre- and post-treatment tumor tissue were compared. **RESULTS:** While PD-L1 expression was >1% in 35% of patients before neoadjuvant therapy, PD-L1 expression was >1% in 65% of patients after treatment (p = 0.004). VISTA expression was >1% in 41% of patients before treatment, and this rate was 65% after treatment (p = 0.025). **CONCLUSION:** Chemotherapy and chemoradiotherapy can be used as immunizers by increasing PD-L1 and VISTA expression levels.

Characteristics of the immune microenvironment and their clinical significance in non-small cell lung cancer patients with ALK-rearranged mutation Front Immunol. 2022 Sep 8;13:974581. doi: 10.3389/fimmu.2022.974581. eCollection 2022. Bo Zhang 1 2 , et al.
BACKGROUND: Although immune checkpoint inhibitors (ICIs) are one of the most important treatments for advanced-stage non-small-cell lung cancer (NSCLC), NSCLC patients with ALK-rearranged usually don't obtain a clinical benefit. The reason may be related to the unique tumor microenvironment (TME). We evaluated the characteristics of immune biomarkers of the TME and their prognostic value in ALK-rearranged NSCLC. **METHODS:** Tumor samples from patients with ALK-rearranged (N = 39) and EGFR- (N = 40)/KRAS- (N = 30) mutated NSCLC were collected. Immunohistochemistry (IHC) was used to assess the expression of 9 tumor immune markers as well as 6 immune markers of tumor-infiltrating cells. To research the TME of ALK-rearranged NSCLC, EGFR/KRAS-positive patients were used as controls. Furthermore, the correlation between the efficacy and prognosis of patients with advanced-stage (IIIC-IV) ALK rearrangements treated with targeted drugs was analyzed in terms of the TME. **RESULTS:** The proportion of PD-L1+ tumors was lower in ALK-positive NSCLC than in KRAS-positive NSCLC. Besides, the proportion of T cells expressing TIM-3-CD8+ (15.38%), CTLA4-CD8+ (12.82%), LAG3-CD8+ (33.33%) and PD-1-CD8+ (2.56%) in ALK-positive NSCLC was lower than that in EGFR/KRAS-positive NSCLC. The expression of CD3, CD8 T cells and CD20 B cells was lower in ALK-positive NSCLC than in KRAS-positive NSCLC ($p < 0.0001$, < 0.005, and < 0.001, respectively). Nevertheless, the level of CD4 helper T cells was higher in ALK-positive NSCLC than in EGFR/KRAS-positive NSCLC ($p < 0.0001$ and $p < 0.05$, respectively). The repression of TIM3 was higher in ALK-positive NSCLC than in KRAS-positive NSCLC ($p < 0.001$). In addition, our data showed that high expression of PD-L1 (HR = 0.177, 95% CI 0.038-0.852, p = 0.027) and CTLA4 (HR = 0.196, 95% CI 0.041-0.947, p = 0.043) was related to lower OS in advanced-stage ALK- rearranged NSCLC patients treated with ALK tyrosine kinase inhibitors (TKIs).
CONCLUSIONS: Immunosuppressive status was characteristic of the TME in patients with ALK-positive NSCLC compared with EGFR/KRAS-positive NSCLC. High expression of PD-L1 and CTLA4 was an adverse prognostic factor in advanced-stage ALK-rearranged NSCLC patients treated with ALK-TKIs. Immunotherapy for ALK-rearranged patients requires further exploration and validation by clinical trials.

Characterizing the Shifting Real-World Treatment Landscape by PD-L1 Testing Status and Expression Level in Advanced Non-Small Cell Lung Cancer Adv Ther. 2022 Oct;39(10):4645-4662. doi: 10.1007/s12325-022-02260-9. Epub 2022 Aug 10. Wenzhen Ge 1 , et al.

INTRODUCTION: Contemporary real-world data on advanced non-small cell lung cancer (aNSCLC) treatment patterns across programmed cell death-ligand 1 (PD-L1) expression levels and testing status are limited. **METHODS:** A retrospective cohort was selected of adults newly diagnosed with aNSCLC between January 1, 2018, and July 31, 2021, who initiated first-line treatments, which were described by PD-L1 status and expression levels (≥ 50%, 1-49%, < 1%). Treatment received before and after PD-L1 test results were described for patients initiating first-line treatment before PD-L1 results. For patients who initiated chemotherapy alone before PD-L1 results, the probability of receiving immune checkpoint inhibitors (ICIs) after PD-L1 results was estimated by PD-L1 level and associated factors were explored. **RESULTS:** Among 12,202 patients with aNSCLC initiating first-line treatment [54.7% male, mean (standard deviation) age 69.2 (9.4) years], the most common therapies were ICI-based regimens across PD-L1 levels, and chemotherapy alone among PD-L1-untested patients. Use of chemotherapy alone decreased between 2018 and 2019 and stabilized thereafter, accounting for 21-29% of first-line treatments across PD-L1 levels and 48% of untested patients in 2021. Of 1468 patients initiating first-line treatment before PD-L1 results, treatments remained unchanged in most patients after PD-L1 results. Among patients initiating chemotherapy alone before PD-L1 results, the probability of receiving ICIs within 45 days after test results was 40.5% [95% confidence interval (CI) 31.6-48.3%], 28.6% (95% CI 20.3-36.0%), and 22.9% (95% CI 16.9-28.4%) at PD-L1 ≥ 50%, 1-49%, and < 1%, respectively. **CONCLUSION:** While ICI-based regimens accounted for most first-line treatments across PD-L1 levels, chemotherapy alone was initiated in > 20% of patients tested for PD-L1 and 48% of untested patients in 2021. Patients who initiated chemotherapy alone had a low probability of receiving ICIs after PD-L1 test results. These results highlight the need for understanding the role and timing of PD-L1 test results for informing treatment decisions for patients with aNSCLC.

Sintilimab plus docetaxel as second-line therapy of advanced non-small cell lung cancer without targetable mutations: a phase II efficacy and biomarker study BMC Cancer. 2022 Sep 5;22(1):952. doi: 10.1186/s12885-022-10045-0. Yongchang Zhang # 1 2 , et al.

BACKGROUND: Single-agent immunotherapy is currently the recommended second-line therapy for patients with advanced non-small cell lung cancer (NSCLC) without targetable mutations; however, the objective response rate (ORR) remains low. This phase II study evaluated the efficacy of the combination therapy of sintilimab plus docetaxel and explored potential biomarkers for efficacy prediction. **METHODS:** Thirty patients with NSCLC without targetable mutations whose disease progressed from first-line platinum-based chemotherapy from October 2019 to December 2020 were enrolled in this single-arm, single-center, phase II trial. Sintilimab (200 mg) and docetaxel (75 mg/m^2) were administered every 3 weeks until progression. The primary endpoint was ORR. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. Biomarker analyses of blood and tissue samples were also performed. **RESULTS:** Among 30 patients, 11 patients had partial response, resulting in an ORR of 36.7%. The median PFS was 5.0 months (95%CI: 3.9-6.1) and OS was 13.4 months (95%CI: 5.6-21.2). The most common immune-related adverse event of any grade was hepatitis, observed in 23.3% (7/30) of patients. Treatment-emergent adverse events were manageable. Patients detected with high PD-L1 expression in circulating tumor cells (cutoff value ≥32.5% based on the median CTC-PD-L1 expression) achieved significantly higher ORR (60% versus 13.3%, p = 0.021) and significantly longer median PFS (6.0 versus 3.5 months, p = 0.011) and median OS (15.8 versus 9.0 months, p = 0.038) than those with low CTC-PD-L1 level. Patients detected with PD-L1 < 1% and CD8 ≥ 1% expression from their baseline tissue samples had significantly higher ORR (83.3% versus 12.5%, p = 0.026) but similar PFS (p = 0.62) and OS (p = 0.15). **CONCLUSION:** This study demonstrated the effectiveness and safety

of sintilimab plus docetaxel as a second-line treatment of NSCLC without targetable mutations after progression from first-line platinum-based chemotherapy.

Evaluation of Clinical Outcomes of Icotinib in Patients With Clinically Diagnosed Advanced Lung Cancer With EGFR-Sensitizing Variants Assessed by Circulating Tumor DNA Testing: A Phase 2 Nonrandomized Clinical Trial JAMA Oncol. 2022 Sep 1;8(9):1328-1332. doi: 10.1001/jamaoncol.2022.2719. Jiachen Xu 1 , et al.

IMPORTANCE: The inability to obtain a pathological diagnosis in a certain proportion of patients with clinically diagnosed advanced lung cancer impedes precision treatment in clinical practice. **OBJECTIVE:** To evaluate the clinical outcome of first-line icotinib in patients with clinically diagnosed advanced lung cancer with unknown pathological status and positive epidermal growth factor receptor (EGFR)-sensitizing variants assessed by circulating tumor DNA (ctDNA). **DESIGN, SETTING, AND PARTICIPANTS:** The Efficiency of Icotinib in Plasma ctDNA EGFR Mutation-Positive Patients Diagnosed With Lung Cancer (CHALLENGE) trial is a prospective, multicentered, open-label, single-arm phase 2 nonrandomized clinical trial conducted between July 1, 2017, and July 31, 2019. Patients with systemic treatment-naive, clinically diagnosed advanced peripheral lung cancer, unknown pathological status, and positive pretreatment plasma EGFR-sensitizing variants were eligible. A total of 391 potentially eligible Chinese patients from 19 centers in China were screened for ctDNA EGFR variants by 3 independent detection platforms (Super amplification refractory mutation system [SuperARMS] polymerase chain reaction, droplet digital polymerase chain reaction, and next-generation sequencing), and those with EGFR variants tested by any platform were included. Analyses were conducted from September 9 to December 31, 2021. **INTERVENTIONS:** Enrolled patients were treated with oral icotinib tablets (125 mg 3 times daily) until disease progression, death, or treatment discontinuation due to various reasons, such as toxic effects and withdrawing consent. **MAIN OUTCOMES AND MEASURES:** The primary end point was objective response rate (ORR). The secondary end points included progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and the concordance among the 3 detection platforms. **RESULTS:** Of 116 included patients, 76 (65.5%) were female, and the median (range) age was 64 (37-85) years. The median (IQR) follow-up duration was 36.3 (30.2-40.7) months. The ORR was 52.6% (95% CI, 43.1%-61.9%). The median PFS and OS were 10.3 months (95% CI, 8.3-12.2) and 23.2 months (95% CI, 17.7-28.0), respectively, and the DCR was 84.5% (95% CI, 76.6%-90.5%). The concordance rate among the 3 detection platforms was 80.1% (313 of 391), and the clinical outcomes in patients identified as positive by any platform were comparable. **CONCLUSIONS AND RELEVANCE:** This prospective phase 2 nonrandomized clinical trial suggests that for patients with clinically diagnosed advanced lung cancer with unknown pathological status, ctDNA-based EGFR genotyping could help decision-making in particular clinical situations, while still warranting future larger-scaled real-world exploration.

Tepotinib: Management of Adverse Events in Patients With MET Exon 14 Skipping Non-Small Cell Lung Cancer Clin J Oncol Nurs. 2022 Sep 15;26(5):543-551. doi: 10.1188/22.CJON.543-551. Linda Ahn 1 , et al.

BACKGROUND: Tepotinib, a highly selective, oral, once-daily MET inhibitor, has been approved for treatment of metastatic MET exon 14 skipping non-small cell lung cancer. **OBJECTIVES:** This article provides nurse-specific recommendations for identification and management of tepotinib adverse events (AEs). **METHODS:** Guidance on monitoring and proactive/reactive AE management was developed based on published literature and real-world nursing experience. Case studies of VISION trial participants were summarized to illustrate key principles. **FINDINGS:** Tepotinib AEs are generally mild to moderate and manageable, and can include peripheral edema, hypoalbuminemia, nausea, diarrhea, and creatinine increase. Alongside supportive care, tepotinib interruption and dose reduction is recommended for grade 3

AEs. For peripheral edema, proactive monitoring is crucial, and treatment interruption (including frequent, short treatment holidays) should be considered early. Nursing management of tepotinib AEs includes proactive monitoring, patient education, and interprofessional team coordination.

Atezolizumab for Pretreated Non-Small Cell Lung Cancer with Idiopathic Interstitial Pneumonia: Final Analysis of Phase II AMBITIOUS Study Oncologist. 2022 Sep 2;27(9):720-e702. doi: 10.1093/oncolo/oyac118. Satoshi Ikeda 1, et al.

BACKGROUND: Interstitial pneumonia (IP) is a poor prognostic comorbidity in patients with non-small cell lung cancer (NSCLC) and is also a risk factor for pneumonitis. The TORG1936/AMBITIOUS trial, the first known phase II study of atezolizumab in patients with NSCLC with comorbid IP, was terminated early because of the high incidence of severe pneumonitis. **METHODS:** This study included patients with idiopathic chronic fibrotic IP, with a predicted forced vital capacity (%FVC) of >70%, with or without honeycomb lung, who had previously been treated for NSCLC. The patients received atezolizumab every 3 weeks. The primary endpoint was the 1-year survival rate. **RESULTS:** A total of 17 patients were registered; the median %FVC was 85.4%, and 41.2% had honeycomb lungs. The 1-year survival rate was 53.3% (95% CI, 25.9-74.6). The median overall and progression-free survival times were 15.3 months (95% CI, 3.1-not reached) and 3.2 months (95% CI, 1.2-7.4), respectively. The incidence of pneumonitis was 29.4% for all grades, and 23.5% for grade ≥3. Tumor mutational burden and any of the detected somatic mutations were not associated with efficacy or risk of pneumonitis. **CONCLUSION:** Atezolizumab may be one of the treatment options for patients with NSCLC with comorbid IP, despite the high risk of developing pneumonitis. This clinical trial was retrospectively registered in the Japan Registry of Clinical Trials on August 26, 2019, (registry number: jRCTs031190084

Rare EGFR E709-T710delinsX: Molecular characteristics and superior response to afatinib treatment in NSCLC patients Lung Cancer. 2022 Oct;172:117-123. doi: 10.1016/j.lungcan.2022.08.012. Epub 2022 Aug 22. Yihua Huang 1 , et al.

OBJECTIVES: Currently, whether patients with rare epidermal growth factor receptor (EGFR) mutations could benefit from EGFR tyrosine kinase inhibitors (TKIs) demands further studies. Limited clinical data are available regarding the molecular characteristics and clinical response in non-small-cell lung cancer (NSCLC) patients harboring EGFR E709-T710delinsX mutations, a rare mutation type in exon 18 of EGFR. In this study, we aimed to explore the molecular distribution and clinical outcome of EGFR E709-T710delinsX mutated Chinese patients. **METHODS:** Next-generation sequencing (NGS) tests were performed in 15,078 NSCLC patients. A multicenter retrospective cohort involving 17 advanced lung cancer patients with EGFR E709-T710delinsX was collected to evaluate clinical responses to diverse therapies. In silico protein structure modeling was conducted to predict drug response. **RESULTS:** 5905 EGFR mutant patients (39.2%, 5905/15078) were identified, with 26 cases (0.44%, 26/5905) harbored EGFR E709-T710delinsD. Afatinib showed a better overall objective response rate (ORR) compared with the first-generation (1G) EGFR TKIs and chemotherapy with significant difference. Superior progression free survival (PFS) was also observed in patients treated with afatinib (afatinib 10.85 m vs 1G EGFR TKIs 4.0 m vs chemotherapy 2.8 m, p = 0.0007). In silico protein structure modeling predicts better binding of afatinib with EGFR E709-T710delinsD compared with other EGFR TKIs. **CONCLUSIONS:** This is the largest studies for EGFR E709-T710delinsX, with 26 cases with EGFR E709-T710delinsX being identified (0.44% in EGFR mutant NSCLC, 0.17% in NSCLC patients). This study also firstly revealed that afatinib might exert superior antitumor activity to the 1G EGFR TKIs and chemotherapy in EGFR E709-T710delinsX mutant patients.

NSCLC - RADIOTHERAPY

Effect of Education and Standardization of Cardiac Dose Constraints on Heart Dose in Patients With Lung Cancer Receiving Definitive Radiation Therapy Across a Statewide Consortium Pract Radiat Oncol. 2022 Sep-Oct;12(5):e376-e381. doi: 10.1016/j.prro.2022.01.002. Epub 2022 Feb 1. Daniel J Herr 1, et al.

PURPOSE: Cardiac radiation exposure is associated with an increased rate of adverse cardiac events in patients receiving radiation therapy for locally advanced non-small cell lung carcinoma (NSCLC). Previous analysis of practice patterns within the Michigan Radiation Oncology Quality Consortium (MROQC) revealed 1 in 4 patients received a mean heart dose >20 Gy and significant heterogeneity existed among treatment centers in using cardiac dose constraints. The purpose of this study is to analyze the effect of education and initiation of standardized cardiac dose constraints on heart dose across a statewide consortium. **METHODS AND MATERIALS:** From 2012 to 2020, 1681 patients from 27 academic and community centers who received radiation therapy for locally advanced NSCLC were included in this analysis. Dosimetric endpoints including mean heart dose (MHD), mean lung dose, and mean esophagus dose were calculated using data from dose-volume histograms. These dose metrics were grouped by year of treatment initiation for all patients. Education regarding data for cardiac dose constraints first occurred in small lung cancer working group meetings and then consortium-wide starting in 2016. In 2018, a quality metric requiring mean heart dose <20 Gy while maintaining dose coverage (D95) to the target was implemented. Dose metrics were compared before (2012-2016) versus after (2017-2020) initiation of interventions targeting cardiac constraints. Statistical analysis was performed using the Wilcoxon rank sum test. **RESULTS:** After education and implementation of the heart dose performance metric, mean MHD declined from an average of 12.2 Gy preintervention to 10.4 Gy postintervention ($P < .0001$), and the percentage of patients receiving MHD >20 Gy was reduced from 21.1% to 10.3% ($P < .0001$). Mean lung dose and mean esophagus dose did not increase, and target coverage remained unchanged. **CONCLUSIONS:** Education and implementation of a standardized cardiac dose quality measure across a statewide consortium was associated with a reduction of mean heart dose in patients receiving radiation therapy for locally advanced NSCLC. These dose reductions were achieved without sacrificing target coverage, increasing mean lung dose, or increasing mean esophagus dose. Analysis of the clinical ramifications of the reduction in cardiac doses is ongoing.

Trends in Postoperative Intensity-Modulated Radiation Therapy Use and Its Association With Survival Among Patients With Incompletely Resected Non-Small Cell Lung Cancer JAMA Netw Open. 2022 Sep 1;5(9):e2230704. doi: 10.1001/jamanetworkopen.2022.30704. Brian Yu 1 , et al.

IMPORTANCE: National guidelines allow consideration of postoperative radiation therapy (PORT) among patients with incompletely resected non-small cell lung cancer (NSCLC). However, there is a paucity of prospective data because recently completed trials excluded patients with positive surgical margins. In addition, unlike for locally advanced NSCLC, the role of intensity-modulated radiation therapy (IMRT) for PORT remains unclear. **OBJECTIVE:** To evaluate trends of IMRT use for PORT in the US and the association of IMRT with survival outcomes among patients with incompletely resected NSCLC. **DESIGN, SETTING, AND PARTICIPANTS:** This retrospective cohort study used data from the National Cancer Database for patients diagnosed between January 2004 and December 2019 with incompletely resected NSCLC who underwent upfront surgery with positive surgical margins followed by PORT. **EXPOSURES:** IMRT vs 3D conformal radiation therapy (3DCRT) for PORT. **MAIN OUTCOMES AND MEASURES:** The main outcome was overall survival. Multivariable Cox proportional hazards regression assessed the association of IMRT vs 3DCRT with overall survival. Multivariable logistic regression identified variables associated with IMRT. Propensity score matching (1:1) was performed based on variables of interest. **RESULTS:** A total of 4483 patients (2439 men [54.4%]; median age, 67 years [IQR, 60-73 years]) were included in the analysis. Of those, 2116 (47.2%)

underwent 3DCRT and 2367 (52.8%) underwent IMRT. Median follow-up was 48.5 months (IQR, 31.1-77.2 months). The proportion of patients who underwent IMRT increased from 14.3% (13 of 91 patients) in 2004 to 70.7% (33 of 471 patients) in 2019 (P < .001). IMRT was associated with improved overall survival compared with 3DCRT (adjusted hazard ratio, 0.84; 95% CI, 0.78-0.91; P < .001). Similar findings were observed for 1463 propensity score-matched pairs; IMRT was associated with improved 5-year overall survival compared with 3DCRT (37.3% vs 32.2%; hazard ratio, 0.88; 95% CI, 0.80-0.96; P = .003). IMRT use was associated with receipt of treatment at an academic facility (adjusted odds ratio [aOR], 1.15; 95% CI, 1.00-1.33; P = .049), having T4 stage tumors (aOR, 1.50; 95% CI, 1.13-1.99; P = .005) or N2 or N3 stage tumors (aOR, 1.25; 95% CI, 1.04-1.51; P = .02), and receipt of pneumonectomy (aOR, 1.35; 95% CI, 1.02-1.80; P = .04). **CONCLUSION AND RELEVANCE:** This cohort study found that use of IMRT for PORT among patients with incompletely resected NSCLC increased in the US from 2004 to 2019 and was associated with improved survival compared with 3DCRT. Further studies are warranted to investigate the role of different radiation therapy techniques for PORT.

Evaluating the Suitability of 3D Bioprinted Samples for Experimental Radiotherapy: A Pilot Study
Int J Mol Sci. 2022 Sep 1;23(17):9951. doi: 10.3390/ijms23179951. Munir A Al-Zeer 1 , et al.
Radiotherapy is an important component in the treatment of lung cancer, one of the most common cancers worldwide, frequently resulting in death within only a few years of diagnosis. In order to evaluate new therapeutic approaches and compare their efficiency with regard to tumour control at a pre-clinical stage, it is important to develop standardized samples which can serve as inter-institutional outcome controls, independent of differences in local technical parameters or specific techniques. Recent developments in 3D bioprinting techniques could provide a sophisticated solution to this challenge. We have conducted a pilot project to evaluate the suitability of standardized samples generated from 3D printed human lung cancer cells in radiotherapy studies. The samples were irradiated at high dose rates using both broad beam and microbeam techniques. We found the 3D printed constructs to be sufficiently mechanically stable for use in microbeam studies with peak doses up to 400 Gy to test for cytotoxicity, DNA damage, and cancer cell death in vitro. The results of this study show how 3D structures generated from human lung cancer cells in an additive printing process can be used to study the effects of radiotherapy in a standardized manner.

Clinical Outcomes of Stereotactic Ablative Radiotherapy for All Stages of Non-Small Cell Lung Cancer; Definitive versus Consolidative Medicina (Kaunas). 2022 Sep 18;58(9):1304. doi: 10.3390/medicina58091304. Hakyoung Kim 1 ,et al.
BACKGROUND AND OBJECTIVES: Stereotactic ablative radiotherapy (SABR) is not confined to early stage non-small cell lung cancer (NSCLC) and has a potential role in stage IV disease. We aimed to evaluate the effect of SABR on local control rates and survival outcomes in patients with all stages of NSCLC according to the treatment aim. **MATERIALS AND METHODS:** We retrospectively reviewed the medical records of 88 patients with NSCLC who received SABR at the Korea University Guro Hospital between January 2015 and March 2021. Among these, 64 patients with stage I-II NSCLC ineligible for surgery were treated with a definitive aim. Twenty-four patients with stage IV limited metastatic NSCLC showing a favorable response to prior systemic therapy were treated with a consolidative aim. **RESULTS:** The median follow-up time was 34 (range: 5-88) months. Thirty-one patients developed recurrence (35.2%), with distant metastasis being the most common (25/31, 80.6%). In-field local recurrence occurred in four patients (4/88 patients, 4.5%). For patients treated with definitive SABR, the 3-year overall survival (OS) and disease-free survival (DFS) rates were 91.8% and 58.6%, respectively. In patients treated with consolidative SABR, the 3-year OS and DFS rates were 86.7% and 53.8%, respectively. With respect to treatment-related pulmonary toxicity, grade 3 radiation pneumonitis incidence requiring hospitalization was 2.3% (2/88). **CONCLUSIONS:** Definitive SABR is

appropriate for medically inoperable or high surgical risk patients with early stage NSCLC with acceptable treatment-related toxicities. Consolidative SABR improves local control rates and helps achieve long-term survival in patients with limited metastatic NSCLC.

The benefit of radiotherapy in distant metastatic small-cell lung cancer: A retrospective study based on propensity score matching (PSM) Medicine (Baltimore). 2022 Sep 9;101(36):e30510. doi: 10.1097/MD.0000000000030510. Shuai Qie 1 , et al.
Due to extensive tumor spread, systemic chemotherapy is the main treatment for distant metastatic small-cell lung cancer (DM-SCLC). It is still unclear whether adding local radiotherapy (RT) on the basis of chemotherapy can improve the long-term survival of patients with DM-SCLC. This study aims to explore the population with DM-SCLC who can benefit from RT. Patients with metastatic SCLC with complete data were collected from the Surveillance, Epidemiology, and End Results database and divided into 2 groups according to whether RT was given or not. The propensity score matching method was used to balance the covariate differences between the RT group and the non-RT group. Lasso Cox regression model and Cox proportional hazards regression analyses were used to identifying independent risk factors affecting survival. Kaplan-Meier method was used to calculate the survival rate. $P < .05$ was considered statistically significant. After matching, there were 3150 patients in both groups. Sex, tumor size, N stage, RT, chemotherapy, brain metastasis, liver metastasis, age, and site metastasis were independent factors of survival in DM-SCLC. The 1- and 2-year survival rates were 24.5% and 5.8% in the RT group and 14.8% and 2.3% in the non-RT group ($P < .001$). The median survival time of the RT group was 9 months, and that of the non-RT group was 7 months, and the difference was statistically significant ($P < .001$). RT improved survival in all sex subgroups, any N stage subgroup, any tumor size subgroup, no brain metastases subgroup, no liver metastases subgroup, any age subgroup, and 1-2 organ metastases subgroup. RT improves 1- and 2-year survival in DM-SCLC.

Clinical Outcomes of Stereotactic Ablative Radiotherapy for All Stages of Non-Small Cell Lung Cancer; Definitive versus Consolidative
Medicina (Kaunas). 2022 Sep 18;58(9):1304. doi: 10.3390/medicina58091304. Hakyoung Kim 1, et al.
BACKGROUND AND OBJECTIVES: Stereotactic ablative radiotherapy (SABR) is not confined to early stage non-small cell lung cancer (NSCLC) and has a potential role in stage IV disease. We aimed to evaluate the effect of SABR on local control rates and survival outcomes in patients with all stages of NSCLC according to the treatment aim. **MATERIALS AND METHODS:** We retrospectively reviewed the medical records of 88 patients with NSCLC who received SABR at the Korea University Guro Hospital between January 2015 and March 2021. Among these, 64 patients with stage I-II NSCLC ineligible for surgery were treated with a definitive aim. Twenty-four patients with stage IV limited metastatic NSCLC showing a favorable response to prior systemic therapy were treated with a consolidative aim. **RESULTS:** The median follow-up time was 34 (range: 5-88) months. Thirty-one patients developed recurrence (35.2%), with distant metastasis being the most common (25/31, 80.6%). In-field local recurrence occurred in four patients (4/88 patients, 4.5%). For patients treated with definitive SABR, the 3-year overall survival (OS) and disease-free survival (DFS) rates were 91.8% and 58.6%, respectively. In patients treated with consolidative SABR, the 3-year OS and DFS rates were 86.7% and 53.8%, respectively. With respect to treatment-related pulmonary toxicity, grade 3 radiation pneumonitis incidence requiring hospitalization was 2.3% (2/88). **CONCLUSIONS:** Definitive SABR is appropriate for medically inoperable or high surgical risk patients with early stage NSCLC with acceptable treatment-related toxicities. Consolidative SABR improves local control rates and helps achieve long-term survival in patients with limited metastatic NSCLC.

Protocol of the TREASURE study: Thoracic RadiothErapy with Atezolizumab in Small cell lUng canceR Extensive disease - a randomized, open-label, multicenter phase II trial BMC Cancer. 2022 Sep 24;22(1):1011. doi: 10.1186/s12885-022-10074-9. Farastuk Bozorgmehr 1 2, et al.
BACKGROUND: Recently, the combination of the programmed death-ligand 1 (PD-L1) inhibitor atezolizumab with first-line chemotherapy has demonstrated to improve outcome for patients with advanced small cell lung cancer (SCLC), leading to approval of this regimen. At the same time, accumulating (pre-)clinical data suggest synergisms of radiotherapy and immunotherapy via the radiation-mediated induction of anti-tumor immunogenicity. Combining the recent findings, the TREASURE trial aims at further enhancing response to upfront chemo-immunotherapy by the addition of thoracic radiotherapy (TRT). **METHODS/DESIGN:** The TREASURE trial is a randomized, multicenter, phase II clinical trial (ClinicalTrials.gov identifier, NCT04462276). One hundred four patients suffering from extensive disease (ED) SCLC, with any response to the standard of care induction chemo-immunotherapy will be randomized to receive atezolizumab maintenance therapy with or without TRT. The primary endpoint of this study is overall survival (OS). Secondary endpoints include further measures of efficacy, safety, and the collection of biomarker samples. A safety interim analysis will take place after n = 23 patients receiving TRT have been observed for three months after the end of TRT. **DISCUSSION:** This trial will investigate whether treatment efficacy can be improved by adding TRT to atezolizumab maintenance therapy in ED SCLC patients with any response after chemo-immunotherapy. Safety and feasibility of such a regimen will be evaluated, and biomaterials for a translational research project will be collected. Together, the results of this trial will deepen our comprehension of how checkpoint inhibition and radiotherapy interact and contribute to the evolving landscape of SCLC therapy.

SMALL CELL LUNG CANCER - SCLC

PARP inhibitors in small cell lung cancer: The underlying mechanisms and clinical implications
Biomed Pharmacother. 2022 Sep;153:113458. doi: 10.1016/j.biopha.2022.113458. Epub 2022 Jul 23. Xueting Wang 1, et al.
Since the concept, DNA damage repair has been stated as a natural biological event, and research has increasingly revealed its strong association to tumors, aging, immunity, biochemical detection, and other factors. The discovery of abnormal DNA repair in cancers has been heralded as a paradigm shift in the treatment of malignancies. A poly (ADP-ribose) polymerase (PARP) activates poly (ADP-ribosylation) to repair single-strand DNA breaks after DNA damage. In some cancers, such as breast cancer and gastric cancer, a PARP inhibitor can target the DNA damage response pathway, prevent DNA repair, and induce homologous recombination deficiency (HRD) tumors to create the phenomena of synthetic lethality. Increasingly, clinical trials are being submitted to research the uses of PARP inhibitors in various types of cancers. Small cell lung cancer (SCLC) is a quickly growing malignancy with numerous therapeutic limitations and a dismal prognosis. Sequencing of mutant genes revealed multiple gene connections that may contribute to its carcinogenesis, indicating a viable study direction. Furthermore, the therapy of SCLC with PARP inhibitors has been further explored. The mechanism of PARP action, as well as the advancement of its preclinical and clinical applications in SCLC, will be discussed in this review.

Analysis of Circulating Tumor and Cancer Stem Cells Provides New Opportunities in Diagnosis and Treatment of Small Cell Lung Cancer Int J Mol Sci . 2022 Sep 17;23(18):10853. doi: 10.3390/ijms231810853. Evgenii G Skurikhin , et al.
Current methods for diagnosis and treatment of small cell lung cancer (SCLC) have only a modest efficacy. In this pilot study, we analyzed circulating tumor cells (ctcs) and cancer stem cells (cscs) in patients with SCLC to search for new diagnostic and prognostic markers and novel approaches to improve the treatment of the disease. In other forms of lung cancer, we showed a heterogeneity of blood ctcs and

cscs populations, as well as changes in other cell populations (ALDH+, CD87+CD276+, and EGF+Axl+) in smokers. A number of ctcs and cscs in patients with SCLC have been shown to be resistant to chemotherapy (CT). High cytotoxic activity and resistance to apoptosis of reprogrammed CD3+CD8+ T-lymphocytes (rtcells) in relation to naive CD3+CD8+ T-lymphocytes was demonstrated in a smoking patient with SCLC (Patient G) in vitro. The target for rtcells was patient G's blood cscs. Reprogramming of CD3+CD8+ T-lymphocytes was carried out with the MEK1/2 inhibitor and PD-1/PD-L1 pathway blocker nivolumab. The training procedure was performed with a suspension of dead ctcs and cscs obtained from patient's G blood. The presented data show a new avenue for personalized SCLC diagnosis and targeted improvement of chemotherapy based on the use of both ctcs and cscs.

In-depth proteomic analysis reveals unique subtype-specific signatures in human small-cell lung cancer Clin Transl Med. 2022 Sep;12(9):e1060. doi: 10.1002/ctm2.1060. Beáta Szeitz 1, et al.
BACKGROUND: Small-cell lung cancer (SCLC) molecular subtypes have been primarily characterized based on the expression pattern of the following key transcription regulators: ASCL1 (SCLC-A), NEUROD1 (SCLC-N), POU2F3 (SCLC-P) and YAP1 (SCLC-Y). Here, we investigated the proteomic landscape of these molecular subsets with the aim to identify novel subtype-specific proteins of diagnostic and therapeutic relevance. **METHODS:** Pellets and cell media of 26 human SCLC cell lines were subjected to label-free shotgun proteomics for large-scale protein identification and quantitation, followed by in-depth bioinformatic analyses. Proteomic data were correlated with the cell lines' phenotypic characteristics and with public transcriptomic data of SCLC cell lines and tissues. **RESULTS:** Our quantitative proteomic data highlighted that four molecular subtypes are clearly distinguishable at the protein level. The cell lines exhibited diverse neuroendocrine and epithelial-mesenchymal characteristics that varied by subtype. A total of 367 proteins were identified in the cell pellet and 34 in the culture media that showed significant up- or downregulation in one subtype, including known druggable proteins and potential blood-based markers. Pathway enrichment analysis and parallel investigation of transcriptomics from SCLC cell lines outlined unique signatures for each subtype, such as upregulated oxidative phosphorylation in SCLC-A, DNA replication in SCLC-N, neurotrophin signalling in SCLC-P and epithelial-mesenchymal transition in SCLC-Y. Importantly, we identified the YAP1-driven subtype as the most distinct SCLC subgroup. Using sparse partial least squares discriminant analysis, we identified proteins that clearly distinguish four SCLC subtypes based on their expression pattern, including potential diagnostic markers for SCLC-Y (e.g. GPX8, PKD2 and UFO). **CONCLUSIONS:** We report for the first time, the protein expression differences among SCLC subtypes. By shedding light on potential subtype-specific therapeutic vulnerabilities and diagnostic biomarkers, our results may contribute to a better understanding of SCLC biology and the development of novel therapies.

PALLIATIVE AND SUPPORTIVE CARE

Effects of high-quality nursing care on quality of life, survival, and recurrence in patients with advanced nonsmall cell lung cancer Medicine (Baltimore). 2022 Sep 16;101(37):e30569. doi: 10.1097/MD.0000000000030569. Minghuan Wang 1, et al.
BACKGROUND: Postoperative nursing can improve the quality of life (QoL) and functional prognosis for lung cancer patients. The purpose of this study was to evaluate the effects of high-quality nursing on inflammation and prognosis in postoperative patients with advanced nonsmall cell lung cancer (NSCLC). **METHODS:** A total of 372 patients with NSCLC were enrolled between the May 2014 and June 2016. Patients were randomly received high-quality nursing (n = 192) or normal nursing (n = 180). Symptom management, QoL, hospital stay, inflammatory score, survival time, recurrence rate, symptoms, anxiety, depression scale and psychological distress were assessed at baseline and 5-year follow up.
RESULTS: High-quality nursing significantly shortened hospital stay, improved postoperative

inflammation, symptom management, QoL compared to patients received normal nursing. Compare with normal nursing, high-quality nursing decreased anxiety, depression scale and psychological distress for postoperative patients with advanced NSCLC. Outcomes showed that high-quality nursing increased the survival time and decreased recurrence rate for postoperative patients with advanced NSCLC. **CONCLUSION:** In conclusion, data in the current study indicate that high-quality nursing can decrease inflammation and improve prognosis for the postoperative patients with NSCLC.

COMPLEMENTARY AND ALTERNATIVE THERAPY

Network Pharmacology-Integrated Molecular Docking Reveals the Expected Anticancer Mechanism of *Picrorhizae Rhizoma* Extract Biomed Res Int. 2022 Sep 16;2022:3268773. doi: 10.1155/2022/3268773. eCollection 2022. Xiaomeng Hu 1, et al.
This study sought to explore the anticancer mechanism of Picrorhizae Rhizoma (PR) extract based on network pharmacology and molecular docking. The potential chemicals of PR were screened through the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database and relevant literatures. Corresponding targets of active ingredients were found with the help of the UniProtKB database, and therapeutic targets for cancer action were screened with the help of the GeneCards database. We used Cytoscape software to construct the compound-target-pathway network of PR extract. We utilized the STRING database to obtain the protein-protein interaction (PPI) network. We used DAVID database combining Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. Finally, molecular docking was employed for initial efficacy checking. We have identified 16 potential active components of PR through screening, involving 112 disease action targets. Utilizing the GeneCards database, 112 intersecting targets between PR extract and cancer were found, which mainly exerts anticancer effects by regulating tumor necrosis factor (TNF), recombinant caspase 3 (CASP3), c-Jun NH2-terminal kinase (JNK)/JUN, epidermal growth factor receptor (EGFR), and estrogen receptor-1 (ESR1) with some other target genes and pathways associated with cancer. The major anticancer species are prostate cancer, colorectal cancer, small cell lung cancer, etc. In the molecular docking study, herbactin had a strong affinity for TNF. Based on network pharmacology and molecular docking studies, PR and their compounds have demonstrated potential anticancer activities against several key targets. **Our preliminary findings provide** a strong foundation for further experiments with PR constituents.

Analysis of Anti-Cancer and Anti-Inflammatory Properties of 25 High-THC Cannabis Extracts Molecules. 2022 Sep 16;27(18):6057. doi: 10.3390/molecules27186057. Dongping Li 1 , et al.
Cannabis sativa is one of the oldest cultivated plants. Many of the medicinal properties of cannabis are known, although very few cannabis-based formulations became prescribed drugs. Previous research demonstrated that cannabis varieties are very different in their medicinal properties, likely due to the entourage effect-the synergistic or antagonistic effect of various cannabinoids and terpenes. In this work, we analyzed 25 cannabis extracts containing high levels of delta-9-tetrahydrocannabinol (THC). We used HCC1806 squamous cell carcinoma and demonstrated various degrees of efficiency of the tested extracts, from 66% to 92% of growth inhibition of cancer cells. Inflammation was tested by induction of inflammation with TNF-α/IFN-γ in WI38 human lung fibroblasts. The efficiency of the extracts was tested by analyzing the expression of COX2 and IL6; while some extracts aggravated inflammation by increasing the expression of COX2/IL6 by 2-fold, other extracts decreased inflammation, reducing expression of cytokines by over 5-fold. We next analyzed the level of THC, CBD, CBG and CBN and twenty major terpenes and performed clustering and association analysis between the chemical composition of the extracts and their efficiency in inhibiting cancer growth and curbing inflammation. A positive correlation was found between the presence of terpinene (pval = 0.002) and anti-cancer property;

eucalyptol came second, with pval of 0.094. p-cymene and β-myrcene positively correlated with the inhibition of IL6 expression, while camphor correlated negatively. No significant correlation was found for COX2. We then performed a correlation analysis between cannabinoids and terpenes and found a positive correlation for the following pairs: α-pinene vs. CBD, p-cymene vs. CBGA, terpenolene vs. CBGA and isopulegol vs. CBGA. Our work, thus, showed that most of high-THC extracts demonstrate anti-cancer activity, while only certain selected extracts showed anti-inflammatory activity. Presence of certain terpenes, such as terpinene, eucalyptol, cymene, myrcene and camphor, appear to have modulating effects on the activity of cannabinoids.

MISCELLANEOUS WORKS

Association between use of antacid medications (proton pump inhibitors and histamine-2 receptor antagonists) and the incidence of lung cancer: A population-based cohort analysis Medicine (Baltimore). 2022 Sep 9;101(36):e30399. doi: 10.1097/MD.0000000000030399. Subin Go 1 , Dong Yoon Lee 2 , Won-Il Choi 1 , Jihyeon Jeong 3

This study investigated the association between antacid administration and lung cancer incidence in a real-world setting. This was a nationwide, retrospective cohort study. The cohort comprised random samples (n = 1,031,392) from the entire South Korean population in 2002. The duration of antacid administration between January 2006 and December 2010 was recorded for each participant. Newly developed lung cancers were counted during the 5-year observation period (January 1, 2006 to December 31, 2010). A total of 437,370 participants aged ≥ 40 years were included, of whom 301,201 (68.9%) had antacid exposure before the diagnosis of lung cancer. A total of 1230 (0.28%) antacid-exposed patients developed lung cancer. Among patients with no antacid exposure or underexposure (n = 136,171), 597 (0.44%) developed lung cancer. In the multivariable analysis, antacid exposure before the diagnosis of lung cancer was independently associated with a reduced incidence of lung cancer (hazard ratio: 0.64; 95% confidence interval: 0.55-0.74; P < .001). Antacid use might be independently associated with a decreased risk of lung cancer development in this cohort study.

The nomograms for predicting overall and cancer-specific survival in elderly patients with early-stage lung cancer: A population-based study using SEER database Front Public Health. 2022 Sep 8;10:946299. doi: 10.3389/fpubh.2022.946299. eCollection 2022. Gen Yu 1 , et al.

PURPOSE: Lung cancer is the leading cause of death from cancer and the number of operable elderly lung cancer patients is increasing, with advanced age being associated with a poorer prognosis. However, there is no easy and comprehensive prognostic assessment method for these patients. **METHODS:** Clinicopathological data of patients aged 65 years or older with TNM stage I-II lung cancer from 2004 to 2018 were downloaded from the SEER database. Patients from 2004 to 2015 were randomized into a training group (n = 16,457) and a validation group (n = 7,048). Data from 2016 to 2018 (n = 6,231) were used for external validation. Two nomogram prognostic models were created after independent prognostic factors connected to both overall survival (OS) and cancer-specific survival (CSS) in the training set by using univariate and multivariate Cox proportional hazards regression analysis. In turn, overall survival (OS) and cancer-specific survival (CSS) were predicted for patients at 1, 3, and 5 years. Based on the concordance index (C-index), calibration curves, area under the receiver operating characteristics (ROC) curve (AUC), the time-dependent area under the ROC curve, the validity, accuracy, discrimination, predictive ability, and clinical utility of the models were evaluated. Decision curve analysis (DCA) was used to assess the clinical value of the models. **RESULTS:** A total of 29,736 patients were included. Univariate and multivariate analyses suggested that age, race, gender, marriage, disease grade, AJCC stage, T-stage, surgery, radiotherapy, chemotherapy, and tumor size were independent risk factors for patient prognosis. These 11 variables were included in nomogram to predict OS and CSS of patients. C-

indexes of OS for the training, validation and external validation sets were 0.730 (95% CI, 0.709-0.751), 0.734 (95% CI, 0.722-0.746), and 0.750 (95% CI, 0.734-0.766), respectively. The AUC results for the training and validation sets indicated good accuracy for this nomogram. The calibration curves demonstrated a high degree of concordance between actual and anticipated values, and the DCA demonstrated that the nomograms had better clinical application than the traditional TNM staging approach. **CONCLUSION:** This study identified risk factors for survival in operable elderly lung cancer patients and established a new column line graph for predicting OS and CSS in these patients. The model has good clinical application and can be a good clinical decision-making tool for physicians and patients.

African American race as a risk factor associated with a second primary lung cancer after initial primary head and neck cancer Head Neck. 2022 Oct;44(10):2069-2076. doi: 10.1002/hed.27107. Epub 2022 Jun 17. Yusra F Shao, et al.
BACKGROUND: Initial primary head and neck cancer (IPHNC) is associated with second primary lung cancer (SPLC). We studied this association in a population with a high proportion of African American (AA) patients. **METHODS:** Patients with IPHNC and SPLC treated between 2000 and 2017 were reviewed for demographic, disease, and treatment-related characteristics and compared to age-and-stage-matched controls without SPLC. Logistic and Cox regression models were used to analyze the relationship of these characteristics with the development of SPLC and overall survival (OS). **RESULTS:** Eighty-seven patients and controls were compared respectively. AA race was associated with a significantly higher risk of developing SPLC (OR 2.92, 95% CI 1.35-6.66). After correcting for immortal time bias, patients with SPLC had a significantly lower OS when compared with controls (HR 0.248, 95% CI 0.170-0.362) **CONCLUSIONS:** We show that AA race is associated with an increased risk of SPLC after IPHNC; reasons of this increased risk warrant further investigation.

Psychological states regarding adjuvant chemotherapy in patients with non-small cell lung cancer Cancer Treat Res Commun. 2022;32:100591. doi: 10.1016/j.ctarc.2022.100591. Epub 2022 Jun 14. Takahiro Mimae 1 , Miyako Satouchi 2 , Morihito Okada 3
BACKGROUND: Understanding the anxieties and emotions of patients with lung cancer before and after radical surgery is crucial in the decision to undergo postoperative adjuvant chemotherapy. However, the psychological states and changes associated with adjuvant chemotherapy during perioperative periods in patients with non-small cell lung cancer (NSCLC) remain unclear. **PATIENTS AND METHODS:** Participants with a self-reported diagnosis of pathological stage II or III NSCLC who underwent complete surgical resection and received information on postoperative adjuvant chemotherapy (n = 101) were sampled from an online panel in Japan from October 9 to November 19, 2020. Eligible and consenting participants completed a self-administered online questionnaire survey about their disease, and their psychological states were assessed. **RESULTS:** The majority of patients (39, 38.6%) were 60-69 years of age, and 87 (86.1%) were men. A total of 59 (58.4%) and 42 (41.6%) patients had pathological stages II and III, respectively. Regardless of the situation, more than 75% of the patients were anxious about the possibility of recurrence after complete surgical resection for lung cancer. Approximately 70% of respondents selected the option of "I will get adjuvant chemotherapy" on any precondition. Among them, almost all respondents selected the option "want to do everything I can do now to prevent recurrence." **CONCLUSION:** In this small sample of respondents with NSCLC from Japan, it is important for surgeons and physicians to explain the condition and corresponding therapy for lung cancer, while considering the possibility of recurrence in any situation, even before surgery as a curative intent.

Prevalence and consequences of non-adherence to an evidence-based approach for incidental pulmonary nodules PLoS One. 2022 Sep 9;17(9):e0274107. doi: 10.1371/journal.pone.0274107. eCollection 2022. Max T Wayne 1 , Hallie C Prescott 1 2 , Douglas A Arenberg 1.
IMPORTANCE: Distinguishing benign from malignant pulmonary nodules is challenging. Evidence-based guidelines exist, but their impact on patient-centered outcomes is unknown. **OBJECTIVE:** To understand if the evaluation of incidental pulmonary nodules that follows an evidence-based management strategy is associated with fewer invasive procedures for benign lesions and/or fewer delays in cancer diagnosis. **DESIGN:** Retrospective cohort study. **SETTING:** Large academic medical center. **PARTICIPANTS:** Adults (≥18 years age) with an incidental pulmonary nodule discovered between January 2012 and December 2014. Patients with calcified nodules, prior nodules, prior diagnosis of cancer, high suspicion for pulmonary metastasis, or limited life expectancy were excluded. **EXPOSURE:** Nodule management strategy (pre-specified based on evidence-based practices). **OUTCOME:** Composite of any invasive procedure for a benign nodule or delay in diagnosis in patients with cancer (>3 month delay once probability of cancer was >15%). **RESULTS:** Of 314 patients that met inclusion criteria, median age was 61, 46.5% were men, and 66.5% had current or former tobacco use. The mean nodule size was 10.3 mm, mean probability of cancer was 11.8%, and 14.3% of nodules were malignant. Evaluation followed an evidence-based strategy in 245 patients (78.0%), and deviated in 69 patients (22%). The composite outcome occurred in 26 (8.3%) patients. Among patients whose nodule evaluation was concordant with an evidence-based evaluation, 6.1% (15/245) experienced the composite outcome versus 15.9% (11/69) of patients with an evaluation that deviated from evidence-based recommendations (P<0.01). **CONCLUSIONS AND RELEVANCE:** At a large academic medical center, more than 1 in 5 patients with an incidental pulmonary nodule underwent evaluation that deviated from evidence-based practice recommendations. Nodule evaluation that deviated from an evidence-based strategy was associated with biopsy of benign lesions and delays in cancer diagnosis, suggesting a need to improve guideline uptake.

Propensity score-based analysis of stereotactic body radiotherapy, lobectomy and sublobar resection for stage I non-small cell lung cancer J Radiat Res. 2022 Sep 21;63(5):758-771. doi: 10.1093/jrr/rrac041. Noriko Kishi 1, et al.
We applied two propensity score-based analyses to simultaneously compare three treatment modalities-stereotactic body radiotherapy (SBRT), lobectomy, or sublobar resection (SLR)-for stage I non-small cell lung cancer (NSCLC), with the aim of clarifying the average treatment effect (ATE) and formulating a risk-adapted approach to treatment selection. A retrospective review of 823 patients aged ≥65 years who underwent SBRT, lobectomy, or SLR for stage I NSCLC was conducted. The following two analyses using machine learning-based propensity scores were performed: (i) propensity score weighting (PSW) to assess the ATE in the entire cohort, and (ii) propensity score subclassification (PSS) to evaluate treatment effects of subgroups. PSW showed no significant difference in the 5-year overall survival (OS) between SBRT and SLR (60.0% vs 61.2%; P = 0.70) and significant difference between SBRT and lobectomy (60.0% vs 77.6%; P = 0.026). Local (LR) and distant recurrence (DR) rates were significantly lower in lobectomy than in SBRT, whereas there was no significant difference between SBRT and SLR. PSS identified four subgroups with different patient characteristics: lobectomy-oriented (5-year cumulative incidences of non-lung cancer death, 7.5%), SLR-oriented (14.2%), SBRT-oriented (23.8%) and treatment-neutral subgroups (16.1%). Each subgroup showed different survival trends regarding the three treatments. The ATE of SBRT was not significantly different from that of SLR, but it was inferior to lobectomy. Four subgroups with different risks of non-lung cancer death and different survival trends for each treatment were identified. These would help decision-making for patients with stage I NSCLC.

Social factors and behavioural reactions to radon test outcomes underlie differences in radiation exposure dose, independent of household radon level Sci Rep. 2022 Sep 14;12(1):15471. doi: 10.1038/s41598-022-19499-5. Jesse L Irvine # 1 , et al.
Radioactive radon gas inhalation causes lung cancer, and public health strategies have responded by promoting testing and exposure reduction by individuals. However, a better understanding of how radon exposure disparities are driven by psychological and social variables is required. Here, we explored how behavioural factors modified residential radon-related radiation doses incurred by 2390 people who performed a radon test. The average time from first awareness to receiving a radon test outcome was 6.8-25.5 months, depending on behaviour and attitudes. 20.5% displayed radon test urgency that reduced irradiation between awareness and outcome to 1.8 mSv from a typical 3.5 mSv, while 14.8% (more likely to be men) displayed delaying behaviours that increased exposure to 8.0 mSv. Of those with low radon, 45.9% indicated no future testing intention, underscoring the importance of original tests to reliably establish risk. Among people finding high radon, 38% mitigated quickly, 29% reported economic impediments, and 33% displayed delaying behaviours. Economic barriers and delaying behaviours resulted in 8.4 mSv/year or 10.3 mSv/year long term excess exposure, respectively, increasing lifetime risk of lung cancer by ~ 30-40%. Excess radiation doses incurred from behaviour were independent of household radon level, highlighting the strong influence of psychological and socioeconomic factors on radon exposure and lung cancer risks.

A New Approach to Simplifying and Harmonizing Cancer Clinical Trials-Standardizing Eligibility Criteria JAMA Oncol 2022 Sep 1;8(9):1333-1339. doi: 10.1001/jamaoncol.2022.1664. David E Gerber 1, Harpreet Singh 2, Erin Larkins 2, Andrea Ferris 3, Patrick M Forde 4, Wendy Selig 5, Upal Basu Roy 3
IMPORTANCE: Clinical trial sponsors rely on eligibility criteria to control the characteristics of patients in their studies, promote the safety of participants, and optimize the interpretation of results. However, in recent years, complex and often overly restrictive inclusion and exclusion criteria have created substantial barriers to patient access to novel therapies, hindered trial recruitment and completion, and limited generalizability of trial results. A LUNGevity Foundation working group developed a framework for lung cancer clinical trial eligibility criteria. The goals of this framework are to (1) simplify eligibility criteria, (2) facilitate stakeholders' (patients, clinicians, and sponsors) search for appropriate trials, and (3) harmonize trial populations to support intertrial comparisons of treatment effects. **OBSERVATIONS**: Clinicians and representatives from the pharmaceutical industry, the National Cancer Institute, the US Food and Drug Administration (FDA), the European Medicines Agency, and the LUNGevity Foundation undertook a process to identify and prioritize key items for inclusion in trial eligibility criteria. The group generated a prioritized library of terms to guide investigators and sponsors in the design of first-line, advanced non-small cell lung cancer clinical trials intended to support marketing application. These recommendations address disease stage and histologic features, enrollment biomarkers, performance status, organ function, brain metastases, and comorbidities. This effort forms the basis for a forthcoming FDA draft guidance for industry. **CONCLUSIONS AND RELEVANCE:** As an initial step, the recommended cross-trial standardization of eligibility criteria may harmonize trial populations. Going forward, by connecting diverse stakeholders and providing formal opportunity for public input, the emerging FDA draft guidance may also provide an opportunity to revise and simplify long-standing approaches to trial eligibility. This work serves as a prototype for similar efforts now underway for other cancers.