Caring Ambassadors Lung Cancer Program
Literature Review, December 2022

SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

Lung Cancer Screening Lee E, Kazerooni EA. Lung Cancer Screening. *Semin Respir Crit Care Med*. 2022;43(6):839-850. doi:10.1055/s-0042-1757885
Lung cancer is a leading cause of cancer death in the United States and globally with the majority of lung cancer cases attributable to cigarette smoking. Given the high societal and personal cost of a diagnosis of lung cancer including that most cases of lung cancer when diagnosed are found at a late stage, work over the past 40 years has aimed to detect lung cancer earlier when curative treatment is possible. Screening trials using chest radiography and sputum failed to show a reduction in lung cancer mortality however multiple studies using low dose CT have shown the ability to detect lung cancer early and a survival benefit to those screened. This review will discuss the history of lung cancer screening, current recommendations and screening guidelines, and implementation and components of a lung cancer screening program.

Patterns of Extrathoracic Metastasis in Lung Cancer Patients Park HK, Han J, Kwon GY, Yeo MK, Bae GE. Patterns of Extrathoracic Metastasis in Lung Cancer Patients. *Curr Oncol*. 2022;29(11):8794-8801. Published 2022 Nov 16. doi:10.3390/curroncol29110691
Metastasis is a major cause of death in lung cancer patients. Therefore, a deeper understanding of the metastatic mechanisms is important for developing better management strategies for lung cancer patients. This study evaluated the patterns of extrathoracic metastases in lung cancer. We retrieved data for 25,103 lung cancer patients from an institutional database and then evaluated the impacts of clinicopathologic factors on metastasis patterns. We found that 36.5% of patients had extrathoracic metastasis. Younger patients had a significantly higher extrathoracic metastasis rate in most histologic subtypes. Metastases to the bone (58.3%), central nervous system (CNS) (44.3%), liver (26.6%) and adrenal gland (18.3%) accounted for 85.5% of all extrathoracic metastases. Patients with nonmucinous adenocarcinoma had significantly higher bone metastasis rate. Patients with small cell carcinoma and large cell neuroendocrine carcinoma (LCNEC) had significantly higher liver metastasis rates. Further, patients with LCNEC also had a significantly lower bone metastasis rate, and patients with squamous cell carcinoma had a significantly lower CNS metastasis rate. Patients with multiple cancers had similar patterns of metastasis

compared to patients with only lung cancer. In conclusion, different histologic subtypes of lung cancer have different metastatic patterns. Our study might help clinicians decide on follow-up strategies.

Cross modality fusion for modality-specific lung tumor segmentation in PET-CT images Zhang X, Zhang B, Deng S, Meng Q, Chen X, Xiang D. Cross modality fusion for modality-specific lung tumor segmentation in PET-CT images. *Phys Med Biol*. 2022;67(22):10.1088/1361-6560/ac994e. Published 2022 Nov 7. doi:10.1088/1361-6560/ac994e

Although positron emission tomography-computed tomography (PET-CT) images have been widely used, it is still challenging to accurately segment the lung tumor. The respiration, movement and imaging modality lead to large modality discrepancy of the lung tumors between PET images and CT images. To overcome these difficulties, a novel network is designed to simultaneously obtain the corresponding lung tumors of PET images and CT images. The proposed network can fuse the complementary information and preserve modality-specific features of PET images and CT images. Due to the complementarity between PET images and CT images, the two modality images should be fused for automatic lung tumor segmentation. Therefore, cross modality decoding blocks are designed to extract modality-specific features of PET images and CT images with the constraints of the other modality. The edge consistency loss is also designed to solve the problem of blurred boundaries of PET images and CT images. The proposed method is tested on 126 PET-CT images with non-small cell lung cancer, and Dice similarity coefficient scores of lung tumor segmentation reach 75.66 ± 19.42 in CT images and 79.85 ± 16.76 in PET images, respectively. Extensive comparisons with state-of-the-art lung tumor segmentation methods have also been performed to demonstrate the superiority of the proposed network.

Smoking History as a Potential Predictor of Immune Checkpoint Inhibitor Efficacy in Metastatic Non-Small Cell Lung Cancer Wang X, Ricciuti B, Alessi JV, et al. Smoking History as a Potential Predictor of Immune Checkpoint Inhibitor Efficacy in Metastatic Non-Small Cell Lung Cancer. *J Natl Cancer Inst*. 2021;113(12):1761-1769. doi:10.1093/jnci/djab116

Background: Despite the therapeutic efficacy of immune checkpoint inhibitors (ICIs) in a subset of patients, consistent and easily obtainable predictors of efficacy remain elusive. **Methods:** This study was conducted on 644 advanced non-small cell lung cancer (NSCLC) patients treated with ICI monotherapy between April 2013 and September 2020 at the Dana-Farber Cancer Institute and Brigham and Women's Hospital. Patient smoking history, clinicopathological characteristics, tumor mutation burden (TMB) by clinical targeted next-generation sequencing, and programmed death ligand-1 (PD-L1) tumor proportion score (TPS) by immunohistochemistry were prospectively collected. The association of smoking history with clinical outcomes of ICI monotherapy in metastatic NSCLC patients was evaluated after adjusting for other potential predictors. All statistical tests were 2-sided. **Results:** Of 644 advanced NSCLC patients, 105 (16.3%) were never smokers, 375 (58.2%) were former smokers (median pack-years = 28), and 164 (25.4%) were current smokers (median pack-years = 40). Multivariable logistic and Cox proportional hazards regression analyses suggested that doubling of smoking pack-years is statistically significantly associated with improved clinical outcomes of patients treated with ICI monotherapy (objective response rate odds ratio = 1.21, 95% confidence interval [CI] = 1.09 to 1.36, P < .001; progression-free survival hazard ratio = 0.92, 95% CI = 0.88 to 0.95, P < .001; overall survival hazard ratio = 0.94, 95% CI = 0.90 to 0.99, P = .01). Predictive models incorporating pack-years and PD-L1 TPS yielded additional information and achieved similar model performance compared with using TMB and PD-L1 TPS. **Conclusions:** Increased smoking exposure had a statistically significant association with improved clinical outcomes in metastatic NSCLC treated with ICI monotherapy independent of PD-L1 TPS. Pack-years may serve as a consistent and readily obtainable surrogate of ICI efficacy when TMB is not available to inform prompt clinical decisions and allow more patients to benefit from ICIs.

Receipt of Recommended Follow-up Care After a Positive Lung Cancer Screening Examination
Rivera MP, Durham DD, Long JM, et al. Receipt of Recommended Follow-up Care After a Positive Lung Cancer Screening Examination. *JAMA Netw Open*. 2022;5(11):e2240403. Published 2022 Nov 1. doi:10.1001/jamanetworkopen.2022.40403
Importance: Maximizing benefits of lung cancer screening requires timely follow-up after a positive screening test. The American College of Radiology (ACR) Lung CT Screening Reporting and Data System (Lung-RADS) recommends testing and follow-up timing based on the screening result.
Objective: To determine rates of and factors associated with recommended follow-up after a positive lung cancer screening examination by Lung-RADS category. **Design, setting, and participants:** This prospective cohort study of lung cancer screening examinations performed from January 1, 2015, through July 31, 2020, with follow-up through July 31, 2021, was conducted at 5 academic and community lung cancer screening sites in North Carolina. Participants included 685 adults with a positive screening examination, Lung-RADS categories 3, 4A, 4B, or 4X. Statistical analysis was performed from December 2020 to March 2022. **Exposures:** Individual age, race, sex, smoking exposure, year of lung cancer screening examination, chronic obstructive pulmonary disease, body mass index, referring clinician specialty, rural or urban residence. **Main outcomes and measures:** Adherence, defined as receipt of recommended follow-up test or procedure after the positive screen per ACR Lung-RADS timeframes: 6 months for Lung-RADS 3 and 3 months for Lung-RADS 4A. For Lung-RADS 4B or 4X, adherence was defined as follow-up care within 4 weeks, as ACR Lung-RADS does not specify a timeframe.
Results: Among the 685 individuals included in this study who underwent lung cancer screening with low-dose computed tomography, 416 (60.7%) were aged at least 65 years, 123 (18.0%) were Black, 562 (82.0%) were White, and 352 (51.4%) were male. Overall adherence to recommended follow-up was 42.6% (292 of 685) and varied by Lung-RADS category: Lung-RADS 3 = 30.0% (109 of 363), Lung-RADS 4A = 49.5% (96 of 194), Lung-RADS 4B or 4X = 68.0% (87 of 128). Extending the follow-up time increased adherence: Lung-RADS 3 = 68.6% (249 of 363) within 9 months, Lung-RADS 4A = 77.3% (150 of 194) within 5 months, and Lung-RADS 4B or 4X = 80.5% (103 of 128) within 62 days. For Lung-RADS 3, recommended follow-up was less likely among those currently smoking vs those who quit (adjusted odds ratio [aOR], 0.48; 95% CI, 0.29-0.78). In Lung-RADS 4A, recommended follow-up was less likely in Black individuals vs White individuals (aOR, 0.35; 95% CI, 0.15-0.86). For Lung-RADS 4B or 4X, recommended follow-up was more likely in female individuals vs male individuals (aOR, 2.82; 95% CI, 1.09-7.28) and less likely in those currently smoking vs those who quit (aOR, 0.31; 95% CI, 0.12-0.80). **Conclusions and relevance:** In this cohort study, adherence to recommended follow-up after a positive screening examination was low but improved among nodules with a higher suspicion of cancer and after extending the follow-up timeline. However, the association of extending the follow-up time of screen-detected nodules with outcomes at the population level, outside of a clinical trial, is unknown. These findings suggest that studies to understand why recommended follow-up is lower in Black individuals, male individuals, and individuals currently smoking are needed to develop strategies to improve adherence.

Facilitators and Barriers to Implementation of Lung Cancer Screening: A Framework-Driven Systematic Review Sedani AE, Davis OC, Clifton SC, Campbell JE, Chou AF. Facilitators and Barriers to Implementation of Lung Cancer Screening: A Framework-Driven Systematic Review. *J Natl Cancer Inst*. 2022;114(11):1449-1467. doi:10.1093/jnci/djac154
Background: The purpose of this study is to undertake a comprehensive systematic review to describe multilevel factors (barriers and facilitators) that may influence the implementation of low-dose chest computed tomography for lung cancer screening in the United States. **Methods:** Systematic literature searches were performed using 6 online databases and citation indexes for peer-reviewed studies, for articles published from 2013 to 2021. Studies were classified into 3 perspectives, based on the study's unit

of analysis: system, health-care provider, and patient. Barriers and facilitators identified for each study included in our final review were then coded and categorized using the Consolidate Framework for Implementation Research domains. **Results:** At the system level, the 2 most common constructs were external policy and incentives and executing the implementation process. At the provider level, the most common constructs were evidence strength and quality of the intervention characteristics, patient needs and resources, implementation climate, and an individual's knowledge and beliefs about the intervention. At the patient level, the most common constructs were patient needs and resources, individual's knowledge and beliefs about the intervention, and engaging in the implementation process. These constructs can act as facilitators or barriers to lung cancer screening implementation.
Conclusions: Applying the Consolidate Framework for Implementation Research domains and constructs to understand and specify factors facilitating uptake of lung cancer screening as well as cataloging the lessons learned from previous efforts helps inform the development and implementation processes of lung cancer screening programs in the community setting.

Assessment of Uptake Appropriateness of Computed Tomography for Lung Cancer Screening According to Patients Meeting Eligibility Criteria of the US Preventive Services Task Force

Liu Y, Pan IE, Tak HJ, Vlahos I, Volk R, Shih YT. Assessment of Uptake Appropriateness of Computed Tomography for Lung Cancer Screening According to Patients Meeting Eligibility Criteria of the US Preventive Services Task Force. *JAMA Netw Open*. 2022;5(11):e2243163. Published 2022 Nov 1. doi:10.1001/jamanetworkopen.2022.43163

Importance: Currently, computed tomography (CT) is used for lung cancer screening (LCS) among populations with various levels of compliance to the eligibility criteria from the US Preventive Services Task Force (USPSTF) recommendations and may represent suboptimal allocation of health care resources. **Objective:** To evaluate the appropriateness of CT LCS according to the USPSTF eligibility criteria. **Design, setting, and participants:** This cross-sectional study used the 2019 Behavioral Risk Factor Surveillance System (BRFSS) survey. Participants included individuals who responded to the LCS module administered in 20 states and had valid answers to questions regarding screening and smoking history. Data were analyzed between October 2021 and August 2022. **Exposures:** Screening eligibility groups were categorized according to the USPSTF 2013 recommendations, and subgroups of individuals who underwent LCS were analyzed. **Main outcomes and measures:** Main outcomes included LCS among the screening-eligible population and the proportions of the screened populations according to compliance categories established from the USPSTF 2013 and 2021 recommendations. In addition, the association between respondents' characteristics and LCS was evaluated for the subgroup who were screened despite not meeting any of the 3 USPSTF screening criteria: age, pack-year, and years since quitting smoking. **Results:** A total of 96 097 respondents were identified for the full study cohort, and 2 subgroups were constructed: (1) 3374 respondents who reported having a CT or computerized axial tomography to check for lung cancer and (2) 33 809 respondents who did not meet any screening eligibility criteria. The proportion of participants who were under 50 years old was 53.1%; between 50 and 54, 9.1%; between 55 and 79, 33.8%; and over 80, 4.0%. A total of 51 536 (50.9%) of the participants were female. According to the USPSTF 2013 recommendation, 807 (12.8%) of the screening-eligible population underwent LCS. Among those who were screened, only 807 (20.9%) met all 3 screening eligibility criteria, whereas 538 (20.1%) failed to meet any criteria. Among respondents in subgroup 2, being of older age and having a history of stroke, chronic obstructive pulmonary disease, kidney disease, or diabetes were associated with higher likelihood of LCS. **Conclusions and relevance:** In this cross-sectional study of the BRFSS 2019 survey, the low uptake rate among screening-eligible patients undermined the goal of LCS of early detection. Suboptimal screening patterns could increase health system costs and add financial stress, psychological burden, and physical harms to low-risk patients, while failing to provide high-quality preventive services to individuals at high risk of lung cancer.

Barriers and facilitators for low-dose computed tomography lung cancer screening in rural populations in the United States: a scoping review protocol

Palokas M, Hinton E, Duhe R, et al. Barriers and facilitators for low-dose computed tomography lung cancer screening in rural populations in the United States: a scoping review protocol. *JBI Evid Synth*. 2022;20(11):2727-2733. Published 2022 Nov 1. doi:10.11124/JBIES-21-00337

Objective: The objective of this scoping review is to identify barriers and facilitators for low-dose computed tomography lung cancer screening uptake and adherence among rural populations in the United States. **Introduction:** Lung cancer is the leading cause of cancer-related death in the United States, and cancer patients from rural areas have poorer outcomes than those from metropolitan areas. Evidence exists that lung cancer screening by low-dose computed tomography significantly increases survival time but is also significantly underutilized. **Inclusion criteria:** Studies completed in the United States with adults who fit United States Preventive Services Task Force guidelines for lung cancer screening and who live in rural areas will be included. Studies published in English since 2013 that report on barriers and facilitators for low-dose computed tomography lung cancer screening uptake and adherence will be included in this review. Quantitative, qualitative, or mixed-methods studies will be included, along with opinion pieces published by government agencies or professional cancer-related organizations. **Methods:** The search strategy will locate published primary studies, reviews, and opinion papers, including those by government and nonprofit agencies focused on cancer. The databases to be searched include MEDLINE, CINAHL Complete, Embase, Web of Science, and Cochrane Library. Gray literature databases and sources of unpublished studies will also be searched. Independent reviewers will be used throughout the search and selection process.

Impact of Low-dose Chest CT Screening on the Association Between Rurality and Lung Cancer Outcomes

Hinojos M, Li X, Mikesell S, et al. Impact of Low-dose Chest CT Screening on the Association Between Rurality and Lung Cancer Outcomes. *Am J Clin Oncol*. 2022;45(12):519-525. doi:10.1097/COC.0000000000000956

Introduction: Lung cancer mortality is higher among rural United States populations compared with nonrural ones. Little is known about screening low-dose chest computed tomography (LDCT) outcomes in rural settings. **Materials and methods:** This retrospective cohort study examined all patients (n=1805) who underwent screening LDCT in a prospective registry from March 1, 2015, through December 31, 2019, in a majority-rural health care system. We assessed the proportion of early-stage lung cancers (American Joint Committee on Cancer stage I-II) diagnosed among LDCT-screened patients, and analyzed overall survival after early-stage lung cancer diagnosis according to residency location. **Results:** The screening cohort had a median age of 63 and median 40-pack-year smoking history; 62.4% had a rural residence, 51.2% were female, and 62.7% completed only 1 LDCT scan. Thirty-eight patients were diagnosed with lung cancer (2.1% of the cohort), of which 65.8% were early-stage. On multivariable analysis, rural (vs nonrural) residency was not associated with a lung cancer diagnosis (adjusted hazard ratio 1.59; 95% CI, 0.74-3.40; P =0.24). At a median follow-up of 37.1 months (range, 3.3 to 67.2 months), 88.2% of rural versus 87.5% of nonrural patients with screen-diagnosed early-stage lung cancer were alive (P =0.93). **Conclusions:** In a majority-rural United States population undergoing LDCT, most screen-detected lung cancers were early-stage. There were no significant differences observed between rural and nonrural patients in lung cancer diagnosis rate or early-stage lung cancer survival. Increased implementation of LDCT might blunt the historical association between rural United States populations and worse lung cancer outcomes.

A handheld electronic device with the potential to detect lung cancer biomarkers from exhaled breath

Emam S, Nasrollahpour M, Allen JP, et al. A handheld electronic device with the potential to detect lung cancer biomarkers from exhaled breath. *Biomed Microdevices*. 2022;24(4):41. Published 2022 Nov 18. doi:10.1007/s10544-022-00638-8

Lung cancer is the leading cause of cancer death in the United States. It has the lowest 5-year survival rate among the most common cancers and therefore, early diagnosis is critical to improve the survival rate. In this paper, a new handheld electronic device is proposed to detect nine lung cancer biomarkers in the exhaled breath. An electrochemical gas sensor was produced through deposition of a thin layer of graphene and Prussian blue on a chromium-modified silicon substrate. Selective binding of the analyte was formed by molecular imprinting polymer (MIP). Subsequent polymerization and removal of the analyte yielded a layer of a conductive polymer on top of the sensor containing molecularly imprinted cavities selective for the target molecule. The sensors were tested over 1-20 parts per trillion (ppt) level of concentration while the sensor resistance has been monitored as the sensors react to the analyte by resistance change. Pentane sensor was also tested for selectivity. A printed circuit board was designed to measure the resistance of each sensor and send the data to a developed application in smartphone through Bluetooth. This handheld device has the potential to be used as a diagnostic method in the near future.

Interventional pulmonology use of cell-free DNA assay for metastatic non-small cell lung cancer: the UC Davis experience Phan C, Jespersen F, Weipert C, Li T, Yoneda KY. Interventional pulmonology use of cell-free DNA assay for metastatic non-small cell lung cancer: the UC Davis experience. *Ther Adv Respir Dis*. 2022;16:17534666221135324. doi:10.1177/17534666221135324

Background: Interventional pulmonologists (IPs) are often the first specialist to see patients with suspected metastatic non-small cell lung cancer (mNSCLC). Consequently, they are potentially ideally positioned to expedite the identification of actionable molecular mutations by ordering blood-based cell-free DNA (cfDNA), prior to or upon tissue diagnosis of mNSCLC. **Methods:** Retrospective review of cfDNA ordered by IP as part of a routine clinical practice. Patients were categorized into two groups based on when cfDNA was ordered by IP: (1) IP suspected mNSCLC prior to histologic confirmation or (2) IP diagnosed mNSCLC based on histologic confirmation of NSCLC. **Results:** Twenty patients were identified. Twelve of 13 in group 1 were confirmed to have mNSCLC by oncology and 1 had stage IIIA. Seven of 7 in group 2 were confirmed to have mNSCLC by oncology. Fifteen of 20 also had next-generation tissue molecular testing. Thirteen of 20 (65%) had targetable alterations. Seven of 13 (54%) were identified on cfDNA and tissue, 5/13 (38%) on cfDNA only, and 1/13 (8%) on tissue alone. Tissue results were available a medium of 24 days after, and cfDNA results a medium of 4 days prior to, the patients' first oncology visit. **Conclusions:** IP appears to be able identify patients who have mNSCLC and for whom testing for molecular mutations is appropriate even prior to tissue confirmation of NSCLC. A strategy whereby IP employ blood-based cfDNA testing in suspected and tissue confirmed mNSCLC could potentially provide medical oncologists with more timely information on actionable mutations than tissue-based testing first, potentially expediting patient treatment.

Dynamic Risk Prediction of 30-Day Mortality in Patients With Advanced Lung Cancer: Comparing Five Machine Learning Approaches

Vesteghem C, Szejniuk WM, Brøndum RF, Falkmer UG, Azencott CA, Bøgsted M. Dynamic Risk Prediction of 30-Day Mortality in Patients With Advanced Lung Cancer: Comparing Five Machine Learning Approaches. *JCO Clin Cancer Inform*. 2022;6:e2200054. doi:10.1200/CCI.22.00054

Purpose: Administering systemic anticancer treatment (SACT) to patients near death can negatively affect their health-related quality of life. Late SACT administrations should be avoided in these cases. Machine learning techniques could be used to build decision support tools leveraging registry data for

clinicians to limit late SACT administration. **Materials and methods:** Patients with advanced lung cancer who were treated at the Department of Oncology, Aalborg University Hospital and died between 2010 and 2019 were included (N = 2,368). Diagnoses, treatments, biochemical data, and histopathologic results were used to train predictive models of 30-day mortality using logistic regression with elastic net penalty, random forest, gradient tree boosting, multilayer perceptron, and long short-term memory network. The importance of the variables and the clinical utility of the models were evaluated. **Results:** The random forest and gradient tree boosting models outperformed other models, whereas the artificial neural network-based models underperformed. Adding summary variables had a modest effect on performance with an increase in average precision from 0.500 to 0.505 and from 0.498 to 0.509 for the gradient tree boosting and random forest models, respectively. Biochemical results alone contained most of the information with a limited degradation of the performances when fitting models with only these variables. The utility analysis showed that by applying a simple threshold to the predicted risk of 30-day mortality, 40% of late SACT administrations could have been prevented at the cost of 2% of patients stopping their treatment 90 days before death. **Conclusion:** This study demonstrates the potential of a decision support tool to limit late SACT administration in patients with cancer. Further work is warranted to refine the model, build an easy-to-use prototype, and conduct a prospective validation study.

The usefulness of liquid-based cytology of bronchoalveolar lavage fluid combined with bronchial brush specimens in lung cancer diagnosis Ma S, Yu X, Jin X, et al. The usefulness of liquid-based cytology of bronchoalveolar lavage fluid combined with bronchial brush specimens in lung cancer diagnosis. *J Int Med Res*. 2022;50(11):3000605221132708. doi:10.1177/03000605221132708
Objective: To explore the diagnostic value of liquid-based cytology (LBC) of bronchoalveolar lavage fluid (BALF) combined with bronchial brushing (BB). **Methods:** One hundred patients with pulmonary masses or nodules found by chest computed tomography (CT) or X-ray before bronchoscopy or other diagnostic biopsy examinations were selected consecutively for this retrospective study. BALF and BB were performed for all patients. After conventional smear via BB, we mixed the BALF and BB samples in a prepared thin-layer bottle. **Results:** The sensitivity of LBC of BALF combined with BB was noticeably higher than that of BB alone in the total sample group (65.15% vs. 32.84%, respectively). Similarly, in both the bronchoscopically visible group and invisible group, a higher sensitivity for LBC of BALF with BB vs BB alone (68.89% vs. 39.13%, respectively; 57.14% vs. 19.05%, respectively) was observed. Additionally, the negative predictive value of LBC of BALF with BB was higher than that with BB alone (58.56% vs. 42.31%; 61.29% vs. 44.73%; 53.47% vs. 37.83%; total sample vs visible vs invisible groups, respectively). **Conclusion:** Regardless of whether lesions or nodules are bronchoscopically visible or invisible, LBC of BALF combined with BB may increase the diagnostic value over BB alone in lung cancer diagnosis.

Comparing modalities for risk assessment in patients with pulmonary lesions and nondiagnostic bronchoscopy for suspected lung cancer Yu DH, Shafiq M, Batra H, et al. Comparing modalities for risk assessment in patients with pulmonary lesions and nondiagnostic bronchoscopy for suspected lung cancer. *BMC Pulm Med*. 2022;22(1):442. Published 2022 Nov 24. doi:10.1186/s12890-022-02181-x
Background: Bronchoscopy is commonly utilized for non-surgical sampling of indeterminant pulmonary lesions, but nondiagnostic procedures are common. Accurate assessment of the risk of malignancy is essential for decision making in these patients, yet we lack tools that perform well across this heterogeneous group of patients. We sought to evaluate the accuracy of three previously validated risk models and physician-assessed risk (PAR) in patients with a newly identified lung lesion undergoing bronchoscopy for suspected lung cancer where the result is nondiagnostic. **Methods:** We performed an analysis of prospective data collected for the Percepta Bronchial Genomic Classifier Multicenter Registry. PAR and three previously validated risk models (Mayo Clinic, Veteran's Affairs, and Brock) were used to

determine the probability of lung cancer (low, intermediate, or high) in 375 patients with pulmonary lesions who underwent bronchoscopy for possible lung cancer with nondiagnostic pathology. Results were compared to the actual adjudicated prevalence of malignancy in each pre-test risk group, determined with a minimum of 12 months follow up after bronchoscopy. **Results:** PAR and the risk models performed poorly overall in the assessment of risk in this patient population. PAR most closely matched the observed prevalence of malignancy in patients at 12 months after bronchoscopy, but all modalities had a low area under the curve, and in all clinical models more than half of all the lesions labeled as high risk were truly or likely benign. The studied risk model calculators overestimate the risk of malignancy compared to PAR, particularly in the subset in older patients, irregularly bordered nodules, and masses > 3 cm. Overall, the risk models perform only slightly better when confined to lung nodules < 3 cm in this population. **Conclusion:** The currently available tools for the assessment of risk of malignancy perform suboptimally in patients with nondiagnostic findings following a bronchoscopic evaluation for lung cancer. More accurate and objective tools for risk assessment are needed.

Development of a Molecular Blood-Based Immune Signature Classifier as Biomarker for Risks Assessment in Lung Cancer Screening Fortunato O, Huber V, Segale M, et al. Development of a Molecular Blood-Based Immune Signature Classifier as Biomarker for Risks Assessment in Lung Cancer Screening. *Cancer Epidemiol Biomarkers Prev*. 2022;31(11):2020-2029. doi:10.1158/1055-9965.EPI-22-0689

Background: Low-dose CT (LDCT) screening trials have shown that lung cancer early detection saves lives. However, a better stratification of the screening population is still needed. In this respect, we generated and prospectively validated a plasma miRNA signature classifier (MSC) able to categorize screening participants according to lung cancer risk. Here, we aimed to deeply characterize the peripheral immune profile and develop a diagnostic immune signature classifier to further implement blood testing in lung cancer screening. **Methods:** Peripheral blood mononuclear cell (PBMC) samples collected from 20 patients with LDCT-detected lung cancer and 20 matched cancer-free screening volunteers were analyzed by flow cytometry using multiplex panels characterizing both lymphoid and myeloid immune subsets. Data were validated in PBMC from 40 patients with lung cancer and 40 matched controls and in a lung cancer specificity set including 27 subjects with suspicious lung nodules. A qPCR-based gene expression signature was generated resembling selected immune subsets. **Results:** Monocytic myeloid-derived suppressor cell (MDSC), polymorphonuclear MDSC, intermediate monocytes and CD8+PD-1+ T cells distinguished patients with lung cancer from controls with AUCs values of 0.94/0.72/0.88 in the training, validation, and lung cancer specificity set, respectively. AUCs raised up to 1.00/0.84/0.92 in subgroup analysis considering only MSC-negative subjects. A 14-immune genes expression signature distinguished patients from controls with AUC values of 0.76 in the validation set and 0.83 in MSC-negative subjects. **Conclusions:** An immune-based classifier can enhance the accuracy of blood testing, thus supporting the contribution of systemic immunity to lung carcinogenesis. **Impact:** Implementing LDCT screening trials with minimally invasive blood tests could help reduce unnecessary procedures and optimize cost-effectiveness.

EBUS-TBNA in Extrathoracic Malignancies: Diagnostic and Prognostic Implications Martin-Deleon R, Solarat B, Moisés J, et al. EBUS-TBNA in Extrathoracic Malignancies: Diagnostic and Prognostic Implications. *Lung*. 2022;200(6):747-753. doi:10.1007/s00408-022-00584-5

Purpose: In patients with extrathoracic malignancies (EM) the role of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for the assessment of abnormal mediastinal lymph nodes (MLN) is controversial. The aim of this study was to assess the diagnostic yield and prognostic significance of EBUS-TBNA in these patients. **Methods:** Retrospective analysis of patients with EM and abnormal MLN detected by Computed Tomography (CT) and/or Positron Emission Tomography (PET).

Results: A total of 161 patients with EM and abnormal MLN were included (93 males, 58%). The most common EM was melanoma (19%) and gastrointestinal cancer (17%). Assessed lymph nodes were mediastinal in 70% of cases and hilar in 30%. The most frequently sampled lymph nodes were subcarinal (45%) and lower right paratracheal (21%). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of EBUS-TBNA for the diagnosis of malignancy were 88%, 100%, 100% and 87%, respectively. These values were similar regardless the type of EM except for head and neck tumors where the NPV was particularly low (67%). The diagnosis of neoplastic involvement by EBUS-TBNA implied a worse prognosis in terms of overall survival ($p < 0.02$) and cancer-specific survival ($p < 0.001$). **Conclusions:** In patients with EM and abnormal MLN, EBUS-TBNA has a high diagnostic yield. However, the NPV decrease in patients with head and neck tumors. Neoplastic MLN detected by EBUS-TBNA has prognostic implications in these patients.

Molecular Pathways and Mechanisms of BRAF in Cancer Therapy Poulikakos PI, Sullivan RJ, Yaeger R. Molecular Pathways and Mechanisms of BRAF in Cancer Therapy. *Clin Cancer Res*. 2022;28(21):4618-4628. doi:10.1158/1078-0432.CCR-21-2138

With the identification of activating mutations in BRAF across a wide variety of malignancies, substantial effort was placed in designing safe and effective therapeutic strategies to target BRAF. These efforts have led to the development and regulatory approval of three BRAF inhibitors as well as five combinations of a BRAF inhibitor plus an additional agent(s) to manage cancer such as melanoma, non-small cell lung cancer, anaplastic thyroid cancer, and colorectal cancer. To date, each regimen is effective only in patients with tumors harboring BRAFV600 mutations and the duration of benefit is often short-lived. Further limitations preventing optimal management of BRAF-mutant malignancies are that treatments of non-V600 BRAF mutations have been less profound and combination therapy is likely necessary to overcome resistance mechanisms, but multi-drug regimens are often too toxic. With the emergence of a deeper understanding of how BRAF mutations signal through the RAS/MAPK pathway, newer RAF inhibitors are being developed that may be more effective and potentially safer and more rational combination therapies are being tested in the clinic. In this review, we identify the mechanics of RAF signaling through the RAS/MAPK pathway, present existing data on single-agent and combination RAF targeting efforts, describe emerging combinations, summarize the toxicity of the various agents in clinical testing, and speculate as to where the field may be headed.

The role of immune profile in predicting outcomes in cancer patients treated with immunotherapy Botticelli A, Pomati G, Cirillo A, et al. The role of immune profile in predicting outcomes in cancer patients treated with immunotherapy. *Front Immunol*. 2022;13:974087. Published 2022 Nov 3. doi:10.3389/fimmu.2022.974087

Background: Despite the efficacy of immunotherapy, only a small percentage of patients achieves a long-term benefit in terms of overall survival. The aim of this study was to define an immune profile predicting the response to immune checkpoint inhibitors (ICIs). **Methods:** Patients with advanced solid tumors, who underwent ICI treatment were enrolled in this prospective study. Blood samples were collected at the baseline. Thirteen soluble immune checkpoints, 3 soluble adhesion molecules, 5 chemokines and 11 cytokines were analyzed. The results were associated with oncological outcomes. **Results:** Regardless of tumor type, patients with values of sTIM3, IFNα, IFNγ, IL1β, IL1α, IL12p70, MIP1β, IL13, sCD28, sGITR, sPDL1, IL10 and TNFα below the median had longer overall survival ($p<0.05$). By using cluster analysis and grouping the patients according to the trend of the molecules, two clusters were found. Cluster A had a significantly higher mean progression free survival (Cluster A=11.9 months vs Cluster B=3.5 months, $p<0.01$), a higher percentage of disease stability (Cluster A=34.5% vs. Cluster B=0%, $p<0.05$) and a lower percentage of disease progression (Cluster A=55.2% vs. Cluster B = 94.4%, $p=0.04$). **Conclusion:** The combined evaluation of soluble molecules, rather than a single

circulating factor, may be more suitable to represent the fitness of the immune system status in each patient and could allow to identify two different prognostic and predictive outcome profiles.

Preoperative blood markers for prediction of recurrence-free survival after surgical treatment of patients with stage III lung adenocarcinoma Tahanovich AD, Kauhanka NN, Murashka DI, et al. Preoperative blood markers for prediction of recurrence-free survival after surgical treatment of patients with stage III lung adenocarcinoma. *Klin Lab Diagn*. 2022;67(11):640-646. doi:10.51620/0869-2084-2022-67-11-640-646

The possibility of the preoperative level of 42 indicators characterizing the cellular composition and metabolism in blood of patients with stage III lung adenocarcinoma (AC) to predict their relapse-free survival was studied. Blood samples of 451 patients with newly diagnosed AK stage III after their surgical treatment (resection volume - R0) have been investigated. The duration of the relapse-free period (period of observation - 1 year), cellular composition of the blood, concentration of C-RP, albumin, Cyfra 21-1 antigens, SCC, TPA, chemokines CXCL5, CXCL8, pyruvate kinase TuM2 PK isoenzyme, HIF-1α and hyaluronic acid in blood serum so as the proportion of blood cells with CXCR1 and CXCR2, CD44V6 receptors in blood serum were measured. To determine the dependence of the duration of the relapse-free period after the treatment on the observation time, Kaplan-Meier graphs were built. The relationship between the determined parameters and survival was judged using single- and multi-factor Cox proportional hazard models. Comparison of groups with different risk of AK recurrence was performed using the Log Rank test and $\chi 2$. The assessment of the predictive information content of laboratory tests was carried out using ROC analysis. It was shown that the concentration of monocytes, eosinophilic leukocytes, the relative quantity of lymphocytes with CXCR1 receptor, the level of Cyfra 21-1 before surgical treatment were associated with the duration of the relapse-free period. A regression equation was compiled, which included the level of Cyfra 21-1, relative content of lymphocytes with CXCR1, and the eosinophilic leukocytes / monocytes ratio. Based on the threshold value Y=0,597, a Kaplan-Meier plot of patient survival was built and the results of it correspond to the TNM stratification. The prognostic sensitivity of the results of the equation - 85,7%, the specificity - 94,7%.

ACR Appropriateness Criteria® Malignant or Aggressive Primary Musculoskeletal Tumor-Staging and Surveillance: 2022 Update Expert Panel on Musculoskeletal Imaging, Stanborough R, Demertzis JL, et al. ACR Appropriateness Criteria® Malignant or Aggressive Primary Musculoskeletal Tumor-Staging and Surveillance: 2022 Update. *J Am Coll Radiol*. 2022;19(11S):S374-S389. doi:10.1016/j.jacr.2022.09.015

Malignant or aggressive primary musculoskeletal tumors are rare and encompass a wide variety of bone and soft tissue tumors. Given the most common site for metastasis from these primary musculoskeletal tumors is to the lung, chest imaging is integral in both staging and surveillance. Extrapulmonary metastases are rarely encountered with only a few exceptions. Following primary tumor resection, surveillance of the primary tumor site is generally recommended. Local surveillance imaging recommendations differ between primary tumors of bone origin versus soft tissue origin. This document consolidates the current evidence and expert opinion for the imaging staging and surveillance of these tumors into five clinical scenarios. The ACR Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed annually by a multidisciplinary expert panel. The guideline development and revision process support the systematic analysis of the medical literature from peer-reviewed journals. Established methodology principles such as Grading of Recommendations Assessment, Development, and Evaluation or GRADE are adapted to evaluate the evidence. The RAND/UCLA Appropriateness Method User Manual provides the methodology to determine the appropriateness of imaging and treatment procedures for specific clinical scenarios. In those instances in

which peer-reviewed literature is lacking or equivocal, experts may be the primary evidentiary source available to formulate a recommendation.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Is there a role for lung surgery in initially unresectable non-small cell lung cancer after tyrosine kinase inhibitor treatment? Diong NC, Liu CC, Shih CS, Wu MC, Huang CJ, Hung CF. Is there a role for lung surgery in initially unresectable non-small cell lung cancer after tyrosine kinase inhibitor treatment?. World J Surg Oncol. 2022;20(1):370. Published 2022 Nov 26. doi:10.1186/s12957-022-02833-6

Background: The role of lung surgery in initially unresectable non-small cell lung cancer (NSCLC) after tyrosine kinase inhibitor (TKI) treatment remains unclear. We aimed to assess the survival benefits of patients who underwent surgery for regressed or regrown tumors after receiving TKI treatment. **Methods:** The details of patients diagnosed with unresectable NSCLC treated with TKI followed by lung resection from 2010 to 2020 were retrieved from our database. The primary endpoint was 3-year overall survival (OS), whereas the secondary endpoints were a 2-year progression-free survival (PFS), feasibility, and the safety of pulmonary resection. The statistical tests used were Fisher's exact test, Kruskal Wallis test, Kaplan-Meier method, Cox proportional hazards model, and Firth correction. **Results:** Nineteen out of thirty-two patients were selected for the study. The patients underwent lung surgery after confirmed tumor regression (17 [89.5%]) and regrowth (two [10.5%]). All surgeries were performed via video-assisted thoracoscopic surgery: 14 (73.7%) lobectomies and five (26.3%) sublobar resections after a median duration of 5 months of TKI. Two (10.5%) postoperative complications and no 30-day postoperative mortality were observed. The median postoperative follow-up was 22 months. The 2-year PFS and 3-year OS rates were 43.9% and 61.5%, respectively. Patients who underwent surgery for regressed disease showed a significantly better OS than for regrowth disease (HR=0.086, 95% CI 0.008-0.957, p=0.046). TKI-adjuvant demonstrated a better PFS than non-TKI adjuvant (HR=0.146, 95% CI 0.027-0.782, p=0.025). **Conclusion:** Lung surgery after TKI treatment is feasible and safe and prolongs survival via local control and directed consequential therapy. Lung surgery should be adopted in multimodality therapy for initially unresectable NSCLC.

Pulmonary function changes after sublobar resection in patients with peripheral non-subpleural nodules Feng KP, Shen ZQ, Xu C, et al. Pulmonary function changes after sublobar resection in patients with peripheral non-subpleural nodules. *BMC Surg*. 2022;22(1):390. Published 2022 Nov 11. doi:10.1186/s12893-022-01828-0

Background: In the treatment of peripheral early-staged lung cancer and benign lesions, segmentectomy and wedge resection are both reliable treatment methods. It is debatable that how much pulmonary function will be lost after different sublobar resection in the treatment of early-staged deep-located peripheral NSCLC (non-small cell lung cancer). The purpose of this study was to explore postoperative pulmonary function changes of sublobar resection in enrolled patients with non-subpleural peripheral nodules. **Methods:** We collected clinical data of patients undergoing VATS (video-assisted thoracoscopic surgery) segmentectomy or wedge resection for single nodule. These nodules were confirmed as peripheral non-subpleural nodules by preoperative 3D imaging. Patients were divided into two groups according to the operation procedure. Demographic characteristics, pulmonary function, postoperative outcomes, and others were collected. All data was gathered at the First Affiliated Hospital of Soochow University. Outcomes after wedge resection were compared with those after segmentectomy resection.

Results: A total of 88 patients were included in this study, including 46 patients with VATS wedge resection and 42 patients with VATS segmentectomy. No difference was detected when comparing FEV_1 (forced expiratory volume in 1 s) loss between these two groups (17.6 ± 2.1%, wedge resection vs. 19.4 ± 5.4%, segmentectomy, P = 0.176). FVC (forced vital capacity) loss (8.7 ± 2.3%, wedge resection vs. 17.1 ± 2.2%, segmentectomy, P < 0.001) and MVV (maximum ventilatory volume) loss (11.5 ± 3.1%, wedge resection vs. 20.6 ± 7.8%, segmentectomy, P < 0.001) in segmentectomy group was significantly higher than those in wedge resection group. Discrepancies were investigated when comparing duration of surgery (70 ± 22 min, wedge resection vs. 111 ± 52 min, segmentectomy, P = 0.0002), postoperative drainage (85 ± 45 mL, wedge resection vs. 287 ± 672 mL, segmentectomy, P = 0.0123), and treatment hospitalization expenses [35148 ± 889CNY, wedge resection vs. 52,502 (38,276-57,772) CNY, segmentectomy, P < 0.0002]. No significant difference was found between air leak time (1.7 ± 0.7 days, wedge resection vs. 2.5 ± 1.7 days, segmentectomy, P = 0.062) and hospitalization time (2.7 ± 0.7 days, wedge resection vs. 3.5 ± 1.7 days, segmentectomy, P = 0.051). **Conclusions:** For patients with peripheral non-subpleural nodules, we observed that patients who underwent wedge resection had less lung function loss than those who underwent segmentectomy when their lung function was reviewed at the 6th month after surgery. Patients undergoing wedge resection had partial advantages over patients with segmental resection in terms of hospitalization cost, operation time and postoperative drainage, etc. Wedge resection, as a treatment for peripheral non-subpleural pulmonary nodules, seemed to have more advantages in preserving patients' pulmonary function.

Impact of Central Airway Infiltration Type in Primary Lung Cancer Patients Treated With Sleeve Lobectomy Tsukioka T, Izumi N, Komatsu H, et al. Impact of Central Airway Infiltration Type in Primary Lung Cancer Patients Treated With Sleeve Lobectomy. *In Vivo*. 2022;36(6):2981-2985. doi:10.21873/invivo.13042

Background/aim: There are two types of lung cancer cell infiltration into the central airway. One is when a centrally located lung cancer directly infiltrates the central airway and the other is when cancer cells in the metastatic hilar lymph node infiltrate the central airway. We aimed to identify the impact of central airway infiltration type on the clinical features of patients undergoing sleeve lobectomy. **Patients and methods:** The clinical courses of 58 primary lung cancer patients who underwent sleeve lobectomy between January 2010 and December 2020 were investigated. **Results:** Primary tumors directly infiltrated into the central airway in 42 patients, whereas 16 patients had infiltration of cancer cells from the metastatic hilar lymph node. Primary tumor infiltration was a poor prognostic factor according to both univariate (p=0.016) and multivariate analyses (p=0.042). Operation times (p=0.240) and incidences of adverse events (p=0.926) were not associated with the type of central airway infiltration.
Conclusion: The type of airway infiltration was an independent poor prognostic factor after sleeve lobectomy in primary lung cancer patients. Our findings may guide the selection of optimal treatments for this patient population.

Mortality and lung function decline in patients who develop chronic pulmonary aspergillosis after lung cancer surgery Kim BG, Choi YS, Shin SH, et al. Mortality and lung function decline in patients who develop chronic pulmonary aspergillosis after lung cancer surgery. *BMC Pulm Med*. 2022;22(1):436. Published 2022 Nov 22. doi:10.1186/s12890-022-02253-y

Background: Lung cancer surgery is reported as a risk factor for chronic pulmonary aspergillosis (CPA). However, limited data are available on its clinical impact. We aimed to determine the effect of developed CPA after lung cancer surgery on mortality and lung function decline. **Methods:** We retrospectively identified the development of CPA after lung cancer surgery between 2010 and 2016. The effect of CPA on mortality was evaluated using multivariable Cox proportional hazard analyses. The effect of CPA on lung function decline was evaluated using multiple linear regression analyses. **Results:** During a median

follow-up duration of 5.01 (IQR, 3.41-6.70) years in 6777 patients, 93 developed CPA at a median of 3.01 (IQR, 1.60-4.64) years. The development of CPA did not affect mortality in multivariable analysis. However, the decline in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) were greater in patients with CPA than in those without (FVC, - 71.0 [- 272.9 to - 19.4] vs. - 10.9 [- 82.6 to 57.9] mL/year, $p < 0.001$; FEV_1, - 52.9 [- 192.2 to 3.9] vs. - 20.0 [- 72.6 to 28.6] mL/year, $p = 0.010$). After adjusting for confounding factors, patients with CPA had greater FVC decline (β coefficient, - 103.6; 95% CI - 179.2 to - 27.9; $p = 0.007$) than those without CPA. However, the FEV_1 decline (β coefficient, - 14.4; 95% CI - 72.1 to 43.4; $p = 0.626$) was not significantly different.
Conclusion: Although the development of CPA after lung cancer surgery did not increase mortality, the impact on restrictive lung function deterioration was profound.

Surgery versus radiotherapy in octogenarians with stage Ia non-small cell lung cancer: propensity score matching analysis of the SEER database Ni L, Lin G, Zhang Z, Sun D, Liu Z, Liu X. Surgery versus radiotherapy in octogenarians with stage Ia non-small cell lung cancer: propensity score matching analysis of the SEER database. *BMC Pulm Med*. 2022;22(1):411. Published 2022 Nov 10. doi:10.1186/s12890-022-02177-7
Objectives: To compare overall survival (OS) and cancer-specific survival (CSS) outcomes of surgery with radiotherapy in octogenarians with stage Ia non-small cell lung cancer (NSCLC). **Materials and methods:** Patients aged ≥ 80 years with clinical stage Ia (T1N0M0) NSCLC between 2012 and 2017 were identified from the population-based Surveillance, Epidemiology, and End Results (SEER) database. Patients were assigned into surgery and radiotherapy groups. Multivariate Cox regression analysis was used to identify survival-associated factors. Treatment groups were adjusted by propensity score matching (PSM) analysis while OS and CSS outcomes were compared among groups by Kaplan-Meier analysis. **Results:** A total of 1641 patients were identified, with 46.0% in the surgical group and 54.0% in the radiotherapy group. Compared to surgery, radiotherapy-treated patients were older, later diagnosed, had more often unmarried, more squamous cell carcinoma, more unknown grade and increased tumor sizes. Radiotherapy was associated with a significantly worse OS, compared to surgery (hazard ratio 2.426; 95% CI 2.003-2.939; $P < .001$). After PSM, OS ($P < 0.001$) and CSS ($P < 0.001$) were higher in the surgery group. The 1-, 3-, and 5-year OS rates of surgical and radiotherapy group were 90.0%, 76.9%, 59.9%, and 86.0%, 54.3%, 28.0%, respectively. The 1-, 3-, and 5-year CSS rates of surgical and radiotherapy group were 94.5%, 86.1%, 78.0% and 90.7%, 74.5%, 61.0%, respectively. There were no survival differences between the matched surgery without lymph node examination (LNE) and radiotherapy group, as well as between the matched surgery and radiotherapy who were recommended but refused surgery group.
Conclusions: In octogenarians with stage Ia NSCLC, surgery with lymph node dissection offers better OS and CSS outcomes than radiotherapy.

Aggressive histological component in subsolid lung adenocarcinoma: priority for resection without delay Yotsukura M, Nakagawa K, Takemura C, et al. Aggressive histological component in subsolid lung adenocarcinoma: priority for resection without delay. *Jpn J Clin Oncol*. 2022;52(11):1321-1326. doi:10.1093/jjco/hyac131
Introduction: This study explored the predictors of a histological aggressive component in ground glass opacity-containing lung adenocarcinoma. **Methods:** Of the 2388 patients who underwent resection for lung cancer at our institute between 2017 and 2020, we collected data on the 501 patients with ground glass opacity-containing adenocarcinoma with a total diameter of ≤2 cm. Using a historical cohort, we identified histological aggressive components that were related to a poor prognosis in early-stage adenocarcinoma. A multivariable analysis was conducted to identify predictors for the presence of a histological aggressive component. **Results:** Lymphovascular invasion and predominant micropapillary or solid patterns were identified as histological aggressive components by a prognostic analysis using a

historical cohort. Of the 501 patients included, 36 (7.2%) had at least one histological aggressive component. A multivariate analysis showed that a consolidation/tumour ratio > 0.5 (P < 0.01), maximum standardized uptake value on positron emission tomography ≥1.5 (P = 0.01) and smoking index >20 pack-years (P = 0.01) were predictors of the presence of a histological aggressive component. A total of 98% of cases without any of the above factors did not have a histological aggressive component.
Conclusions: Approximately 7% of ground glass opacity-containing small adenocarcinomas contained histological aggressive component. A consolidation/tumour ratio > 0.5, maximum standardized uptake value ≥ 1.5 and smoking index >20 pack-years were predictors for such cases. These predictors may be useful for screening patients with a potentially high risk of a poor prognosis and for prioritizing resection without delay.

The perioperative outcomes of uniport versus two-port and three-port video-assisted thoracoscopic surgery in lung cancer: a systematic review and meta-analysis
Cheng YF, Huang CL, Hung WH, Cheng CY, Wang BY. The perioperative outcomes of uniport versus two-port and three-port video-assisted thoracoscopic surgery in lung cancer: a systematic review and meta-analysis. *J Cardiothorac Surg*. 2022;17(1):284. Published 2022 Nov 8. doi:10.1186/s13019-022-02034-y
Background: Uniport video-assisted thoracoscopic surgery (VATS) has been applied widely for the treatment of lung cancer in recent years. Some studies have reported that uniport VATS might provide better outcomes than multiport VATS. However, the perioperative outcomes of uniport VATS compared with two-port and three-port VATS, respectively, have yet to be studied at a comprehensive scale. This meta-analysis study compares the perioperative efficacy among uniport, two-port, and three-port VATS.
Methods: We searched studies published before October 1, 2019, by using Web of Science databases, Ovid Medline, Embase, and PubMed. Studies that compared uniport VATS with two-port or three-port VATS for patients with lung cancer were included. Operative time, perioperative blood loss, number of lymph nodes retrieved, conversion rate, duration of postoperative chest tube drainage, length of hospital stay (LoS), visual analogue pain scores on postoperative day (POD) 1 and POD 3, and overall morbidity were evaluated. **Results:** Sixteen studies that compared uniport VATS with two-port or three-port VATS in the treatment of lung cancer were included. Uniport VATS showed less blood loss, a shorter duration of postoperative drainage and a lower visual analogue pain score on POD 3 than two-port VATS; it showed a shorter duration of postoperative drainage, a shorter LoS, and lower visual analogue pain scores on POD 1 and POD 3 than three-port VATS. There were no significant differences in the number of lymph nodes retrieved, operative time, conversion rate, and overall morbidity rate when comparing uniport VATS with two-port VATS or three-port VATS. **Conclusions:** Uniport VATS might provide better perioperative outcomes than either two-port or three-port VATS in lung cancer treatment.

Comparison of the geriatric nutritional risk index and the prognostic nutritional index in determining survival outcome in patients with non-small cell lung cancer undergoing surgical resection: A cohort study An S, Han GY, Eo W, Kim DH, Lee S. Comparison of the geriatric nutritional risk index and the prognostic nutritional index in determining survival outcome in patients with non-small cell lung cancer undergoing surgical resection: A cohort study. *Medicine (Baltimore)*. 2022;101(45):e31591. doi:10.1097/MD.0000000000031591
To assess the clinical feasibility of the geriatric nutritional risk index (GNRI) and prognostic nutritional index (PNI) as determinants of survival in patients with stage I to III non-small cell lung cancer (NSCLC). This retrospective study included patients with stage I to III NSCLC from all age groups. Hazard ratios (HRs) for overall survival (OS), cancer-specific survival (CSS), and relapse-free survival (RFS) were calculated using the Cox regression analysis. The concordance index (C-index) of the models was evaluated following the establishment of the prognostic models for survival. The median patient age

was 69 years, and 64.6% of the patients were male. In total, 172 (65.4%) patients were classified as having stage I disease, 52 (19.8%) as stage II disease, and 39 (14.8%) as stage III disease. Using multivariate Cox regression analysis, the HRs of GNRI for OS, CSS, and RFS were 0.37 (P = .003), 0.47 (P = .041), and 0.38 (P < .001), respectively. However, the HRs of the PNI for survival outcomes were not statistically significant. Overall, age, sex, tumor-node-metastasis (TNM) stage, pleural invasion (PI), and GNRI were significant determinants of OS and constituted the OS model (concordance index [C-index], 0.824). In addition, age, TNM stage, PI, and GNRI were significant determinants of CSS and constituted the CSS model (C-index, 0.828). Finally, TNM stage, PI, lymphatic invasion, and GNRI were significant determinants of RFS and constituted the RFS model (C-index, 0.783). Our study showed that GNRI, but not PNI, was a predictor of OS, CSS, and RFS in patients with stage I-III NSCLC across all age groups. Excellent discriminant power was observed for OS, CSS, and RFS models.

Is video-assisted thoracoscopic surgery comparable with thoracotomy in perioperative and long-term survival outcomes for non-small-cell lung cancer after neoadjuvant treatment? Wang YF, Deng HY, Huang W, Zhou Q. Is video-assisted thoracoscopic surgery comparable with thoracotomy in perioperative and long-term survival outcomes for non-small-cell lung cancer after neoadjuvant treatment?. *Interact Cardiovasc Thorac Surg*. 2022;35(6):ivac271. doi:10.1093/icvts/ivac271
A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was 'Is video-assisted thoracoscopic surgery comparable with thoracotomy in perioperative and long-term survival outcomes for patients with non-small cell lung cancer following neoadjuvant therapy intended for anatomical lung resection?'. Altogether 655 papers were found using the reported search, of which 12 studies represented the best evidence to answer the clinical question. The author, journal, date and country of publication, patient group studied, study type and relevant outcomes and results of these papers are tabulated. Almost all of the enrolled cohort studies reported that video-assisted thoracoscopic surgery (VATS) was comparable with thoracotomy in negative surgical margin rate, postoperative mortality, complication rate, overall survival and disease-free survival. Moreover, 7 studies found patients in the VATS group had a significantly shorter hospital stay. Furthermore, in these well-matched cohort studies (6 studies), it still held true that VATS was comparable with thoracotomy in long-term prognosis with enhanced recovery. However, the issue regarding surgical radicality and intraoperative conversion to thoracotomy still should be noted carefully among these patients receiving VATS surgery because all the current available evidence was retrospective based on relatively small sample sizes. Nevertheless, thoracic surgeons should not consider VATS inferior to thoracotomy for patients after neoadjuvant treatment. VATS surgery could be an alternative for selected patients with locally advanced but relatively small, peripheral, fewer positive N2 lymph nodes and non-squamous NSCLC intended for anatomic lung resection.

Recent advances in postoperative pulmonary rehabilitation of patients with non-small cell lung cancer (Review) Su XE, Hong WP, He HF, et al. Recent advances in postoperative pulmonary rehabilitation of patients with non-small cell lung cancer (Review). *Int J Oncol*. 2022;61(6):156. doi:10.3892/ijo.2022.5446
Non-small cell lung cancer (NSCLC) accounts for ~85% of lung cancer cases and has high morbidity and mortality rates. Over the past decade, treatment strategies for NSCLC have progressed rapidly, particularly with the increasing use of screening programs, leading to improvements in the initial diagnosis and treatment of early-stage and preinvasive tumors. Surgical intervention remains the primary treatment for early-stage NSCLC. Thoracoscopic lobectomy has become the main treatment for early-stage NSCLC, as it results in less postoperative bleeding and pain and fewer complications. However, the complication rate for thoracoscopic lobectomy due to sputum retention and weakened respiratory muscle strength remains as high as 19-59%. Treating NSCLC remains challenging in terms of

postoperative pulmonary rehabilitation. In the present review, recent advances in postoperative pulmonary rehabilitation for patients with NSCLC were presented in order to assist researchers in developing improved treatments to enhance postoperative pulmonary rehabilitation for such patients.

Sleeve lobectomy in patients with non-small-cell lung cancer: a report from the European Society of Thoracic Surgery database 2021 Gonzalez M, Chriqui LE, Décaluwé H, et al. Sleeve lobectomy in patients with non-small-cell lung cancer: a report from the European Society of Thoracic Surgery database 2021. *Eur J Cardiothorac Surg*. 2022;62(6):ezac502. doi:10.1093/ejcts/ezac502
Objectives: For centrally located lung tumours, sleeve lobectomy is preferred over pneumectomy. We report on the surgical practices and perioperative outcomes of sleeve resections based on data from the European Society of Thoracic Surgeons database. **Methods:** We retrieved data of patients undergoing sleeve lobectomy or bilobectomy from 2007 to 2021. We evaluated baseline characteristics, surgical approach, neoadjuvant treatments, morbidity and postoperative outcomes of open and video-assisted thoracoscopic surgery (VATS) procedures. **Results:** In total, 1652 patients (median age: 63 years; females/males: 446/1206) underwent sleeve lobectomy (n = 1536) or bilobectomy (n = 116) by open thoracotomy (n = 1491; 90.2%) or VATS (n = 161; 9.8%) with a thoracotomy conversion rate of 21.1% (n = 34); 398 (24.1%) patients received neoadjuvant treatment. Overall morbidity and 30-day mortality were 40.6% and 2.2%, respectively. Bronchial anastomotic complications occurred in 29 patients (1.8%) with conservative treatment in 6 cases (20.7%) and operative management in 23 (79.3%). On multivariable analysis, factors related to the elevated risk of cardiopulmonary complications were body mass index < 20 [odds ratio (OR): 2.26; P < 0.001] and bilobectomy (OR : 2.28, P < 0.001). Age <60 years (OR: 0.71, P = 0.013), female sex (OR: 0.54, P < 0.001) and VATS (0.64, P < 0.001) were associated with decreased risk. Neoadjuvant treatment was not associated with increased risks of cardiopulmonary complications (OR: 1.05; P = 0.664). Compared to open thoracotomy, VATS was associated with significantly decreased overall morbidity (30.4% vs 41.7%, P = 0.006) and length of stay (median: 5 days vs 8 days; P < 0.001). **Conclusions:** Sleeve lobectomies can be safely performed after neoadjuvant treatment. The VATS approach fosters shorter length of stay and decreased morbidity.

Operating time: an independent and modifiable risk factor for short-term complications after video-thoracoscopic pulmonary lobectomy Gómez-Hernández MT, Forcada C, Varela G, Jiménez MF; Spanish Group of Video-assisted Thoracic Surgery (GEVATS). Operating time: an independent and modifiable risk factor for short-term complications after video-thoracoscopic pulmonary lobectomy. *Eur J Cardiothorac Surg*. 2022;62(6):ezac503. doi:10.1093/ejcts/ezac503
Objectives: The relationship between operating time and postoperative morbidity has not been fully characterized in lung resection surgery. We aimed to determine the variables associated with prolonged operative times and their influence on postoperative complications after video-thoracoscopic lobectomy. **Methods:** Patients undergoing thoracoscopic lobectomy for lung cancer from December 2016 to March 2018, within the prospective registry of the Spanish Video-Assisted Thoracic Surgery Group were identified. Operating time was stratified by quartiles and complication rates analysed using chi-squared test. Primary outcomes included 30-day overall, pulmonary and cardiovascular complications and wound infection. Multivariable logistic regression analyses were performed to identify variables independently associated with operating time and their influence on the occurrence of postoperative complications. **Results:** Data of 1518 cases were examined. The median operating time was 174 min (interquartile range: 130-210 min). Overall morbidity rates significantly increased with surgical duration (20.5% vs 34.4% in the 1st and 4th quartiles, respectively, P < 0.05) and so did pulmonary complications (14.6% vs 26.4% in the 1st and 4th quartiles, respectively, P < 0.05). Differences were not found regarding cardiovascular and wound complications. After multivariable logistic regression analysis, operating time remained as an independent risk factor for overall (odds ratios, 2.05) and pulmonary complications (odds

ratios, 2.01). Male sex, predicted postoperative diffusing capacity of the lung for carbon monoxide, number of lymphatic stations harvested, pleural adhesions, fissures completeness, lobectomy site, surgeon seniority, individual video-thoracoscopic surgeon experience and fissureless technique were identified as predictive factors for long operative time. **Conclusions:** Prolonged operating time is associated with increased odds of postoperative complications. Modifiable factors contributing to prolonged operating time may serve as a target for quality improvement.

Application of bilateral simultaneous sequential single-incision video-assisted thoracic surgery in multiple nodules both lungs: a single-center experience of 10 cases Shi W, Hu Y, Chang G, et al. Application of bilateral simultaneous sequential single-incision video-assisted thoracic surgery in multiple nodules both lungs: a single-center experience of 10 cases. *BMC Surg*. 2022;22(1):386. Published 2022 Nov 10. doi:10.1186/s12893-022-01841-3

Objective: To discuss the application of bilateral simultaneous sequential single-incision video-assisted thoracic surgery in multiple nodules in both lungs. **Methods:** A retrospective analysis of 10 patients in Zhengzhou People's Hospital who underwent single-incision thoracoscopic surgery to treat multiple nodules in both lungs at the same time from September 2019 to January 2021, and analyze the perioperative indicators (general condition, smoking history, family history, follow-up time of pulmonary nodules, size, location, height and weight, pulmonary function, intraoperative blood loss, operation time, color and volume of drainage fluid, catheterization time, perioperative complications, length of stay, pathology, patient satisfaction, etc.). **Results:** All 10 patients used single-incision thoracoscopy to complete bilateral simultaneous sequential operations, aged 32 to 70 years, 8 female patients, 2 male patients, preoperative follow-up time ranging from 1 day to 2 years, a total of 23 lung nodules were removed except for the benign lesions in one nodule in the 2 patients, the other nodules were tumorous lesions (91.3%). The average total hospital stay was 10.5 days (8-14 days), and the average operation time was 194.5 min (145-292 min). The blood loss ranged from 10 to 280 ml, all patients had no serious complications during the perioperative period, and they recovered well and were discharged smoothly, and the satisfaction reached 100%. **Conclusion:** Single-incision bilateral simultaneous sequential thoracoscopy have certain advantages in the treatment of patients with multiple nodules in both lungs, conforms to the concept of rapid recovery, and is a feasible choice in the shared decision making of doctors and patients.

Identification of the intersegmental plane by arterial ligation method during thoracoscopic segmentectomy

He H, Zhao H, Ma L, et al. Identification of the intersegmental plane by arterial ligation method during thoracoscopic segmentectomy. *J Cardiothorac Surg*. 2022;17(1):281. Published 2022 Nov 4. doi:10.1186/s13019-022-02011-5

Background: Thoracoscopic segmentectomy is a common surgical procedure in thoracic surgery today. However, identifying the intersegmental plane is difficult in the surgical process. Therefore, we evaluated the feasibility of the arterial ligation method for determining the intersegmental plane and compared the demarcation status with the intravenous indocyanine green (ICG). **Methods:** We retrospectively reviewed the records of 35 patients with peripheral small lung nodules who underwent thoracoscopic segmentectomy between May and December 2020. First, the preoperative three-dimensional reconstruction was performed to distinguish the location of lung nodules and the anatomical structures of targeted segmental arteries, veins, and bronchi. Second, the targeted segmental arteries were ligated, and the intersegmental plane was determined by the inflation-deflation technique. The waiting time for the appearance of the inflation-deflation line was recorded. Thirdly, the intersegmental plane was identified again using the ICG fluorescence method. Finally, the consistency of the two intersegmental planes was evaluated. **Results:** The intersegmental planes were successfully observed in all patients using the arterial

ligation method. Thirty-four patients underwent segmentectomy as planned, and one patient finally underwent lobectomy due to insufficient surgical margin. The waiting time for the appearance of the intersegmental plane by arterial ligation method was 13.7 ± 3.2 min (6-19 min). The intersegmental planes determined by the arterial ligation method and the ICG fluorescence method were comparable, with a maximum distance of no more than 5 mm between the two planes. The mean operative duration was 119.1 ± 34.9 min, and the mean blood loss was 76.9 ± 70.3 ml. No evident air leakage was found during the operation. Only one patient experienced a prolonged air leak (≥ 5 days) during the postoperative recovery. No atelectasis occurred in all cases. The chest tube duration was 3.1 ± 0.9 days. **Conclusion:** The arterial ligation method can efficiently and accurately identify the intersegmental plane, comparable to the ICG fluorescence method.

The left upper lobe challenge in video-assisted thoracoscopic surgery-use of a composite score to improve the assessment of simulated lobectomy
Haidari TA, Bjerrum F, Grimstrup S, et al. The left upper lobe challenge in video-assisted thoracoscopic surgery-use of a composite score to improve the assessment of simulated lobectomy. Eur J Cardiothorac Surg. 2022;62(6):ezac465. doi:10.1093/ejcts/ezac465
Aim: The aim of this study is to develop a reliable composite score based on simulator metrics to assess competency in virtual reality video-assisted thoracoscopic surgery lobectomy and explore the benefits of combining it with expert rater assessments. **Methods:** Standardized objective assessments (time, bleeding, economy of movement) and subjective expert rater assessments from 2 previous studies were combined. A linear mixed model including experience level, lobe and the number of previous simulated procedures was applied for the repeated measurements. Reliability for each of the 4 assessments was calculated using Cronbach's alpha. The Nelder-Mead numerical optimization algorithm was used for optimal weighting of scores. A pass-fail standard for the composite score was determined using the contrasting groups' method. **Results:** In total, 123 virtual reality video-assisted thoracoscopic surgery lobectomies were included. Across the 4 different assessments, there were significant effects (P < 0.01) of experience, lobe, and simulator experience, but not for simulator attempts on bleeding (P = 0.98). The left upper lobe was significantly more difficult compared to other lobes (P = 0.02). A maximum reliability of 0.92 could be achieved by combining the standardized simulator metrics with standardized expert rater scores. The pass/fail level for the composite score when including 1 expert rater was 0.33.
Conclusions: Combining simulator metrics with 1 or 2 raters increases reliability and can serve as a more objective method for assessing surgical trainees. The composite score may be used to implement a standardized and feasible simulation-based mastery training program in video-assisted thoracoscopic surgery lobectomy.

Can the Risk Analysis Index for Frailty Predict Morbidity and Mortality in Patients Undergoing High-risk Surgery? Wan MA, Clark JM, Nuño M, Cooke DT, Brown LM. Can the Risk Analysis Index for Frailty Predict Morbidity and Mortality in Patients Undergoing High-risk Surgery?. *Ann Surg*. 2022;276(6):e721-e727. doi:10.1097/SLA.0000000000004626
Objective: To determine the effectiveness of the revised Risk Analysis Index (RAI-rev), administrative Risk Analysis Index (RAI-A), cancer-corrected Risk Analysis Index [RAI-rev (cancer-corrected)], and 5-variable modified Frailty Index for predicting 30-day morbidity and mortality in patients undergoing high-risk surgery. **Background:** There are several frailty composite measures, but none have been evaluated for predicting morbidity and mortality in patients undergoing high-risk surgery.
Methods: Using the National Surgical Quality Improvement Program database, we performed a retrospective study of patients who underwentcolectomy/proctectomy, coronary artery bypass graft (CABG), pancreaticoduodenectomy, lung resection, or esophagectomy from 2006 to 2017. RAI-rev, RAI-A, RAI-rev (cancer corrected), and 5-variable modified Frailty Index scores were calculated. Pearson's

chi-square tests and C-statistics were used to assess the predictive accuracy of each score's logistic regression model. **Results:** In the cohort of 283,545 patients, there were 178,311 (63%) colectomy/proctectomy, 38,167 (14%) pancreaticoduodenectomy, 40,328 (14%) lung resection, 16,127 (6%) CABG, and 10,602 (3%) esophagectomy cases. The RAI-rev was a fair predictor of mortality in the total cohort (C-statistic, 0.71, 95% CI 0.70-0.71, P < 0.001) and for patients who underwent colectomy/proctectomy (C-statistic 0.73, 95% CI 0.72-0.74, P < 0.001) and CABG (C-statistic 0.70, 95% CI 0.68-0.73, P < 0.001), but a poor predictor of mortality in all other operation cohorts. The RAI-A was a fair predictor of mortality for colectomy/proctectomy patients (C-statistic 0.74, 95% CI 0.73- 0.74, P < 0.001). All indices were poor predictors of morbidity. The RAI-rev (cancer corrected) did not improve the accuracy of morbidity and mortality prediction.
Conclusion: The presently studied frailty indices are ineffective predictors of 30-day morbidity and mortality for patients undergoing high-risk operations.

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

Mobocertinib in non-small cell lung cancer Liu S, Lowder KE. Mobocertinib in non-small cell lung cancer. *Drugs Today (Barc)*. 2022;58(11):523-530. doi:10.1358/dot.2022.58.11.3408816
Tyrosine kinase inhibitors (TKIs) have provided great benefit for patients with EGFR-mutant non-small cell lung cancer (NSCLC). While prior TKIs have demonstrated limited efficacy against exon 20 insertion mutations of EGFR (EGFR Ex20Ins), mobocertinib (TAK-788) is designed to specifically inhibit these Ex20Ins mutations. In a phase I/II clinical trial, mobocertinib demonstrated meaningful benefits among a cohort of platinum-pretreated patients with EGFR Ex20Ins mutant NSCLC. For this cohort, the objective response rate was 28% (95% confidence interval [CI], 20%-37%). The median progression-free survival and duration of response were 7.3 months (95% CI, 5.5-9.2) and 17.5 months (95% CI, 7.4-20.3), respectively, both by independent review committee assessment. On the basis of these results, mobocertinib was granted accelerated approval as the first TKI for treatment of this indication by the U.S. Food and Drug Administration (FDA) in 2021. This review summarizes the preclinical development of mobocertinib and the early-phase clinical data leading to its approval and discusses potential directions for mobocertinib's development.

Sequential treatment in advanced non-small cell lung cancer harboring EGFR mutations Hsu PC, Chang JW, Chang CF, et al. Sequential treatment in advanced non-small cell lung cancer harboring EGFR mutations. *Ther Adv Respir Dis*. 2022;16:17534666221132731. doi:10.1177/17534666221132731
Background: Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are standard treatments for advanced EGFR-mutated non-small cell lung cancer (NSCLC) patients. Osimertinib is an effective therapy for NSCLC patients with acquired resistance due to T790M mutation after first- and second-generation EGFR-TKI treatment. This study aimed to analyze the clinical outcomes of sequential therapy following first-line EGFR-TKIs and the predictive factors of an acquired T790M mutation.
Methods: Between January 2014 and December 2018, data from 2190 advanced NSCLC patients with common EGFR mutations (exon 19 deletion and L858R) receiving first- and second-generation EGFR-TKIs in Linkou, Kaohsiung, Chiayi and Keelung Chang Gung Memorial Hospitals were retrospectively retrieved and analyzed. **Results:** Until August 2021, among 1943 patients who experienced progressive disease, 526 underwent T790M mutation tests, and their T790M-positive rate was 53.6%. Exon 19 deletion mutation and progression-free survival (PFS) of >12 months were positively associated with secondary T790M mutation. Different first-line first- and second-generation EGFR-TKI therapies did not affect the appearance of acquired T790M mutations. The median overall survival (OS) was 58.3 [95% confidence interval (CI): 49.0-67.5] months among the patients with T790M mutation who received second-line osimertinib therapy compared with 31.0 (95% CI: 27.5-34.5) months among the patients

without T790M mutation who received chemotherapy alone. The multivariate analysis showed that a poor performance status (score: >2), nonadenocarcinoma histology, stage IV cancer, liver metastasis, brain metastasis, PFS while on first-line EGFR-TKIs, and subsequent chemotherapy without third-generation EGFR-TKIs were significant independent unfavorable prognostic factors for OS. **Conclusion:** This study demonstrated the efficacy of first-line EGFR-TKIs and sequential osimertinib therapy. The results of our study suggest that T790M mutation tests are important for the use of subsequent osimertinib, which yielded favorable survival outcomes.

Two New Drugs Approved for Non-Small Cell Lung Cancer Aschenbrenner DS. Two New Drugs Approved for Non-Small Cell Lung Cancer. *Am J Nurs*. 2022;122(12):22-23. doi:10.1097/01.NAJ.0000904080.71037.14
The Food and Drug Administration (FDA) has approved capmatinib (Tabrecta) for the treatment of metastatic non-small cell lung cancer in adults whose tumors have a mutation leading to mesenchymal-epithelial transition exon 14 skipping.Nurses should monitor patients for serious adverse effects such as interstitial lung disease/pneumonitis, hepatotoxicity, pancreatic toxicity, photosensitivity, and embryo-fetal toxicity.The FDA has granted accelerated approval to fam-trastuzumab deruxtecan-nxki (Enhertu) for the treatment of unresectable or metastatic non-small cell lung cancer in adults whose tumors have activating human epidermal growth factor receptor 2 mutations and who have received a prior systemic therapy.Enhertu carries a boxed warning regarding the risk of interstitial lung disease and embryo-fetal toxicity.

Sotorasib: A Review in KRAS G12C Mutation-Positive Non-small Cell Lung Cancer Lee A. Sotorasib: A Review in KRAS G12C Mutation-Positive Non-small Cell Lung Cancer [published correction appears in Target Oncol. 2022 Dec 2;:]. *Target Oncol*. 2022;17(6):727-733. doi:10.1007/s11523-022-00922-w
KRAS is a protein that is involved in cell signalling pathways, including those that are associated with cell growth and differentiation. KRAS mutations are detected in 23% of patients with non-small cell lung cancer (NSCLC), with the G12C mutation being the most common. G12C-mutant KRAS ($KRAS^{G12C}$) is kept in an activated state, which is associated with cancer. Sotorasib (LUMAKRAS™ in the USA and LUMYKRAS™ in the EU), which is taken orally once daily, is the first approved drug that inhibits $KRAS^{G12C}$; it permanently binds to $KRAS^{G12C}$ and locks it in an inactivated state. Sotorasib is approved for adults who have advanced, previously treated, KRAS G12C mutation-positive NSCLC. In a clinical trial in patients with KRAS G12C mutation-positive NSCLC, a clinically relevant proportion of patients responded to sotorasib treatment. Furthermore, the duration of effectiveness with sotorasib was considered to be clinically relevant. Adverse reactions with sotorasib treatment were manageable; the dose may be decreased and/or sotorasib treatment may be temporarily stopped to manage adverse reactions. Overall, sotorasib is a promising treatment option for patients with KRAS G12C mutation-positive NSCLC who have received at least one prior systemic therapy.

Editorial: Recent Approval of Sotorasib as the First Targeted Therapy for KRAS G12C-Mutated Advanced Non-Small Cell Lung Cancer (NSCLC) Parums DV. Editorial: Recent Approval of Sotorasib as the First Targeted Therapy for KRAS G12C-Mutated Advanced Non-Small Cell Lung Cancer (NSCLC). Med Sci Monit. 2022;28:e938746. Published 2022 Nov 1. doi:10.12659/MSM.938746
In the past two decades, there have been rapid advances in the number and range of regulatory approvals of targeted therapy for patients with advanced non-small cell lung cancer (NSCLC) and other cancers. The Kirsten rat sarcoma viral oncogene homolog (KRAS) gene has a high mutation rate in human cancers and is associated with some of the most aggressive types of cancer, including NSCLC, pancreatic ductal adenocarcinoma (PDAC), and colorectal cancer (CRC). Until recently, several common and highly

aggressive cancers with KRAS mutations expressing the 'death star' KRAS proteins were considered 'undruggable' and not amenable to targeted therapy. The main KRAS mutations are single-base missense mutations, with 98% occurring at codon 12 (G12C). KRAS G12C is the most common KRAS mutation in NSCLC. Sotorasib is a first-in-class specific small molecule that irreversibly inhibits KRAS G12C. Based on the results from the phase 1/2 CodeBreaK 100 safety and tolerability study, on May 28, 2021, the US Food and Drug Administration (FDA) granted accelerated approval for sotorasib for adults with advanced NSCLC and KRAS G12C mutation. This Editorial aims to present the current status of regulatory approval and the supporting clinical trial data for sotorasib, the first targeted therapy for patients with advanced NSCLC with the KRAS G12C mutation.

Immunotherapy for bilateral multiple ground glass opacities: An exploratory study for synchronous multiple primary lung cancer Xu L, Shi M, Wang S, et al. Immunotherapy for bilateral multiple ground glass opacities: An exploratory study for synchronous multiple primary lung cancer. *Front Immunol*. 2022;13:1009621. Published 2022 Oct 25. doi:10.3389/fimmu.2022.1009621
Background: Bilateral multiple ground glass opacities (GGOs) are observed in quite a part of patients with early-stage lung adenocarcinoma. For this so-called synchronous multiple primary lung cancer (sMPLC), targeting immune checkpoint is a favorable option in addition to surgical resection. The purpose of this study is to reveal the safety and efficacy of performing immune checkpoint inhibitors (ICIs) on patients with sMPLC and to explore the biomarkers of the efficacy. **Methods:** A total of 21 patients with sMPLC were enrolled and all included cases were pathologically confirmed adenocarcinoma after conducting surgical treatment for unilateral GGOs. ICIs of Sintilimab were then used to target programmed death 1 (200mg i.v., Q3W) for up to 10 cycles. Seven patients of them received the other surgery for contralateral GGOs, and multiomics assessments, including neoantigens, somatic mutations, and methylated loci, were further performed to investigate potential biomarkers. **Results:** Grade 1 or 2 treatment-related adverse events (AEs) occurred in most of the patients (12/21, 57.1%), and one subject withdrawn for grade 3 AEs. For the seven patients underwent twice surgeries, twelve and thirteen GGOs were achieved before and after the use of ICIs separately, and a favorable efficacy was observed among six lesions after immunotherapy (> 50% pathologic tumor regression). Tumor infiltration T-cell and B-cell were further shown to be associated with the biological activity of ICIs. According to mechanism-based multiomics analyses, *MUC19*- and *PCDHB5*- mutations were indicated to correlate with a favorable prognosis of sMPLC underwent immunotherapy, and our results suggested that immunogenetic mutation and associated promoter methylation could provide a quantitative explanation for the pathologic response of GGOs. **Conclusion:** Our study provides evidence that the use of ICIs contributed favorable efficacy and safety to patients with sMPLC. Immune infiltration and immunogenic biomarkers are revealed to be implications of performing ICIs on sMPLC. These preliminary findings exhibit the prospects in performing neoadjuvant or adjuvant immunotherapies on patients with sMPLC.

Efficacy of Intrapleural or Intrapericardial Injection of Single Bevacizumab in the Treatment of Lung Cancer-Mediated Malignant Effusion He D, Guo Z, Xie Z, Zhang Y, Deng Q, Yang H. Efficacy of Intrapleural or Intrapericardial Injection of Single Bevacizumab in the Treatment of Lung Cancer-Mediated Malignant Effusion. *Can Respir J*. 2022;2022:6763625. Published 2022 Oct 31. doi:10.1155/2022/6763625
The usage of bevacizumab for malignant pleural effusion (MPE) or malignant pericardial effusion (MPCE) has attracted increasing interest from researchers, but the precise ways of bevacizumab administration remain unknown. Patients with histologically or cytologically confirmed non-small-cell lung cancer (NSCLC) with MPE or MPCE were enrolled in the study and treated with a low dose of single bevacizumab (100 mg) intrapleurally or intrapericardially injected after the drainage of the effusions. The Lung Cancer Symptom Scale (LCSS), efficacy, and safety of drug administration were

used as evaluation parameters in this study. The results indicated that lung cancer-related symptoms were significantly improved following treatment, compared with symptoms before the treatment (LCSS, score 494 ± 78 vs. score 377 ± 77, mean ± SD) ($P < 0.001$). Malignant effusions were well controlled, and the median time to progression (TTP) was 91 days and 111 days in MPE and MPCE, respectively. In addition, no severe side effects were observed, except in one patient with mild dizziness. In summary, the low dose of single bevacizumab (100 mg) with intrapleural or intrapericardial injection is effective and safe in the treatment of lung cancer-mediated malignant effusion, rapidly improving the malignant effusion-related symptoms and quality of life in patients with NSCLC.

Poziotinib in non-small-cell lung cancer patients with HER2 exon 20 mutations: A pooled analysis of randomized clinical trials

Wang BC, Kuang BH, Liu XX, Lin GH. Poziotinib in non-small-cell lung cancer patients with HER2 exon 20 mutations: A pooled analysis of randomized clinical trials. *Medicine (Baltimore)*. 2022;101(44):e31337. doi:10.1097/MD.0000000000031337

Background: Non-small-cell lung cancer (NSCLC) harboring human epidermal growth factor receptor 2 (HER2) exon 20 mutant occurs in 3% of NSCLCs. Targeted agents for this population remain an unmet need. In this analysis, we pooled-analyzed the efficacy and safety of poziotinib, a novel tyrosine kinase inhibitor, in HER2 exon 20 mutant NSCLC. **Methods:** PubMed, Embase, Web of Science, and Cochrane CENTRAL databases were systematically searched on March 9, 2022. The primary endpoints were objective response rate (ORR) and disease control rate. The secondary endpoint was treatment-related adverse events. **Results:** Three prospective clinical trials, involving 126 patients, were identified. The pooled ORR and disease control rate of poziotinib in HER2 exon 20 mutant NSCLC were 27% (95% CI, 19-35) and 72% (95% CI, 64-80), respectively. Patients with G778_P780dupGSP had the highest ORR (88%; 95% CI, 33-100; n = 12), followed by Y772_A775dupYVMA (20%; 95% CI, 12-30; n = 88) and G776delinsVC (19%; 95% CI, 0-50; n = 13). The most common grade 3 to 4 treatment-related adverse events were skin rash (36%), diarrhea (23%), and oral mucositis (13%). **Conclusion:** Poziotinib demonstrates moderate antitumor activity in previously treated HER2 exon 20 mutant NSCLC patients with a manageable safety profile. In addition, different subgroup mutations show various benefits of poziotinib treatment. Large-scale and multiarm clinical trials are warranted to confirm a suitable population and therapeutic strategies.

Impact of opioid analgesics on the efficacy of immune checkpoint inhibitors in a lung cancer population

Yu X, Zhao L, Song B. Impact of opioid analgesics on the efficacy of immune checkpoint inhibitors in a lung cancer population. *BMC Pulm Med*. 2022;22(1):431. Published 2022 Nov 21. doi:10.1186/s12890-022-02210-9

Objective: A retrospective clinical study was conducted to compare the prognosis between the opioid analgesic (OA) treated and OA-untreated groups and to evaluate the effect of opioid analgesics on the efficacy of immune checkpoint inhibitors (ICIs) in the treatment of advanced lung cancer patients. In addition, a subgroup analysis of the clinical characteristics of the enrolled patients was performed to explore possible influencing factors. **Methods:** This study reviewed the medical records of eligible patients who received ICIs at our institution. The clinicopathological features and clinical outcomes were compared. Also, the use of OA was collected. Patient survival, the incidence of immune-related adverse events (irAEs), and other baseline variables were examined in both cohorts according to whether OA was used. **Results:** A total of 132 patients were included in the study. Of them, 39 (29.5%) were in the OA-treated group. No significant differences in baseline characteristics were observed between the OA-treated and untreated groups. The combined application of OA treatment significantly shortened progression-free survival (PFS) ($P < 0.001$) and overall survival (OS) ($P = 0.002$). However, both groups experienced

similar incidences and gradations of irAEs. According to multivariate analysis, OA treatment resulted in significantly worse PFS (HR = 4.994, 95% CI 3.217-7.753, P < 0.001) and OS (HR = 3.618, 95% CI 2.030-6.240, P < 0.001). **Conclusions:** Clinical outcomes of ICIs were significantly diminished in a cohort of Chinese patients with advanced lung cancer receiving OA therapy.

Association between immune-mediated adverse events and efficacy in metastatic non-small-cell lung cancer patients treated with durvalumab and tremelimumab Dey A, Austin M, Kluger HM, et al. Association between immune-mediated adverse events and efficacy in metastatic non-small-cell lung cancer patients treated with durvalumab and tremelimumab. *Front Immunol*. 2022;13:1026964. Published 2022 Nov 3. doi:10.3389/fimmu.2022.1026964

Purpose: Immune-mediated adverse events (imAEs) may be associated with response to immune checkpoint inhibitors. We assessed the relationship between imAE development and efficacy in metastatic non-small-cell lung cancer patients treated with durvalumab (anti-programmed cell death ligand-1 [PD-L1]) alone or in combination with tremelimumab (anti-cytotoxic T-lymphocyte-associated protein 4). **Methods:** The analysis used individual patient-level data from 307 and 310 patients in the monotherapy and combination arms of MYSTIC, respectively. We evaluated the association between treatment efficacy and development of imAEs using univariate and multivariate survival analyses. Using machine learning, we built a predictive model utilizing baseline clinical and laboratory features to identify patients at risk of developing imAEs and further evaluated patient survival based on a threshold index extracted from the model. **Results:** Patients who developed any grade of imAE had improved overall survival versus patients without (hazard ratio [HR] 0.51; 95% confidence interval [CI]: 0.41-0.62). imAE development was associated with improved overall survival (HR 0.54; 95% CI 0.44-0.66) in a multivariate Cox proportional hazard model considering patient demographic features and baseline characteristics. Higher odds of imAE development were observed (odds ratio 3.023; 95% CI: 1.56-5.83) in responders versus non-responders in patients treated with immunotherapy. Based on baseline characteristics, the random forest classification algorithm was used to formulate a predictive model to identify patients at increased risk of developing imAEs during treatment. **Conclusion:** *Post-hoc* exploratory analysis found that the efficacy of immunotherapy was improved in patients who developed on-treatment imAEs. This was independent of severity of imAEs or the need for steroid treatment, which is important in allowing patients to remain on treatment and derive optimal clinical benefit. Further research is warranted to establish the correlation between incidence of imAEs and efficacy in this patient population.

Non-small Cell Lung Cancer with EGFR or HER2 Exon 20 Insertion Mutations: Diagnosis and Treatment Options Brazel D, Kroening G, Nagasaka M. Non-small Cell Lung Cancer with EGFR or HER2 Exon 20 Insertion Mutations: Diagnosis and Treatment Options. *BioDrugs*. 2022;36(6):717-729. doi:10.1007/s40259-022-00556-4

Molecular testing is performed upon diagnosis of non-small cell lung cancer (NSCLC) because of the large success of targeted therapies for oncogenic mutations. Epidermal growth factor receptor (EGFR) mutations are the most commonly identified mutation in NSCLC, and EGFR exon 20 insertion mutations (exon20ins) are the third most common mutation in EGFR following EGFR exon 19 deletions and exon 21 L858R mutations. EGFR exon20ins have regularly demonstrated resistance to classical EGFR inhibition. Two treatments-mobocertinib and amivantamab-have recently been the first drugs to be approved by the US Food and Drug Administration (FDA) for treatment of lung cancers with these mutations following platinum-based therapy. Research surrounding these two drugs demonstrates strong efficacy, but with an intense array of side effects. Another targetable driver mutation is the human epidermal growth factor receptor 2 (HER2) exon20ins, representing approximately 2-3% of NSCLC patients. This mutation has been heavily studied in vitro as well as clinically, and trastuzumab deruxtecan was just recently granted accelerated FDA approval based on the high efficacy demonstrated in the

Destiny-Lung01 study. However, similar to their EGFR counterparts, HER2 inhibitors also have evidence of toxicity in clinical studies. In this paper, we discuss the limited response of EGFR and HER2 exon20ins to a wide range of standard treatment regimens, such as platinum-based chemotherapy and classic EGFR tyrosine kinase inhibitors, as well as immunotherapy. We also review recently approved and upcoming targeted therapeutic options, considering what research is presently being done regarding efficacy and the reduction of side effects, as well as the agents' risks and benefits for incorporation into an approved treatment regimen.

A Phase II Trial on Osimertinib as a First-Line Treatment for EGFR Mutation-Positive Advanced NSCLC in Elderly Patients: The SPIRAL-0 Study
Chihara Y, Takeda T, Goto Y, et al. A Phase II Trial on Osimertinib as a First-Line Treatment for EGFR Mutation-Positive Advanced NSCLC in Elderly Patients: The SPIRAL-0 Study. *Oncologist*. 2022;27(11):903-e834. doi:10.1093/oncolo/oyac193
Background: Osimertinib is one of the standard first-line treatments for advanced non-small cell lung cancer in patients with epidermal growth factor receptor (EGFR) mutations, because it achieves significantly longer progression-free survival (PFS) than conventional first-line treatments (hazard ratio: 0.46). However, the efficacy and safety of osimertinib as a first-line treatment for patients aged ≥75 years remain unclear. **Methods:** This phase II study was performed to prospectively investigate the efficacy and safety of osimertinib for elderly patients with EGFR mutation-positive advanced non-small cell lung cancer. The primary endpoint was 1-year PFS rate; secondary endpoints were overall response rate (ORR), PFS, overall survival (OS), and safety. **Results:** Thirty-eight patients were included in the analysis. The 1-year PFS rate was 59.4% (95% confidence interval [CI], 46.1%-72.7%), which did not meet the primary endpoint (the threshold 1-year PFS rate of 50% predicted using data from the NEJ003 study). The most common grade 3/4 adverse events were rash/dermatitis acneiform/ALT increased/hypokalemia (2 patients, 5%). Seven patients developed pneumonitis (17.5%). There were no other cases of treatment discontinuation due to adverse events other than pneumonitis.
Conclusion: Although this study did not meet the primary endpoint, osimertinib was tolerable for elderly patients with EGFR mutation-positive advanced non-small cell lung cancer.

Immune checkpoint inhibitors in lung tumors with rare histologies and other thoracic malignancies
Andrini E, Federico AD, Sisi M, et al. Immune checkpoint inhibitors in lung tumors with rare histologies and other thoracic malignancies. *Immunotherapy*. 2022;14(16):1329-1340. doi:10.2217/imt-2022-0060
In recent years, immunotherapy has significantly changed the treatment of locally advanced/metastatic non-small-cell lung cancer (NSCLC). Conversely, the role of immunotherapy in NSCLC with uncommon histologies remains unclear, while in other rare thoracic malignancies, such as malignant pleural mesothelioma and thymic epithelial tumors, the use of immune checkpoint inhibitors is modifying therapeutic strategies with solid hopes for the future. However, larger prospective studies are urgently needed to define the best treatment strategies and the role of immunotherapy in these orphan tumors. This review provides a comprehensive overview of the emerging role of immunotherapy in the treatment of patients affected by these rare thoracic malignancies.

The benefits and harms of adjuvant chemotherapy for non-small cell lung cancer in patients with major comorbidities: A simulation study Leiter A, Kong CY, Gould MK, et al. The benefits and harms of adjuvant chemotherapy for non-small cell lung cancer in patients with major comorbidities: A simulation study. *PLoS One*. 2022;17(11):e0263911. Published 2022 Nov 15. doi:10.1371/journal.pone.0263911
Background: Randomized controlled trials (RCTs) have demonstrated a survival benefit for adjuvant platinum-based chemotherapy after resection of locoregional non-small cell lung cancer (NSCLC). The

relative benefits and harms and optimal approach to treatment for NSCLC patients who have major comorbidities (chronic obstructive pulmonary disease [COPD], coronary artery disease [CAD], and congestive heart failure [CHF]) are unclear, however. **Methods:** We used a simulation model to run in-silico comparative trials of adjuvant chemotherapy versus observation in locoregional NSCLC in patients with comorbidities. The model estimated quality-adjusted life years (QALYs) gained by each treatment strategy stratified by age, comorbidity, and stage. The model was parameterized using outcomes and quality-of-life data from RCTs and primary analyses from large cancer databases. **Results:** Adjuvant chemotherapy was associated with clinically significant QALY gains for all patient age/stage combinations with COPD except for patients >80 years old with Stage IB and IIA cancers. For patients with CHF and Stage IB and IIA disease, adjuvant chemotherapy was not advantageous; in contrast, it was associated with QALY gains for more advanced stages for younger patients with CHF. For stages IIB and IIIA NSCLC, most patient groups benefited from adjuvant chemotherapy. However, In general, patients with multiple comorbidities benefited less from adjuvant chemotherapy than those with single comorbidities and women with comorbidities in older age categories benefited more from adjuvant chemotherapy than their male counterparts. **Conclusions:** Older, multimorbid patients may derive QALY gains from adjuvant chemotherapy after NSCLC surgery. These results help extend existing clinical trial data to specific unstudied, high-risk populations and may reduce the uncertainty regarding adjuvant chemotherapy use in these patients.

Clinical Features, Survival, and Burden of Toxicities in Survivors More Than One Year After Lung Cancer Immunotherapy Hsu ML, Murray JC, Psoter KJ, et al. Clinical Features, Survival, and Burden of Toxicities in Survivors More Than One Year After Lung Cancer Immunotherapy. Oncologist. 2022;27(11):971-981. doi:10.1093/oncolo/oyac140
Introduction: Anti-PD-(L)1 immune checkpoint inhibitors (ICI) improve survival in patients with advanced non-small cell lung cancer (aNSCLC). The clinical features, survival, and burden of toxicities of patients with aNSCLC alive >1 year from ICI initiation are poorly understood. **Materials and methods:** We defined ICI survivors as patients alive >1 year after ICI start and retrospectively reviewed demographics, treatment, and immune-related adverse events (irAEs). Long-term irAEs were defined as ongoing irAEs lasting >1 year; burden of toxicity measures were based on percentage of days a patient experienced toxicity. Using linear and logistic regression, we evaluated association between demographics and disease characteristics with burden of toxicity. **Results:** We identified 114 ICI survivors from 317 patients with aNSCLC. Half (52%) experienced an irAE of any grade, and 23.7% developed long-term irAEs. More ICI survivors with irAES in the first year had never smoked ($P = .018$) or received ICIs as frontline therapy ($P = .015$). The burden of toxicity in the first year significantly correlated with the burden of toxicity afterward ($\rho = 0.72$; $P < .001$). No patients with progressive disease had a high burden of toxicity, and they experienced 30.6% fewer days with toxicity than those with stable disease. Increased duration of therapy was associated with higher odds of experiencing toxicity. Half of ICI survivors with irAEs were still receiving treatment for unresolved irAEs at time of death or last follow-up. **Conclusion:** Significant proportions of ICI survivors have unresolved long-term toxicities. These data support a growing need to understand long-term toxicity to optimize management of those treated with ICIs.

Gastrointestinal toxicity of systemic oncology immunotherapy Bureš J, Kohoutová D, Zavoral M. Gastrointestinal toxicity of systemic oncology immunotherapy. Gastrointestinální toxicita systémové onkologické imunoterapie. *Klin Onkol*. 2022;35(5):346-357. doi:10.48095/ccko2022346
Background: Systemic anti-cancer immunotherapy provides a substantial progress in options of current oncology treatment. Yet, this therapeutic approach is potentially associated with a significant gastrointestinal toxicity. **Aim:** The purpose of this paper is to provide a comprehensive review on

pathogenesis, clinical features, dia gnostics and therapy of these toxicities. Review of current knowledge: Check-point inhibitors brought a major progress in anti-cancer immunotherapy and improved significantly prognosis of several malignancies (e. g. metastatic malignant melanoma, non-small-cell lung cancer, gastric and colorectal cancers in high-risk population associated with presence of pathogenic mutations, renal cell carcinoma, squamous cell carcinoma of the head and neck and urothelial carcinoma). They include monoclonal antibodies targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA4; e. g. ipilimumab, tremelimumab), programmed death-1 receptor (PD-1; e. g. pembrolizumab, nivolumab) and its ligand PD-L1 (e. gatezolizumab, avelumab). Chimeric antigen receptor (CAR) T-cell therapy is another new option for haematological malignancies and metastatic colorectal cancer. Major symptoms of gastrointestinal toxicity caused by systemic immunotherapy include diarrhoea (20-50%), entero-colitis (1-10%) and laboratory or clinical signs of hepatopathy (~10%). Anti-cancer immunotherapy can be also complicated by infections (Clostridium difficile, Mycoplasma and/ or cytomegalovirus). There is no data on other possible complications so far. However, it can be assumed that these will also include bile acid malabsorption as well as small intestinal bacterial overgrowth syndrome. Treatment of gastrointestinal complications of immunotherapy should be graded according to their severity. It includes symptomatic medications (e. g. loperamide), systemic glucocorticoids and anti-TNF monoclonal antibodies (alone or together with mycofenolate mofetil or tacrolimus in the most severe cases). **Conclusions:** Awareness of possible complications of systemic anti-cancer immunotherapy is crucial for patients safety. It is mandatory to consider immune-related adverse events, complicating infections, bile acids malabsorption and small intestinal bacterial overgrowth syndrome. Prompt proper diagnostics and immediate vigorous therapy influence the outcome of patients significantly. A strictly individualized approach is indispensable.

First-line treatments for patients with advanced ALK gene rearrangements in NSCLC: a systematic review and network meta-analysis Tao J, Zheng C, Zhang C, et al. First-line treatments for patients with advanced ALK gene rearrangements in NSCLC: a systematic review and network meta-analysis. *J Int Med Res*. 2022;50(11):3000605221132703. doi:10.1177/03000605221132703
Objective: To conduct a network meta-analysis of randomised controlled trials to determine the optimal clinical choice of first-line therapy for patients with ALK receptor tyrosine kinase (*ALK*) gene rearrangement non-small cell lung cancer (NSCLC). **Methods:** Clinical trials in patients with histologically confirmed *ALK* gene rearrangement NSCLC, that included ALK inhibitors as first-line therapy, were identified using database searches. A Bayesian network meta-analysis was conducted to calculate the efficacy and safety of the included first-line treatments. **Results:** Nine trials with 2,407 patients were included for analyses. Lorlatinib was better than brigatinib for progression-free survival (PFS) (hazard ratio 0.79, 95% confidence interval 0.63, 0.98). In subgroup analyses, lorlatinib exhibited the highest probability of best PFS ranking in patients with or without baseline brain metastases (38% and 80%, respectively); brigatinib had the highest probability of best PFS ranking among Asian patients (47%). Alectinib offered the highest survival advantage (57% probability), while lorlatinib was likely to be the best treatment for an objective response (41% probability). Alectinib displayed the highest probability of being ranked lowest for grade ≥3 adverse events (86%). **Conclusions:** Lorlatinib was associated with the best PFS overall, and was suitable for patients with or without brain metastases. Brigatinib was associated with the best PFS in Asian patients.

A Bayesian network analysis of immunotherapy and taxane chemotherapy as second- or later-line treatments in non-small cell lung cancer
Liu XX, Lin GH, Wang BC. A Bayesian network analysis of immunotherapy and taxane chemotherapy as second- or later-line treatments in non-small cell lung cancer. *Medicine (Baltimore)*. 2022;101(45):e31751. doi:10.1097/MD.0000000000031751

Background: Taxane chemotherapy represents the standard of care in the second-line setting for non-small cell lung cancer (NSCLC) patients, but immunotherapy agents pose great challenges. Whether immunotherapy/chemotherapy alone or combination therapy has more benefits remains controversial. In this study, we provided comparisons to integrate the efficacy of immunotherapy and taxane chemotherapy as second- or later-line treatments in advanced NSCLC. **Methods:** PubMed, Web of Science, Embase, and Cochrane Central Register of Controlled Trials were systematically searched from inception to September 1, 2020. Randomized controlled trials comparing immunotherapy and taxane chemotherapy were enrolled in the Bayesian network analysis. Overall survival (OS) and progression-free survival (PFS) with hazard ratios (HRs) were investigated. **Results:** Eight trials in 13 studies with 4398 patients comparing seven treatments were identified. Pembrolizumab 10 mg/kg was associated with the best improved OS, with significant differences versus docetaxel (HR 0.81, 95% credible interval [CrI] 0.74-0.88), avelumab (HR 0.84, 95% CrI 0.75-0.95), and pembrolizumab 200 mg plus docetaxel (HR 0.75, 95% CrI 0.56-1.00). Although pembrolizumab 200 mg plus docetaxel ranked the last in terms of OS, the combination therapy showed the most favorable PFS. Additionally, the anti-programmed death-ligand 1 (PD-L1) agent, avelumab, was associated with the least improvement in PFS. **Conclusion:** As second- or later-line therapeutic strategies, pembrolizumab 10 mg/kg provided the largest OS benefits and pembrolizumab 200 mg plus docetaxel improved PFS to the greatest extent. Considering that immunotherapy has been recommended to the first-line setting of NSCLC, advanced patients who have not received immunotherapy previously might be the suitable population for our findings.

A real-world pharmacovigilance study of FDA Adverse Event Reporting System (FAERS) events for osimertinib Yin Y, Shu Y, Zhu J, Li F, Li J. A real-world pharmacovigilance study of FDA Adverse Event Reporting System (FAERS) events for osimertinib. *Sci Rep*. 2022;12(1):19555. Published 2022 Nov 15. doi:10.1038/s41598-022-23834-1

Osimertinib was a third-generation, irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), which approved by the US Food and Drug Administration (FDA) in 2015 for treatment of non-small cell lung cancer (NSCLC). Our study was to explore the adverse events (AEs) caused by osimertinib through data mining of the US FDA Adverse Event Reporting System (FAERS), and provide reference for clinical safety. Data of osimertinib were collected from the FAERS database covering the period from first quarter of 2016 to the fourth quarter of 2021. Disproportionality analyses was employed to quantify the associated AE signals of osimertinib and detect the risk signals from the data in the FAERS database. Reporting odds ratio (ROR) was used to detect the risk signals from the data in the FAERS database. The definition relied on system organ class (SOCs) and preferred terms (PTs) by the Medical Dictionary for Regulatory Activities (MedDRA). Totally, 9,704,33 reports were collected from the FAERS database, 10,804 reports of osimertinib were identified as the 'primary suspected (PS)' AEs. Osimertinib induced AEs occurred in 27 organ systems. 68 significant disproportionality PTs satisfying with the four algorithms were retained at the same time. Unexpected significant AEs such as scrotal volvulus, hepatic function abnormal, venous thromboembolisms might also occur. The median onset time of osimertinib-associated AEs was 58 days (interquartile range [IQR] 14-212 days), and the majority of the AEs occurred within the first 30 days after osimertinib initiation. Our study found significant new AEs signals of osimertinib and might provide support for clinical monitoring and risk identification of osimertinib.

Conteltinib (CT-707) in patients with advanced ALK-positive non-small cell lung cancer: a multicenter, open-label, first-in-human phase 1 study Xing P, Zhao Q, Zhang L, et al. Conteltinib (CT-707) in patients with advanced ALK-positive non-small cell lung cancer: a multicenter, open-label, first-in-human phase 1 study. *BMC Med*. 2022;20(1):453. Published 2022 Nov 23. doi:10.1186/s12916-022-02646-0

Background: Conteltinib (CT-707) is a potent second-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) showing promising anti-tumor activities in preclinical studies. This study aimed to assess the safety, pharmacokinetic (PK), and efficacy of conteltinib in patients with ALK-positive non-small cell lung cancer (NSCLC). **Methods:** In this multicenter, single-arm, open-label, first-in-human phase 1 study, conteltinib was taken orally at doses of 50 to 800 mg quaque die (QD) in a dose-escalation phase. If the response was observed in a dose cohort of the dose-escalation phase, dose expansion was started. The primary endpoints were maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and adverse events assessed by investigators. **Results:** Between April 13, 2016, and February 8, 2020, 64 ALK-positive NSCLC patients were enrolled, including 41 (64.1%) patients with ALK TKI-naïve and 23 (35.9%) patients who received crizotinib previously. In the dose-escalation phase, 26 patients were treated with conteltinib at doses of 50 mg, 100 mg, 200 mg, 300 mg, 450 mg, 600 mg, and 800 mg QD. One DLT event was reported at the dose of 600 mg. MTD was not reached. Overall, 58 (90.6%) patients experienced treatment-related adverse events (TRAEs) and 9 (14.1%) patients had grade ≥ 3 TRAEs. The most common TRAEs were diarrhea (46 [71.9%]), serum creatinine elevated (29 [45.3%]), aspartate aminotransferase elevated (25 [39.1%]), and nausea (24 [37.5%]). Among 39 ALK TKI-naïve patients, the overall response rate (ORR) was 64.1% (25 of 39; 95% confidence interval [CI], 47.2-78.8), median progression-free survival (PFS) was 15.9 months (95% CI, 9.26-23.3), and median duration of response (DoR) was 15.0 months (95% CI, 9.06-25.8). Among 21 patients who received crizotinib previously, the ORR was 33.3% (7 of 21; 95% CI, 14.6-57.0), median PFS was 6.73 months (95% CI, 4.73-8.54), and median DoR was 6.60 months (95% CI, 3.77-13.3). **Conclusions:** In this study, conteltinib showed manageable safety profile, favorable PK properties, and anti-tumor activity in advanced ALK-positive NSCLC patients. The recommended phase 2 dose was determined to be 600 mg QD for ALK TKI-naïve patients and 300 mg bis in die (BID) for patients who received crizotinib previously.

Ceritinib (LDK378) prevents bone loss *via* suppressing Akt and NF-κB-induced osteoclast formation

He W, Cao X, Kong K, Rong K, Han S, Qin A. Ceritinib (LDK378) prevents bone loss *via* suppressing Akt and NF-κB-induced osteoclast formation. *Front Endocrinol (Lausanne)*. 2022;13:939959. Published 2022 Nov 8. doi:10.3389/fendo.2022.939959

Background: Ceritinib is used for the treatment of patients with anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer (NSCLC), who are at the risk of developing bone metastasis. During bone metastasis, tumor cells release factors that induce osteoclast formation, resulting in osteolysis. However, the effect of ceritinib on osteoclast formation remains unclear.

Methods: Osteoclastogenesis was induced to assess the effect of ceritinib on osteoclast formation and osteoclast-specific gene expression. Western blotting was used to examine the molecular mechanisms underlying the effect of ceritinib on osteoclast differentiation. An *in vivo* ovariectomized mouse model was established to validate the effect of ceritinib in suppressing osteoclast formation and preventing bone loss. **Results:** The differentiation of osteoclasts and the expression of osteoclast-specific genes were inhibited upon ceritinib stimulation. Ceritinib suppressed Akt and p65 phosphorylation during the receptor activator of nuclear factor kappa-B ligand (RANKL)-induced osteoclastogenesis. The administration of ceritinib to ovariectomized mice ameliorated trabecular bone loss by inhibiting osteoclast formation. **Conclusions:** Ceritinib is beneficial in preventing bone loss by suppressing osteoclastic Akt and nuclear factor κB (NF-κB) signaling.

Alternate Pembrolizumab Dosing Interval in Advanced NSCLC with PD-L1 TPS ≥ 50%: 3 Weekly Compared to 6 Weekly Dosing Jones L, Rittberg R, Leung B, et al. Alternate Pembrolizumab Dosing

Interval in Advanced NSCLC with PD-L1 TPS ≥ 50%: 3 Weekly Compared to 6 Weekly Dosing. *Curr Oncol*. 2022;29(11):8686-8692. Published 2022 Nov 15. doi:10.3390/curroncol29110685
Background: A fixed dose of 200 mg of pembrolizumab every 3 weeks (Q3W) is the standard of care for patients with stage IV non-small cell lung cancer (NSCLC) and PDL1 ≥50%. In April 2020, based on pharmacokinetic modeling without formal comparative studies, the FDA approved 400 mg every 6 weeks (Q6W). Pharmacokinetic studies also suggested comparable target engagement with weight-based and flat dosing for the respective schedules. The objective of this study was to determine if overall survival (OS) differs based on the Q3W vs. Q6W dosing schedule of pembrolizumab. **Methods:** BC Cancer patients with stage IV NSCLC and PDL1 ≥50% treated with pembrolizumab were retrospectively reviewed. Patients were treated with weight-based dosing, per institution standard, of pembrolizumab 2 mg/kg Q3W or 4 mg/kg Q6W. Patient demographics, treatment and outcome were recorded. Patients were assigned to Q3W or Q6W according to the schedule that was used for the majority of treatment (greater than 50%). **Results:** 718 patients with NSCLC and PDL1 ≥50% received first-line pembrolizumab between 2017 and2021, Q3W/Q6W dosing 677/41 patients. Baseline characteristics with respect to age, sex, smoking status, histology and performance status (PS) were similar between groups. In the multivariate model, including age, sex, PS and dosing schedule, the hazard ratio for death (HR) for OS Q3W vs. Q6W was 0.759 ($p = 0.230$). A 2:1 case-matched analysis for OS was performed, controlling for sex, age ± 5 years, PS and duration on pembrolizumab ± 2 months for Q3W vs. Q6W ($n = 113$) with a HR 0.834 ($p = 0.500$). **Conclusions:** There was no OS difference demonstrated with pembrolizumab dosing Q3W compared to Q6W in a multivariate analysis that included age, sex and PS. A case-matched analysis that controlled for these variables and for duration of treatment confirmed these findings. This study supports the use of Q6W pembrolizumab dosing, allowing for less frequent interactions with the medical system.

Medication adherence with denosumab in patients with bone metastases from solid tumors treated in routine clinical settings: a retrospective study Diel IJ, Greil R, Janssen J, et al. Medication adherence with denosumab in patients with bone metastases from solid tumors treated in routine clinical settings: a retrospective study. *Support Care Cancer*. 2022;30(11):9267-9278. doi:10.1007/s00520-022-07333-7
Purpose: To describe (non)adherence with denosumab among patients with solid tumors and bone metastases. **Methods:** This retrospective, observational study pooled data from two completed prospective, multicenter cohort studies (X-TREME; Study 240) in adult patients with bone metastases from primary breast, prostate, lung, kidney, or other solid cancer types and administered denosumab 120 mg in routine clinical practice in Germany and Central and Eastern Europe. The studies were conducted between May 2012 and May 2017; pooled analysis was completed in August 2021. Medication adherence was described according to a three-component consensus taxonomy: initiation (first-ever administration ≤ 90 days from bone metastasis diagnosis), implementation (actual vs prescribed dosing; optimal implementation = regular/consistent dosing), and persistence (≤ 60-day gap between administrations at 3, 6, 9, and 12 months). Descriptive analyses were conducted for each cancer type. **Results:** The analysis included 1748 patients with solid tumors and bone metastases. Adherence with denosumab was generally high across the initiation, implementation, and persistence phases. Most patients experienced timely initiation (from 64.4% [kidney cancer] to 81.2% [breast cancer]) and optimal implementation (from 62.4% [lung cancer] to 72.5% [breast cancer]). The proportion of patients who were persistent with treatment at 6 months ranged from 41.4% (lung cancer) to 77.8% (prostate cancer). **Conclusions:** This study revealed variations by cancer type in the initiation, implementation, and persistence of denosumab in patients with solid tumors and bone metastases in routine clinical practice. Further cancer-specific studies are warranted to examine the determinants of (non)adherence with denosumab, and potential ways to improve medication adherence.

MET-Induced CD73 Restrains STING-Mediated Immunogenicity of EGFR-Mutant Lung Cancer

Yoshida R, Saigi M, Tani T, et al. MET-Induced CD73 Restrains STING-Mediated Immunogenicity of EGFR-Mutant Lung Cancer. *Cancer Res*. 2022;82(21):4079-4092. doi:10.1158/0008-5472.CAN-22-0770

Immunotherapy has shown limited efficacy in patients with EGFR-mutated lung cancer. Efforts to enhance the immunogenicity of EGFR-mutated lung cancer have been unsuccessful to date. Here, we discover that MET amplification, the most common mechanism of resistance to third-generation EGFR tyrosine kinase inhibitors (TKI), activates tumor cell STING, an emerging determinant of cancer immunogenicity (1). However, STING activation was restrained by ectonucleosidase CD73, which is induced in MET-amplified, EGFR-TKI-resistant cells. Systematic genomic analyses and cell line studies confirmed upregulation of CD73 in MET-amplified and MET-activated lung cancer contexts, which depends on coinduction of FOSL1. Pemetrexed (PEM), which is commonly used following EGFR-TKI treatment failure, was identified as an effective potentiator of STING-dependent TBK1-IRF3-STAT1 signaling in MET-amplified, EGFR-TKI-resistant cells. However, PEM treatment also induced adenosine production, which inhibited T-cell responsiveness. In an allogenic humanized mouse model, CD73 deletion enhanced immunogenicity of MET-amplified, EGFR-TKI-resistant cells, and PEM treatment promoted robust responses regardless of CD73 status. Using a physiologic antigen recognition model, inactivation of CD73 significantly increased antigen-specific CD8+ T-cell immunogenicity following PEM treatment. These data reveal that combined PEM and CD73 inhibition can co-opt tumor cell STING induction in TKI-resistant EGFR-mutated lung cancers and promote immunogenicity. **Significance:** MET amplification upregulates CD73 to suppress tumor cell STING induction and T-cell responsiveness in TKI-resistant, EGFR-mutated lung cancer, identifying a strategy to enhance immunogenicity and improve treatment.

MET Signaling Pathways, Resistance Mechanisms, and Opportunities for Target Therapies

Rivas S, Marín A, Samtani S, González-Feliú E, Armisén R. MET Signaling Pathways, Resistance Mechanisms, and Opportunities for Target Therapies. *Int J Mol Sci*. 2022;23(22):13898. Published 2022 Nov 11. doi:10.3390/ijms232213898

The *MET* gene, known as *MET* proto-oncogene receptor tyrosine kinase, was first identified to induce tumor cell migration, invasion, and proliferation/survival through canonical RAS-CDC42-PAK-Rho kinase, RAS-MAPK, PI3K-AKT-mTOR, and β-catenin signaling pathways, and its driver mutations, such as *MET* gene amplification (*MET*amp) and the exon 14 skipping alterations (*MET*ex14), activate cell transformation, cancer progression, and worse patient prognosis, principally in lung cancer through the overactivation of their own oncogenic and MET parallel signaling pathways. Because of this, *MET* driver alterations have become of interest in lung adenocarcinomas since the FDA approval of target therapies for *MET*amp and *MET*ex14 in 2020. However, after using MET target therapies, tumor cells develop adaptative changes, favoring tumor resistance to drugs, the main current challenge to precision medicine. Here, we review a link between the resistance mechanism and MET signaling pathways, which is not only limited to MET. The resistance impacts MET parallel tyrosine kinase receptors and signals shared hubs. Therefore, this information could be relevant in the patient's mutational profile evaluation before the first target therapy prescription and follow-up to reduce the risk of drug resistance. However, to develop a resistance mechanism to a MET inhibitor, patients must have access to the drugs. For instance, none of the FDA approved MET inhibitors are registered as such in Chile and other developing countries. Constant cross-feeding between basic and clinical research will thus be required to meet future challenges imposed by the acquired resistance to targeted therapies.

The Efficacy of Fosbretabulin Disodium Combined with Radiofrequency Ablation in Lung Cancer

Kou J, Liu J, Gu X, Liu N. The Efficacy of Fosbretabulin Disodium Combined with Radiofrequency Ablation in Lung Cancer. *Radiat Res*. 2022;198(5):467-474. doi:10.1667/RADE-21-00242.1

Radiofrequency ablation (RFA) is a technology that uses radiofrequency thermal effect to induce coagulation necrosis of tumor tissue under the guidance of imaging. However, distant metastasis of tumor cells caused by tumor angiogenesis can lead to incomplete tumor clearing. In this study, LLC1 cell line was used for the construction of subcutaneous xenografts. Either 10 mg/kg or 20 mg/kg Fosbretabulin disodium (FBTD) was intragastrically administered every 2 days for a week. RFA was performed at the end of medication. The proportion of T cells was examined by flow cytometry. Serum IgG and IgA levels of mice were examined by ELISA. Expression of certain genes was estimated by qRT-PCR assay. In this study, we demonstrated that FBTD was able to significantly enhance RFA-induced immune function in tumor-bearing mice by upregulating RFA-induced CD8+ killer T cells. Consistently, 10 mg/kg or 20 mg/kg FBTD therapy upregulated the percentage of IFNγ+ and TNFα+ CD8+ tumor infiltrating lymphocytes in tumor-bearing mice compared to the RFA alone or FBTD alone group. Mechanistically, we reported that FBTD inhibited the RFA-induced PD-1 and PD-L1 upregulation in vivo. In conclusion, we demonstrated that FBTD promoted the antitumor effects of RFA in lung tumor-bearing mice in this study.

NSCLC - RADIOTHERAPY

Radiation pneumonitis prediction after stereotactic body radiation therapy based on 3D dose distribution: dosiomics and/or deep learning-based radiomics features Huang Y, Feng A, Lin Y, et al. Radiation pneumonitis prediction after stereotactic body radiation therapy based on 3D dose distribution: dosiomics and/or deep learning-based radiomics features. *Radiat Oncol*. 2022;17(1):188. Published 2022 Nov 17. doi:10.1186/s13014-022-02154-8

Background: This study was designed to establish radiation pneumonitis (RP) prediction models using dosiomics and/or deep learning-based radiomics (DLR) features based on 3D dose distribution. **Methods:** A total of 140 patients with non-small cell lung cancer who received stereotactic body radiation therapy (SBRT) were retrospectively included in this study. These patients were randomly divided into the training (n = 112) and test (n = 28) sets. Besides, 107 dosiomics features were extracted by Pyradiomics, and 1316 DLR features were extracted by ResNet50. Feature visualization was performed based on Spearman's correlation coefficients, and feature selection was performed based on the least absolute shrinkage and selection operator. Three different models were constructed based on random forest, including (1) a dosiomics model (a model constructed based on dosiomics features), (2) a DLR model (a model constructed based on DLR features), and (3) a hybrid model (a model constructed based on dosiomics and DLR features). Subsequently, the performance of these three models was compared with receiver operating characteristic curves. Finally, these dosiomics and DLR features were analyzed with Spearman's correlation coefficients. **Results:** In the training set, the area under the curve (AUC) of the dosiomics, DLR, and hybrid models was 0.9986, 0.9992, and 0.9993, respectively; the accuracy of these three models was 0.9643, 0.9464, and 0.9642, respectively. In the test set, the AUC of these three models was 0.8462, 0.8750, and 0.9000, respectively; the accuracy of these three models was 0.8214, 0.7857, and 0.8571, respectively. The hybrid model based on dosiomics and DLR features outperformed other two models. Correlation analysis between dosiomics features and DLR features showed weak correlations. The dosiomics features that correlated DLR features with the Spearman's rho $|\rho| \geq 0.8$ were all first-order features. **Conclusion:** The hybrid features based on dosiomics and DLR features from 3D dose distribution could improve the performance of RP prediction after SBRT.

Risk analysis of grade ≥ 2 radiation pneumonitis based on radiotherapy timeline in stage III/IV non-small cell lung cancer treated with volumetric modulated arc therapy: a retrospective study Yang S, Huang S, Ye X, Xiong K, Zeng B, Shi Y. Risk analysis of grade ≥ 2 radiation pneumonitis based on radiotherapy timeline in stage III/IV non-small cell lung cancer treated with volumetric modulated arc

therapy: a retrospective study. *BMC Pulm Med*. 2022;22(1):402. Published 2022 Nov 7. doi:10.1186/s12890-022-02211-8

Background: Radiotherapy is an important treatment for patients with stage III/IV non-small cell lung cancer (NSCLC), and due to its high incidence of radiation pneumonitis, it is essential to identify high-risk people as early as possible. The present work investigates the value of the application of different phase data throughout the radiotherapy process in analyzing risk of grade ≥ 2 radiation pneumonitis in stage III/IV NSCLC. Furthermore, the phase data fusion was gradually performed with the radiotherapy timeline to develop a risk assessment model. **Methods:** This study retrospectively collected data from 91 stage III/IV NSCLC cases treated with Volumetric modulated arc therapy (VMAT). Patient data were collected according to the radiotherapy timeline for four phases: clinical characteristics, radiomics features, radiation dosimetry parameters, and hematological indexes during treatment. Risk assessment models for single-phase and stepwise fusion phases were established according to logistic regression. In addition, a nomogram of the final fusion phase model and risk classification system was generated. Receiver operating characteristic (ROC), decision curve, and calibration curve analysis were conducted to internally validate the nomogram to analyze its discrimination. **Results:** Smoking status, PTV and lung radiomics feature, lung and esophageal dosimetry parameters, and platelets at the third week of radiotherapy were independent risk factors for the four single-phase models. The ROC result analysis of the risk assessment models created by stepwise phase fusion were: (area under curve [AUC]: 0.67,95% confidence interval [CI]: 0.52-0.81), (AUC: 0.82,95%CI: 0.70-0.94), (AUC: 0.90,95%CI: 0.80-1.00), and (AUC:0.90,95%CI: 0.80-1.00), respectively. The nomogram based on the final fusion phase model was validated using calibration curve analysis and decision curve analysis, demonstrating good consistency and clinical utility. The nomogram-based risk classification system could correctly classify cases into three diverse risk groups: low-(ratio:3.6%; 0 < score < 135), intermediate-(ratio:30.7%, 135 < score < 160) and high-risk group (ratio:80.0%, score > 160). **Conclusions:** In our study, the risk assessment model makes it easy for physicians to assess the risk of grade ≥ 2 radiation pneumonitis at various phases in the radiotherapy process, and the risk classification system and nomogram identify the patient's risk level after completion of radiation therapy.

Treatment With Stereotactic Ablative Radiotherapy for Up to 5 Oligometastases in Patients With Cancer: Primary Toxic Effect Results of the Nonrandomized Phase 2 SABR-5 Clinical Trial

Olson R, Jiang W, Liu M, et al. Treatment With Stereotactic Ablative Radiotherapy for Up to 5 Oligometastases in Patients With Cancer: Primary Toxic Effect Results of the Nonrandomized Phase 2 SABR-5 Clinical Trial. *JAMA Oncol*. 2022;8(11):1644-1650. doi:10.1001/jamaoncol.2022.4394

Importance: After the publication of the landmark SABR-COMET trial, concerns arose regarding high-grade toxic effects of treatment with stereotactic ablative body radiotherapy (SABR) for oligometastases. **Objective:** To document toxic effects of treatment with SABR in a large cohort from a population-based, provincial cancer program. **Design, setting, and participants:** From November 2016 to July 2020, 381 patients across all 6 cancer centers in British Columbia were treated in this single-arm, phase 2 trial of treatment with SABR for patients with oligometastatic or oligoprogressive disease. During this period, patients were only eligible to receive treatment with SABR in these settings in trials within British Columbia; therefore, this analysis is population based, with resultant minimal selection bias compared with previously published SABR series. **Interventions:** Stereotactic ablative body radiotherapy to up to 5 metastases. **Main outcomes and measures:** Rate of grade 2, 3, 4, and 5 toxic effects associated with SABR. **Findings:** Among 381 participants (122 women [32%]), the mean (SD; range) age was 68 (11.1; 30-97) years, and the median (range) follow-up was 25 (1-54) months. The most common histological findings were prostate cancer (123 [32%]), colorectal cancer (63 [17%]), breast cancer (42 [11%]), and lung cancer (33 [9%]). The number of SABR-treated sites were 1 (263 [69%]), 2 (82 [22%]), and 3 or more (36 [10%]). The most common sites of SABR were lung (188 [34%]), nonspine bone (136 [25%]),

spine (85 [16%]), lymph nodes (78 [14%]), liver (29 [5%]), and adrenal (15 [3%]). Rates of grade 2, 3, 4, and 5 toxic effects associated with SABR (based on the highest-grade toxic effect per patient) were 14.2%; (95% CI, 10.7%-17.7%), 4.2% (95% CI, 2.2%-6.2%), 0%, and 0.3% (95% CI, 0%-0.8%), respectively. The cumulative incidence of grade 2 or higher toxic effects associated with SABR at year 2 by Kaplan-Meier analysis was 8%, and for grade 3 or higher, 4%. **Conclusions and relevance:** This single-arm, phase 2 clinical trial found that the incidence of grade 3 or higher SABR toxic effects in this population-based study was less than 5%. Furthermore, the rates of grade 2 or higher toxic effects (18.6%) were lower than previously published for SABR-COMET (29%). These results suggest that SABR treatment for oligometastases has acceptable rates of toxic effects and potentially support further enrollment in randomized phase 3 clinical trials.

Definitive Local Consolidative Therapy for Oligometastatic Solid Tumors: Results From the Lead-in Phase of the Randomized Basket Trial EXTEND

Sherry AD, Bathala TK, Liu S, et al. Definitive Local Consolidative Therapy for Oligometastatic Solid Tumors: Results From the Lead-in Phase of the Randomized Basket Trial EXTEND. *Int J Radiat Oncol Biol Phys*. 2022;114(5):910-918. doi:10.1016/j.ijrobp.2022.05.023

Purpose: The benefit of local consolidative therapy (LCT) for oligometastasis across histologies remains uncertain. EXTernal beam radiation to Eliminate Nominal metastatic Disease (EXTEND; NCT03599765) is a randomized phase 2 basket trial evaluating the effectiveness of LCT for oligometastatic solid tumors. We report here the prospective results of the single-arm "lead-in" phase intended to identify histologies most likely to accrue to histology-specific endpoints in the randomized phase. **Methods and materials:** Eligible histologies included colorectal, sarcoma, lung, head and neck, ovarian, renal, melanoma, pancreatic, prostate, cervix/uterine, breast, and hepatobiliary. Patients received LCT to all sites of active metastatic disease and primary/regional disease (as applicable) plus standard-of-care systemic therapy or observation. The primary endpoint in EXTEND was progression-free survival (PFS), and the primary endpoint of the lead-phase was histology-specific accrual feasibility. Adverse events were graded by Common Terminology Criteria for Adverse Events version 4.0. **Results:** From August 2018 through January 2019, 50 patients were enrolled and 49 received definitive LCT. Prostate, breast, and kidney were the highest enrolling histologies and identified for independent accrual in the randomization phase. Most patients (73%) had 1 or 2 metastases, most often in lung or bone (79%), and received ablative radiation (62%). Median follow-up for censored patients was 38 months (range, 16-42 months). Median PFS was 13 months (95% confidence interval, 9-24), 3-year overall survival rate was 73% (95% confidence interval, 57%-83%), and local control rate was 98% (93 of 95 tumors). Two patients (4%) had Common Terminology Criteria for Adverse Events grade 3 toxic effects related to LCT; no patient had grade 4 or 5 toxic effects. **Conclusions:** The prospective lead-in phase of the EXTEND basket trial demonstrated feasible accrual, encouraging PFS, and low rates of severe toxic effects at mature follow-up. The randomized phase is ongoing with histology-based baskets that will provide histology-specific evidence for LCT in oligometastatic disease.

Association of Sinoatrial Node Radiation Dose With Atrial Fibrillation and Mortality in Patients With Lung Cancer

Kim KH, Oh J, Yang G, et al. Association of Sinoatrial Node Radiation Dose With Atrial Fibrillation and Mortality in Patients With Lung Cancer. *JAMA Oncol*. 2022;8(11):1624-1634. doi:10.1001/jamaoncol.2022.4202

Importance: Atrial fibrillation (AF) can develop following thoracic irradiation. However, the critical cardiac substructure responsible for AF has not been properly studied. **Objective:** To describe the incidence of AF in patients with lung cancer and determine predictive cardiac dosimetric parameters.

Design, setting, and participants: This retrospective cohort study was performed at a single referral center and included 239 patients diagnosed with limited-stage small cell lung cancer (SCLC) and 321 patients diagnosed with locally advanced non-small cell lung cancer (NSCLC) between August 2008 and December 2019 who were treated with definitive chemoradiotherapy. **Exposures:** Radiation dose exposure to cardiac substructures, including the chambers, coronary arteries, and cardiac conduction nodes, were calculated for each patient. **Main outcomes and measures:** Main outcomes were AF and overall survival. **Results:** Of the 239 and 321 patients with SCLC and NSCLC, the median (IQR) age was 68 (60-73) years and 67 (61-75) years, and 207 (86.6%) and 261 (81.3%) were men, respectively. At a median (IQR) follow-up time of 32.7 (22.1-56.6) months, 9 and 17 patients experienced new-onset AF in the SCLC and NSCLC cohorts, respectively. The maximum dose delivered to the sinoatrial node (SAN Dmax) exhibited the highest predictive value for prediction of AF. A higher SAN Dmax significantly predicted an increased risk of AF in patients with SCLC (adjusted hazard ratio [aHR], 14.91; 95% CI, 4.00-55.56; P < .001) and NSCLC (aHR, 15.67; 95% CI, 2.08-118.20; P = .008). However, SAN Dmax was not associated with non-AF cardiac events. Increased SAN Dmax was significantly associated with poor overall survival in patients with SCLC (aHR, 2.68; 95% CI, 1.53-4.71; P < .001) and NSCLC (aHR, 1.97; 95% CI, 1.45-2.68; P < .001). **Conclusions and relevance:** In this cohort study, results suggest that incidental irradiation of the SAN during chemoradiotherapy may be associated with the development of AF and increased mortality. This supports the need to minimize radiation dose exposure to the SAN during radiotherapy planning and to consider close follow-up for the early detection of AF in patients receiving thoracic irradiation.

Radiation treatment response and hypoxia biomarkers revealed by machine learning assisted Raman spectroscopy in tumour cells and xenograft tissues

Deng X, Milligan K, Brolo A, Lum JJ, Andrews JL, Jirasek A. Radiation treatment response and hypoxia biomarkers revealed by machine learning assisted Raman spectroscopy in tumour cells and xenograft tissues. *Analyst*. 2022;147(22):5091-5104. Published 2022 Nov 7. doi:10.1039/d2an01222g

Recent advancements in anatomical imaging of tumours as treatment targets have led to improvements in RT. However, it is unlikely that improved anatomical imaging alone will be the sole driver for new advances in personalised RT. Biochemically based radiobiological information is likely to be required for next-generation improvements in the personalisation of radiotherapy dose prescriptions to individual patients. In this paper, we use Raman spectroscopy (RS), an optical technique, to monitor individual biochemical response to radiation within a tumour microenvironment. We spatially correlate individual biochemical responses to augmentatively derived hypoxic maps within the tumour microenvironment. Furthermore, we pair RS with a data analytical framework combining (i) group and basis restricted non-negative matrix factorization (GBR-NMF), (ii) a random forest (RF) classifier, (iii) and a feature metric importance calculation method, Shapley Additive exPlanations (SHAP), in order to ascertain the relative importance of individual biochemicals in describing the overall biological response as observed with RS. The current study found that the GBR-NMF-RF-SHAP model helped identify a wide range of radiation response biomarkers and hypoxia indicators (*e.g.*, glycogen, lipids, DNA, amino acids) in H460 human lung cancer cells and H460 xenografts. Correlations between the hypoxic regions and Raman chemical biomarkers (*e.g.*, glycogen, alanine, and arginine) were also identified in H460 xenografts. To summarize, GBR-NMF-RF-SHAP combined with RS can be applied to monitor the RT-induced biochemical response within cellular and tissue environments. Individual biochemicals were identified that (i) contributed to overall biological response to radiation, and (ii) spatially correlated with hypoxic regions of the tumour. RS combined with our analytical pipeline shows promise for further understanding of individual biochemical dynamics in radiation response for use in cancer therapy.

Everything You Always Wanted to Know about Sarcopenia but Were Afraid to Ask: A Quick Guide for Radiation Oncologists (Impact of Sarcopenia in Radiotherapy: The AFRAID Project)

Medici F, Rizzo S, Buwenge M, et al. Everything You Always Wanted to Know about Sarcopenia but Were Afraid to Ask: A Quick Guide for Radiation Oncologists (Impact of Sarcopenia in Radiotherapy: The AFRAID Project). *Curr Oncol*. 2022;29(11):8513-8528. Published 2022 Nov 8. doi:10.3390/curroncol29110671

Sarcopenia (SP) is a syndrome characterized by age-associated loss of skeletal muscle mass and function. SP worsens both acute and late radiation-induced toxicity, prognosis, and quality of life. Myosteatosis is a pathological infiltration of muscle tissue by adipose tissue which often precedes SP and has a proven correlation with prognosis in cancer patients. Sarcopenic obesity is considered a "hidden form" of SP (due to large fat mass) and is independently related to higher mortality and worse complications after surgery and systemic treatments with worse prognostic impact compared to SP alone. The evaluation of SP is commonly based on CT images at the level of the middle of the third lumbar vertebra. On this scan, all muscle structures are contoured and then the outlined surface area is calculated. Several studies reported a negative impact of SP on overall survival in patients undergoing RT for tumors of the head and neck, esophagus, rectum, pancreas, cervix, and lung. Furthermore, several appetite-reducing side effects of RT, along with more complex radiation-induced mechanisms, can lead to SP through, but not limited to, reduced nutrition. In particular, in pediatric patients, total body irradiation was associated with the onset of SP and other changes in body composition leading to an increased risk of cardiometabolic morbidity in surviving adults. Finally, some preliminary studies showed the possibility of effectively treating SP and preventing the worsening of SP during RT. Future studies should be able to provide information on how to prevent and manage SP before, during, or after RT, in both adult and pediatric patients.

SMALL CELL LUNG CANCER - SCLC

The role of stem cells in small-cell lung cancer: evidence from chemoresistance to immunotherapy

Guo W, Qiao T, Li T. The role of stem cells in small-cell lung cancer: evidence from chemoresistance to immunotherapy. *Semin Cancer Biol*. 2022;87:160-169. Published 2022 Nov 9. doi:10.1016/j.semcancer.2022.11.006

Small cell lung cancer (SCLC) is the most aggressive subtype of lung cancer, accounting for approximately 15% among all lung cancers. Despite the ability of chemotherapy, the first-line treatment for SCLC, to rapidly shrink tumors, nearly all patients experience recurrence and metastasis within a few months. Cancer stem cells (CSCs) are a small population of tumor cells responsible for tumorigenesis, metastasis, and recurrence after treatment, which play a crucial role in chemoresistance by promoting DNA repair and expression of drug resistance-associated proteins. Thus, targeting CSCs has been successful in certain malignancies. Tumor therapy has entered the era of immunotherapy and numerous preclinical trials have demonstrated the effectiveness of immunotherapeutic approaches targeting CSCs, such as tumor vaccines and chimeric antigen receptor (CAR) T cell, and the feasibility of combining them with chemotherapy. Therefore, a deeper understanding of the interaction between CSCs and immune system is essential to facilitate the advances of new immunotherapies approaches targeting CSCs as well as combination with standard drugs such as chemotherapy. This narrative review summarizes the mechanisms of chemoresistance of CSCs in SCLC and the latest advances in targeted therapies. Thereafter, we discuss the effects of CSCs on tumor immune microenvironment in SCLC and corresponding immunotherapeutic approaches. Eventually, we propose that the combination of immunotherapy targeting CSCs with standard drugs is a promising direction for SCLC therapies.

Galectin-1, a novel promising target for outcome prediction and treatment in SCLC Corral JM, Puerto-Nevado LD, Cedeño M, et al. Galectin-1, a novel promising target for outcome prediction and treatment in SCLC. *Biomed Pharmacother*. 2022;156:113987. doi:10.1016/j.biopha.2022.113987
Introduction: small-cell lung cancer (SCLC) is one of the most lethal malignancies. Its management is complex due to the lack of biomarkers and limited therapies. Galectin-1 (Gal-1) plays a major role in cancer development and progression. The aim of this study is to assess whether Gal-1 has a predictive role in the disease evolution and its therapeutic potential. **Material and methods:** The expression level of Gal-1 was examined by using a public RNA-sequencing (77 SCLC patients) and in-house immunohistochemistry (IHC) performed on biopsies from 81 patients. Survival curves and Cox regression analysis were used to assess the prognostic potential of Gal-1. In addition, a SCLC-PDX model was carried out and treated with either OTX008, an inhibitor of Gal-1, or vehicle to assess the effects of Gal-1 inhibition on this disease in vivo. **Results:** Galectin-1 gene (LGALS1) expression showed a strong negative correlation with outcome in SCLC patients with advanced disease ($p = 0.007$). IHC unveiled that overall survival (OS) was significantly lower among extensive-stage SCLC (ES-SCLC) patient group with increased level of Gal-1 and platelet-to-lymphocyte ratio (PLR) (HR=3.07, 95% CI: 1.62, 5.79, $p < 0.001$). The SCLC-PDX model showed a significant reduction in tumor size (tumor growth inhibition [TGI] index 73%) without side effects. **Discussion:** in this study, high levels of Gal-1 and PLR were associated with poorer OS in SCLC patients, supporting their utility as clinical prognostic biomarkers. Moreover, the in vivo model suggests the inhibition of Gal-1 as a novel potential therapy for this disease with very poor prognosis.

Advances in biology and novel treatments of SCLC: The four-color problem in uncharted territory Kashima J, Okuma Y. Advances in biology and novel treatments of SCLC: The four-color problem in uncharted territory. *Semin Cancer Biol*. 2022;86(Pt 2):386-395. doi:10.1016/j.semcancer.2022.05.005
Treatment for small cell lung cancer (SCLC) has not changed significantly compared to the overwhelming development of targeted therapies for non-small cell lung cancer. However, recent epigenetic and expressional analyses have revealed that SCLC can be divided into four distinct subtypes, which may lead to precision treatments. The situation appears slightly similar to the "four-color problem," a classic mathematical problem stating that no more than four colors are required to color the regions so that no two adjacent areas have the same color. This review introduces the framework for subtyping SCLC into four molecular subtypes and the promising targeted treatment for each subtype.

Low level of complement factor H increases the risk of cancer-related death in patients with small-cell lung cancer
Xiang M, Zhang H, Kou L, Chen J, Xu Z, He J. Low level of complement factor H increases the risk of cancer-related death in patients with small-cell lung cancer. *Postgrad Med J*. 2022;98(1166):919-924. doi:10.1136/postgradmedj-2021-141186
Introduction: Pulmonary cancer is a kind of deeply invasive tumour which is difficult to treat, and its mortality rate is high. Previous research has shown that activation of complement could contribute to the progression of non-small-cell lung cancer (SCLC). However, little research has been done on SCLC. **Methods:** Complement factor H (CFH), complements C3 as well as C4 were measured in patients, and the prognostic impact of different parameters was assessed by log-rank function analysis and Cox multifactor models. Besides, we constructed a predictive model based on complement fractions and validated the accuracy of the model. **Results:** Among these 242 patients, 200 (82.6%) died. The median survival time was 18.3 months. We found by multifactorial analysis that high levels of CFH decreased the risk of death (HR 0.23, 95% CI 0.10 to 0.57, $p<0.001$), while elevated complement C4 displayed poor prognosis (HR 2.28, 95% CI 1.66 to 3.13, $p<0.001$). We screened variables by Cox models and

constructed CFH-based prediction models to plot a nomogram by internal validation. The nomogram showed excellent accuracy in assessing the probability of death, yielding an adjusted C-statistics of 0.905. **Conclusions:** CFH can be recognised as a biomarker to predict the risk of death in SCLC. The prediction model established based on CFH, C3 and C4 levels has good accuracy in patients' prognostic assessment.

Rb Tumor Suppressor in Small Cell Lung Cancer: Combined Genomic and IHC Analysis with a Description of a Distinct Rb-Proficient Subset Febres-Aldana CA, Chang JC, Ptashkin R, et al. Rb Tumor Suppressor in Small Cell Lung Cancer: Combined Genomic and IHC Analysis with a Description of a Distinct Rb-Proficient Subset. *Clin Cancer Res*. 2022;28(21):4702-4713. doi:10.1158/1078-0432.CCR-22-1115

Purpose: RB1 mutations and loss of retinoblastoma (Rb) expression represent consistent but not entirely invariable hallmarks of small cell lung cancer (SCLC). The prevalence and characteristics of SCLC retaining wild-type Rb are not well-established. Furthermore, the performance of targeted next-generation sequencing (NGS) versus immunohistochemistry for Rb assessment is not well-defined. **Experimental design:** A total of 208 clinical SCLC samples were analyzed by comprehensive targeted NGS, covering all exons of RB1, and Rb IHC. On the basis of established coordination of Rb/p16/cyclinD1 expression, p16-high/cyclinD1-low profile was used as a marker of constitutive Rb deficiency. **Results:** Fourteen of 208 (6%) SCLC expressed wild-type Rb, accompanied by a unique p16-low/cyclinD1-high profile supporting Rb proficiency. Rb-proficient SCLC was associated with neuroendocrine-low phenotype, combined SCLC with non-SCLC (NSCLC) histology and aggressive behavior. These tumors exclusively harbored CCND1 amplification (29%), and were markedly enriched in CDKN2A mutations (50%) and NSCLC-type alterations (KEAP1, STK11, FGFR1). The remaining 194 of 208 SCLC were Rb-deficient (p16-high/cyclinD1-low), including 184 cases with Rb loss (of which 29% lacked detectable RB1 alterations by clinical NGS pipeline), and 10 cases with mutated but expressed Rb. **Conclusions:** This is the largest study to date to concurrently analyze Rb by NGS and IHC in SCLC, identifying a 6% rate of Rb proficiency. Pathologic-genomic data implicate NSCLC-related progenitors as a putative source of Rb-proficient SCLC. Consistent upstream Rb inactivation via CDKN2A/p16↓ and CCND1/cyclinD1↑ suggests the potential utility of CDK4/6 inhibitors in this aggressive SCLC subset. The study also clarifies technical aspects of Rb status determination in clinical practice, highlighting the limitations of exon-only sequencing for RB1 interrogation.

A phase II study of carboplatin and etoposide plus durvalumab for previously untreated extensive-stage small-cell lung cancer (ES-SCLC) patients with a poor performance status (PS): NEJ045A study protocol Asao T, Watanabe S, Tanaka T, Morita S, Kobayashi K. A phase II study of carboplatin and etoposide plus durvalumab for previously untreated extensive-stage small-cell lung cancer (ES-SCLC) patients with a poor performance status (PS): NEJ045A study protocol. *BMC Cancer*. 2022;22(1):1135. Published 2022 Nov 4. doi:10.1186/s12885-022-10222-1

Background: Small-cell lung cancer (SCLC) accounts for 12-15% of lung cancers and has a limited prognosis, with approximately one-third of SCLC patients having a poor performance status (PS). Patients with extensive-stage (ES) SCLC and a poor PS have a poor prognosis. For this population, overall survival from carboplatin and etoposide treatment is 7-8 months, and treatment development is an unmet medical need. Recently, the combination of an anti-PD-L1 (a ligand for programmed cell death 1) antibody and platinum-based chemotherapy has become the standard of care for ES-SCLC patients with a good PS (PS 0-1). We hypothesized that the combination of the anti-PD-L1 antibody durvalumab with carboplatin and etoposide would be feasible and effective for such patients. **Methods:** We initiated a multicenter phase II study of durvalumab combined with carboplatin and etoposide in previously untreated ES-SCLC patients with a poor PS (PS 2-3). Eligible patients will receive durvalumab plus carboplatin and etoposide every 3 to 4 weeks for up to 4 cycles, followed by durvalumab every 4 weeks

until progression or unacceptable toxicity. The dosages of carboplatin and etoposide for the second and subsequent cycles will be adaptively determined based on the adverse events of the first cycle. A total of 56 patients (43 patients with a PS of 2 and 13 patients with a PS of 3) will be enrolled in this study, with a 24-month enrollment period and a 12-month follow-up. The primary endpoint is the tolerability of carboplatin and etoposide plus durvalumab in previously untreated ES-SCLC patients with a poor PS. The secondary endpoints are the 1-year survival rate, objective response rate, progression-free survival, overall survival, ratio of PS improvement, and safety. **Discussion:** The results of this study are intended to establish the safety and efficacy of carboplatin and etoposide plus durvalumab in patients with ES-SCLC and a poor PS.

PALLIATIVE AND SUPPORTIVE CARE

Prognostic Awareness and Discussions of Incurability in Patients with Pretreated Non-Small Cell Lung Cancer and Caregivers: A Prospective Cohort Study Hasegawa T, Okuyama T, Uemura T, et al. Prognostic Awareness and Discussions of Incurability in Patients with Pretreated Non-Small Cell Lung Cancer and Caregivers: A Prospective Cohort Study. *Oncologist*. 2022;27(11):982-990. doi:10.1093/oncolo/oyac178

Background: Although patients with advanced cancer often have poor prognostic awareness, the most effective communication approach for improving prognostic awareness is unclear. In addition, the association between prognostic awareness and preferences for future medical treatment remains unexplored. **Materials and methods:** We performed a prospective observational study of consecutive patients with advanced or post-operative recurrent non-small cell lung cancer whose disease had progressed after first-line chemotherapy, and their caregivers. We evaluated patterns of clinical discussions about incurability, prognostic awareness, and preference for future medical treatment at baseline and 3 months later. **Results:** We obtained 200 valid responses to the questionnaires at baseline and 147 valid responses 3 months later. In addition, 180 caregivers returned valid responses. A total of 54% of patients and 51% of caregivers had accurate awareness at baseline, and 52% of patients had accurate awareness 3 months later. Multiple logistic regression analysis revealed that patients who were informed about incurability in recent and past discussions were significantly more likely to have accurate awareness 3 months later, compared with those who were only informed recently (adjusted odds ratio 5.08; 95% CI, 1.31-19.78; P = .019). Accurate awareness at 3 months was significantly negatively associated with preference for life-prolonging treatment at 3 months after adjusting for covariates (adjusted odds ratio 0.39; 95% CI, 0.17-0.90; P = .028). **Conclusion:** Patients with advanced cancer who had both recent and past discussions about incurability with their oncologists have more accurate prognostic awareness. Improving prognostic awareness could reduce the preference for life-prolonging treatment.

Multicentre, randomised, open-label, parallel-group, clinical phase II study to evaluate immunonutrition in improving efficacy of immunotherapy in patients with metastatic non-small cell lung cancer, undergoing systematic nutritional counseling Caccialanza R, Cereda E, Agustoni F, et al. Multicentre, randomised, open-label, parallel-group, clinical phase II study to evaluate immunonutrition in improving efficacy of immunotherapy in patients with metastatic non-small cell lung cancer, undergoing systematic nutritional counseling. *BMC Cancer*. 2022;22(1):1212. Published 2022 Nov 24. doi:10.1186/s12885-022-10296-x

Background: Nutritional support, including nutritional counseling and oral nutritional supplements (ONS), has been recommended as a first-line strategy in patients with non-small cell lung cancer (NSCLC). Evidence on the efficacy of immunonutrition during immunotherapy in these patients is

positive, but still limited some secondary endpoints, such as treatment toxicity and tolerance. We hypothesize that early systematic provision of ONS with a high-protein-high calorie mixture containing immunonutrients (Impact®) in addition to nutritional counseling, compared to nutritional counseling alone, is beneficial to patients with NSCLC receiving immunotherapy with or without chemotherapy. We designed the present study to evaluate the efficacy of early systematic provision of ONS enriched with immunonutrients compared to nutritional counseling alone, in patients with NSCLC undergoing immunotherapy. Study endpoints were: treatment response (primary endpoint: progression-free survival), treatment tolerance and toxicity, body weight, body composition, protein-calorie intake, quality of life, fatigue, muscle strength and immunological profile. **Methods:** This is a pragmatic, multicentre, randomized (1:1), parallel-group, open label, controlled, pilot clinical trial (N = 180). **Discussion:** The improvement of efficacy of nutritional support in oncology still deserves many efforts. Immunonutrition represents a promising approach also in patients with NSCLC, but evidence on its efficacy on clinical outcomes during immunotherapy is still inconclusive. The present pilot study, which guarantees early high-quality nutritional care (assessment and treatment) to all patients in agreement with current guidelines and recommendations, could represent one of the first proofs of efficacy of early oral immunonutrition in patients with cancer undergoing immunotherapy. Further large randomized trials addressing the improvement of supportive care could be hypothesized, accordingly.

Vocal cord augmentation in a palliative setting for patients with lung cancer and mediastinal involvement

Lauridsen UM, Schultz JDJH, Nyhus CH, Sørensen JR. Vocal cord augmentation in a palliative setting for patients with lung cancer and mediastinal involvement. *Ugeskr Laeger*. 2022;184(47):V05220332. Injection augmentation of the vocal cords is a recognized treatment modality in patients with glottal closure deficiency caused by paresis or paralysis of the vocal cord. The treatment can improve voice quality and also quality of life. It is preferable to minimize waiting time for the procedure for patients with lung cancer and mediastinal involvement, because the one-year mortality is above 40%, as argued in this review.

A Randomized Trial of a Nurse-Led Palliative Care Intervention for Patients with Newly Diagnosed Lung Cancer Reinke LF, Sullivan DR, Slatore C, et al. A Randomized Trial of a Nurse-Led Palliative Care Intervention for Patients with Newly Diagnosed Lung Cancer. *J Palliat Med*. 2022;25(11):1668-1676. doi:10.1089/jpm.2022.0008

Background: Specialist palliative care improves quality of life (QOL), symptom burden, and may prolong survival among patients with advanced lung cancer. Previous trials focused on advanced disease, and less is known about patients across a broad range of stages. ***Objective:*** We sought to assess the effect of a nurse-led telephone-based primary palliative care intervention that focused on patients across a broad range of stages. ***Design, Setting, and Participants:*** We conducted a multisite randomized controlled trial in the United States involving patients diagnosed within two months with any stage or histology of lung cancer to compare the effects of a telephone-based palliative care intervention delivered by registered nurses trained in primary palliative care versus usual care. ***Main Outcomes and Measures:*** The primary outcome was the Functional Assessment of Cancer Therapy-Lung Scale Total Outcome Index (FACT-L TOI), which measures QOL and symptoms. We estimated having 80% power to detect a 5-point change from baseline to three months. Secondary outcome was a change in satisfaction of care, measured by the FAMCARE-P13. ***Results:*** A total of 151 patients were enrolled over 30 months. Patients were, on average, male (98%), age 70 years, White (85%), and 36% diagnosed with stage I-II, and 64% had stage III-IV. In comparison to usual care, patients in the nurse-led intervention did not report improvement in QOL from baseline to three months follow-up or demonstrate differences in treatment effect by site or cancer stage: FACT-L TOI 1.03 (95% confidence interval [CI]: -3.98 to 6.04). Satisfaction with care did

not significantly improve: 0.66 (95% CI: -2.01 to 3.33). ***Conclusions:*** Among patients with newly diagnosed lung cancer, a nurse-led, primary palliative care intervention did not significantly improve QOL, symptom burden, or satisfaction of care. In contrast to several clinical trials demonstrating the effectiveness of delivering specialty palliative care with disease-modifying treatments on QOL among patients with advanced lung cancer, this intervention did not significantly improve QOL among patients with any stage lung cancer. Future research should identify which specific components of primary palliative care improve outcomes for patients newly diagnosed with lung cancer.

Smoking Cessation Interventions Gaddey HL, Dakkak M, Jackson NM. Smoking Cessation Interventions. *Am Fam Physician*. 2022;106(5):513-522.
In the United States, 1 in 5 adults uses tobacco products. Cigarette smoking is the leading cause of preventable disease and death in the United States despite its known health effects. Although nearly one-half of people who smoke try to quit each year, only up to 1 in 20 who quit without support achieve abstinence for at least six months. All patients, including school-aged children and adolescents, should be asked if they smoke and offered evidence-based treatments for smoking cessation. Use of the 5 A's framework (ask, advise, assess, assist, arrange) can help clinicians promote smoking cessation. Clinical studies have demonstrated that combining pharmacotherapy with effective behavior strategies is significantly more effective than either approach alone. Pharmacotherapies approved by the U.S. Food and Drug Administration for smoking cessation include nicotine replacement therapy, bupropion, and varenicline. Extended use (greater than 12 weeks) of a controller therapy (varenicline, bupropion, or nicotine patch) is associated with significantly higher sustained quit rates and lower relapse rates than standard use (six to 12 weeks). e-Cigarettes are not approved by the U.S. Food and Drug Administration for smoking cessation, and evidence supporting their benefit is inconclusive. Lung cancer screening is recommended for adults 50 to 80 years of age who have a 20-pack-year smoking history and currently smoke or have quit within the past 15 years. Lung cancer screening should be combined with smoking cessation tools and treatment.

Video and In-Person Palliative Care Delivery Challenges before and during the COVID-19 Pandemic Chua IS, Olmsted M, Plotke R, et al. Video and In-Person Palliative Care Delivery Challenges before and during the COVID-19 Pandemic. J Pain Symptom Manage. 2022;64(6):577-587. doi:10.1016/j.jpainsymman.2022.08.005
Context: Palliative care (PC) clinicians faced many challenges delivering outpatient care during the coronavirus-19 (COVID-19) pandemic. **Objectives:** We described trends for in-person and video visit PC delivery challenges before and during the COVID-19 pandemic in the U.S. **Methods:** We performed a secondary data analysis of patient characteristics and PC clinician surveys from a multisite randomized controlled trial at 20 academic cancer centers. Patients newly diagnosed with advanced lung cancer (N = 653) were randomly assigned to receive either early in-person or telehealth PC and had at least monthly PC clinician visits. PC clinicians completed surveys documenting PC delivery challenges after each encounter. We categorized patients into 3 subgroups according to their PC visit dates relative to the onset of the COVID-19 pandemic in the U.S.-pre-COVID-19 (all visits before March 1, 2020), pre/post-COVID-19 (≥1 visit before and after March 1, 2020), and post-COVID-19 (all visits after March 1, 2020). We performed Pearson's chi-squared, Fisher's exact, and Kruskal-Wallis tests to examine associations. **Results:** We analyzed 2329 surveys for video visits and 2176 surveys for in-person visits. For video visits, the pre-COVID-19 subgroup (25.8% [46/178]) had the most technical difficulties followed by the pre/post-COVID-19 subgroup (17.2% [307/1784]) and then the post-COVID-19 subgroup (11.4% [42/367]) (P = 0.0001). For in-person visits, challenges related to absent patients' family members occurred most often in the post-COVID-19 subgroup (6.2% [16/259]) followed by the pre/post-COVID-19 subgroup (3.6% [50/1374]) and then the pre-COVID-19 subgroup (2.2% [12/543]) (P = 0.02).

Conclusion: Technical difficulties related to PC video visits improved, whereas in-person visit challenges related to absent patients' family members worsened during the pandemic.

Effects of a yoga-based stress reduction intervention on stress, psychological outcomes and cardiometabolic biomarkers in cancer caregivers: A randomized controlled trial

Lee LJ, Shamburek R, Son H, et al. Effects of a yoga-based stress reduction intervention on stress, psychological outcomes and cardiometabolic biomarkers in cancer caregivers: A randomized controlled trial. *PLoS One*. 2022;17(11):e0277009. Published 2022 Nov 10. doi:10.1371/journal.pone.0277009

Caregiving stress is a risk factor for cardiometabolic disease. Therefore, integrating cardiometabolic biomarkers into caregiving research provides a more comprehensive assessment of an individual's health and response to an intervention. The objective of this study was to examine the effects of a yoga-based stress reduction intervention on stress, psychological outcomes, and cardiometabolic biomarkers in cancer caregivers. This prospective randomized controlled trial enrolled family caregivers of adult patients who underwent an allogeneic HSCT at the National Institutes of Health (NIH) Clinical Center. All subjects received usual care education. Participants in the intervention group received an Iyengar yoga intervention self-administered over six weeks using an audio recording file. The primary outcome was perceived stress (measured using the NIH toolbox Perceived Stress). The secondary outcomes were psychological factors (depression and anxiety measured using PROMIS® Depression and Anxiety), and cardiometabolic biomarkers measured by nuclear magnetic resonance spectroscopy. A total of 50 family caregivers (mean [SD] age, 44.9 [15.2] years; 42 [84.0%] women) were randomized, 25 to the intervention group and 25 to the control group. No group differences were noted in stress, depression, and anxiety. Significant interaction effects between group and time were found in large TRL-P ($F(1,43) = 10.16$, $p = 0.003$) and LP-IR ($F(1,42) = 4.28$, $p = 0.045$). Post-hoc analyses revealed that the levels of large TRL-P (mean difference = 1.68, CI = [0.86, 2.51], p< .001) and LP-IR (mean difference = 5.67, CI = [1.15, 10.18], p = 0.015) significantly increased over time in the control group but while remained stable in the intervention group (mean difference = -0.15, CI = [-0.96, 0.66], p = 0.718; mean difference = -0.81, CI = [-5.22, 3.61], p = 0.714, respectively). Even when perceptions of psychological distress remain unchanged, incorporating gentle yoga poses and breathing exercises may reduce the risk of cardiometabolic disease in caregivers by inhibiting the development of insulin resistance. Standard lipids of cardiometabolic risk do not appear to be robust enough to detect short-term early changes of cardiometabolic risk in caregivers.

COMPLEMENTARY & ALTERNATIVE THERAPY

A Chinese classical prescription Qianjinweijing Decoction in treatment of lung cancer: An overview

Liu P, Zhao Q, Xu Y, et al. A Chinese classical prescription Qianjinweijing Decoction in treatment of lung cancer: An overview. *Biomed Pharmacother*. 2022;156:113913. doi:10.1016/j.biopha.2022.113913

Lung cancer is one of the most common malignant tumors in the world, and its incidence and mortality rate rank among the top malignant tumors worldwide, which has become an important killer threatening human survival rate and well-being. Modern medical treatment for lung cancer is mainly based on surgery and radiotherapy, with gene, targeted drugs and immunotherapy as auxiliary treatments, which are effective, but there are problems such as postoperative recurrence, resistance to radiotherapy, toxic side effects and poor compliance. In recent years, with the continuous development of TCM, TCM is popular among physicians and patients for its high efficiency, low toxicity, low side effects and economic benefits, etc. As a classical TCM formula, Qianjin Weijin Decoction(QJWJ) has certain value in the treatment of lung cancer. This paper summarizes and analyzes the clinical research, molecular mechanism, pharmacological effects and chemical composition of QJWJ in the treatment of lung cancer, in order to provide more ideas and theoretical basis for the treatment of lung cancer with QJWJ.

Phytochemistry, allelopathy and anticancer potentiality of Withania somnifera (L.) Dunal (Solanaceae) Ahmed HA, El-Darier SM. Phytochemistry, allelopathy and anticancer potentiality of Withania somnifera (L.) Dunal (Solanaceae). *Braz J Biol*. 2022;84:e263815. Published 2022 Nov 4. doi:10.1590/1519-6984.263815
Withania somnifera is a wild plant that shows great activity and safety against several human diseases. The current research explored the plant's chemical composition and allelopathic effects on Rumex dentatus (recipient plant). Moreover, anticancer activity is also tested against four types of human cancer cell lines. Chemical analysis of W. somnifera showed a high percentage of saponins and tannins, while glycosides, alkaloids, and flavonoids occurred in the second order. Results of the allelopathic experiments revealed significant inhibition of the R. dentatus plumule and radicle lengths as well as their relative dry weights. In addition, significant reductions in some primary metabolites of R. dentatus, like non-reducing and total sugar as well as soluble proteins, were determined. Cytotoxic potentiality of W. somnifera was also proved against four different cancer lines, namely; human hepatocellular carcinoma cell line (HepG2), human non-small cell lung cancer cell line (A549), human breast cancer cell line (MCF7), and colon cancer cell line (CaCo2) with IC50 value of about 38, 19, 27, and 24 μg/ml, respectively.

MISCELLANEOUS WORKS

Stigma in Early-Stage Lung Cancer Bédard S, Sasewich H, Culling J, et al. Stigma in Early-Stage Lung Cancer. *Ann Behav Med*. 2022;56(12):1272-1283. doi:10.1093/abm/kaac021
Background: The phenomenon of lung cancer stigma has been firmly established in the literature. However, studies have predominantly focused on patients with advanced disease, whose experiences may differ from patients with earlier stage, surgically resectable lung cancer and an improved prognosis. **Purpose:** The objective of the study was to examine the stigma experienced in a Canadian population with early-stage, resectable lung cancer. **Methods:** Patients with newly diagnosed lung cancer were enrolled at a tertiary thoracic surgery clinic. The 25-item Lung Cancer Stigma Inventory (LCSI) was self-administered by patients to quantitatively measure experiences of lung cancer stigma. LCSI results informed the development of a semi-structured focus group and individual interviews. **Results:** Of the 53 participants completing the survey, 38 (72%) met established LCSI score threshold, indicating a clinically meaningful level of stigma. No significant relationship was found between total LCSI scores and any demographic variable. Analysis of qualitative data revealed multiple themes related to experiences of lung cancer stigma. The major themes were classified into four categories: impact of the association between lung cancer and smoking, societal attitudes and assumptions, personal choices in relation to diagnosis, and experiences related to care. **Conclusions:** A surgical population of patients with predominantly early-stage lung cancer experienced lung cancer stigma at a high incidence and a level similar to previously studied populations with more advanced disease. The qualitative results support the quantitative findings that respondents experienced more internal stigma than either perceived stigma from others or constrained disclosure related to their diagnosis.

Sociodemographic Survival Disparities for Lung Cancer in the United States, 2000-2016 Brouwer AF, Engle JM, Jeon J, Meza R. Sociodemographic Survival Disparities for Lung Cancer in the United States, 2000-2016. *J Natl Cancer Inst*. 2022;114(11):1492-1500. doi:10.1093/jnci/djac144
Background: Understanding the impact of patient and tumor characteristics on lung cancer survival can help build personalized prognostic models and identify health disparities. **Methods:** We identified 557 555 patients aged 25 years and older diagnosed with lung or bronchus carcinoma from the Surveillance, Epidemiology, and End Results database, 2000-2016. We estimated hazard ratios (HR) for demographic

(sex, age, race and ethnicity), tumor (stage, histology, year of diagnosis), and geographic characteristics (census tract-level urbanicity, socioeconomic status [SES]), as well as selected interactions, on the rate of lung cancer-specific death using multivariable proportional hazards models. **Results:** Women had a higher survival (lower hazard) of lung cancer-specific death than men (HR = 0.83, 95% confidence interval [CI] = 0.82 to 0.83). Hazards differed by race and ethnicity. Regional (HR = 2.41, 95% CI = 2.37 to 2.44) and distant (HR = 6.61, 95% CI = 6.53 to 6.69) tumors were associated with a lower survival (higher hazard) than localized tumors. Small cell tumors were associated with a lower survival (HR = 1.19, 95% CI = 1.18 to 1.20) than non-small cell tumors. Patients diagnosed after 2009 had lower hazards (HR = 0.86, 95% CI = 085 to 0.86) than those diagnosed 2000-2009. Lung cancer-specific survival did not depend on urbanicity after adjusting for census tract-level SES, but survival decreased with decreasing census tract-level SES. Differences in survival between non-Hispanic Black and White patients were greater for younger patients and localized tumors and increased with census tract-level SES. Differences by sex were greatest for young patients and localized tumors. **Conclusions:** Disparities in survival after lung cancer diagnosis remain, with intersectional patterns suggesting differential access to and quality of care. Efforts are needed to ensure that high-risk groups receive guideline-concordant treatment.

Recent Trends in Synchronous Brain Metastasis Incidence and Mortality in the United States: Ten-Year Multicenter Experience Che W, Liu J, Fu T, Wang X, Lyu J. Recent Trends in Synchronous Brain Metastasis Incidence and Mortality in the United States: Ten-Year Multicenter Experience. *Curr Oncol*. 2022;29(11):8374-8389. Published 2022 Nov 2. doi:10.3390/curroncol29110660
Background: Large epidemiological studies describing the trends in incidence rates and mortality of synchronous brain metastases (SBMs) are lacking. The study aimed to provide a comprehensive understanding of the changes in the incidence and mortality of SBMs over the previous ten years. **Methods:** Trends in the incidence of solid malignancies outside of the CNS in patients with SBMs and incidence-based mortality rates were assessed using data from the Surveillance, Epidemiology, and End Results database. Joinpoint analyses were used to calculate annual percent changes (APCs) and 95% CIs. **Results:** Between 2010 and 2019, 66,655 patients, including 34,821 (52.24%) men and 31,834 (47.76%) women, were found to have SBMs, and 57,692 deaths occurred over this period. Lung cancer SBMs, melanoma SBMs, and breast cancer SBMs were ranked in the top three, having the highest age-standardized incidence rates. The incidence of SBMs decreased significantly with an APC of -0.6% from 2010 to 2019, while the APC was 1.2% for lung cancer SBMs, 2.5% for melanoma SBMs, and 0.6% for breast cancer SBMs. The SBM mortality first experienced a rapid increase (APC = 28.6%) from 2010 to 2012 and then showed a significant decline at an APC of -1.8% from 2012 to 2019. Lung cancer SBMs showed similar trends, while melanoma SBM and breast cancer SBM mortality increased continuously. **Conclusions:** SBMs incidence (2010-2019) and incidence-based mortality (2012-2019) declined significantly. These findings can advance our understanding of the prevalence of SBMs.

Body mass index and incidence of lung cancer in the HUNT study: using observational and Mendelian randomization approaches Jiang L, Sun YQ, Brumpton BM, Langhammer A, Chen Y, Mai XM. Body mass index and incidence of lung cancer in the HUNT study: using observational and Mendelian randomization approaches. BMC Cancer. 2022;22(1):1152. Published 2022 Nov 8. doi:10.1186/s12885-022-10215-0
Background: Traditional observational studies have shown an inverse association between body mass index (BMI) and lung cancer risk. Mendelian randomization (MR) analysis using genetic variants as instruments for BMI may clarify the nature of the association. **Aims:** We studied the causal association between BMI and lung cancer incidence using observational and MR approaches. **Methods:** We followed up 62,453 cancer-free Norwegian adults from 1995-97 (HUNT2) until 2017. BMI at baseline in HUNT2 was classified as < 25.0, 25.0-29.9 and ≥ 30.0 kg/m^2. BMI change over ten years between HUNT1 (1984-

86) and HUNT2 was calculated and classified into quartiles. Seventy-five genetic variants were included as instruments for BMI (among which 14 also associated with smoking behavior). Incident lung cancer cases were ascertained from the Cancer Registry of Norway. Cox regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). Multivariable MR was used to examine the effect of BMI after genetically controlling for smoking. **Results:** During a median follow-up of 21.1 years, 1009 participants developed lung cancer including 327 with lung adenocarcinoma. The HRs and 95% CIs for incidence of adenocarcinoma were 0.73 (0.58-0.92) for BMI 25.0-29.9 kg/m^2 and 0.53 (0.37-0.76) for BMI ≥ 30 kg/m^2 compared with BMI < 25.0 kg/m^2 in HUNT2 (P for trend < 0.001). However, there was little evidence of a dose-response relationship between the BMI change from HUNT1 to HUNT2 in quartiles and the incidence of adenocarcinoma (P for trend = 0.08). Furthermore, multivariable MR approach suggested a positive association between genetically determined 1 kg/m^2 increase in BMI and the incidence of adenocarcinoma (HR 1.25, 95% CI 1.02-1.53). No associations were found with other lung cancer histologic types. **Conclusions:** Our study suggests that the inverse association between baseline BMI and lung adenocarcinoma in observational analysis may not be causal. More MR studies are needed to confirm our finding of a positive association between BMI and lung adenocarcinoma.

COVID-19 Candidate Genes and Pathways Potentially Share the Association with Lung Cancer

Alnajeebi AM, Alharbi HFH, Alelwani W, et al. COVID-19 Candidate Genes and Pathways Potentially Share the Association with Lung Cancer. *Comb Chem High Throughput Screen*. 2022;25(14):2463-2472. doi:10.2174/1386207324666210712092649

COVID-19 is considered as the most challenging in the current situation but lung cancer is also the leading cause of death in the global population. These two malignancies are among the leading human diseases and are highly complex in terms of diagnostic and therapeutic approaches as well as the most frequent and highly complex and heterogeneous in nature. Based on the latest update, it is known that the patients suffering from lung cancer, are considered to be significantly at higher risk of COVID-19 infection in terms of survival and there are a number of evidences which support the hypothesis that these diseases may share the same functions and functional components. Multi-level unwanted alterations such as (epi-)genetic alterations, changes at the transcriptional level, and altered signaling pathways (receptor, cytoplasmic, and nuclear level) are the major sources which promote a number of complex diseases and such heterogeneous level of complexities are considered as the major barrier in the development of therapeutics. With so many challenges, it is critical to understand the relationships and the common shared aberrations between them which is difficult to unravel and understand. A simple approach has been applied for this study where differential gene expression analysis, pathway enrichment, and network level understanding are carried out. Since, gene expression changes and genomic alterations are related to the COVID-19 and lung cancer but their pattern varies significantly. Based on the recent studies, it appears that the patients suffering from lung cancer and and simultaneously infected with COVID-19, then survival chance is lessened. So, we have designed our goal to understand the genes commonly overexpressed and commonly enriched pathways in case of COVID-19 and lung cancer. For this purpose, we have presented the summarized review of the previous works where the pathogenesis of lung cancer and COVID-19 infection have been focused and we have also presented the new finding of our analysis. So, this work not only presents the review work but also the research work. This review and research study leads to the conclusion that growth promoting pathways (EGFR, Ras, and PI3K), growth inhibitory pathways (p53 and STK11), apoptotic pathways (Bcl- 2/Bax/Fas), and DDR pathways and genes are commonly and dominantly altered in both the cases COVID-19 and lung cancer.

Small nodules (≤ 6 mm in diameter) of multiple primary lung cancers: prevalence and management

Cheng H, Li WH, Li XJ, et al. Small nodules (≤ 6 mm in diameter) of multiple primary lung cancers:

prevalence and management. *J Cardiothorac Surg*. 2022;17(1):278. Published 2022 Nov 1. doi:10.1186/s13019-022-02022-2

Background: Synchronous multiple primary lung cancers associated with small non-dominant nodules are commonly encountered. However, the incidence, follow-up, and treatment of small non-dominant tumors have been but little studied. We explored the prevalence and management of small non-dominant tumors and factors associated with interval growth. **Methods:** This observational, consecutive, retrospective single-center study enrolled patients diagnosed with synchronous multiple primary lung cancers and small non-dominant tumors (≤ 6 mm in diameter) who underwent resection of the dominant tumor. The incidence, follow-up, and management of small non-dominant tumors and predictors of nodule growth were analyzed. **Results:** There were 88 patients (12% of all lung cancer patients) with pathological diagnoses of synchronous multiple primary lung cancers. A total of 131 (18%) patients were clinically diagnosed with at least one small (≤ 6 mm in diameter) multiple primary lung cancer non-dominant tumor. 94 patients with 125 small-nodule non-dominant tumors clinically diagnosed as multiple primary lung cancers were followed-up for at least 6 months. A total of 29 (29/125, 23.2%) evidenced small pulmonary nodules (≤ 6 mm in diameter) that exhibited interval growth on follow-up computed tomography (CT). On multivariate analysis, a part-solid nodule (compared to a pGGN) (OR 1.23; 95% CI 1.08-1.40) or a solid nodule (compared to a pGGN) (OR 3.50; 95% CI 1.94-6.30) predicted small nodule interval growth. **Conclusion:** We found a relatively high incidence of multiple primary lung cancers with small non-dominant tumors exhibiting interval growth on follow-up CT, suggesting that resection of non-dominant tumors at the time of dominant tumor resection, especially when the nodules are part-solid or solid, is the optimal treatment.

Leveraging the Clinical Timepoints in Lung Cancer Screening to Engage Individuals in Tobacco Treatment

Park ER, Neil JM, Noonan E, et al. Leveraging the Clinical Timepoints in Lung Cancer Screening to Engage Individuals in Tobacco Treatment. *JNCI Cancer Spectr*. 2022;6(6):pkac073. doi:10.1093/jncics/pkac073

The US Preventive Services Task Force recommends lung cancer screening (LCS) to promote early lung cancer detection, and tobacco cessation services are strongly recommended in adjunct. Screen ASSIST (NCT03611881) is a randomized factorial trial to ascertain the best tobacco treatment intervention for smokers undergoing LCS; trial outreach is conducted during 3 recruitment points (RPs): when LCS is ordered (RP1), at screening (RP2), and following results (RP3). Among 177 enrollees enrolled from April 2019 to March 2020, 31.6% enrolled at RP1, 13.0% at RP2, and 55.4% at RP3. The average number of enrollees (per 1000 recruitment days) was 2.26 in RP1, 3.37 in RP2, and 1.04 in RP3. LCS provides an opportunity to offer tobacco treatment at multiple clinical timepoints. Repeated and proactive outreach throughout the LCS experience was beneficial to enrolling patients in tobacco cessation services.

A population-based study on social inequality and barriers to healthcare-seeking with lung cancer symptoms Sætre LMS, Rasmussen S, Balasubramaniam K, Søndergaard J, Jarbøl DE. A population-based study on social inequality and barriers to healthcare-seeking with lung cancer symptoms. *NPJ Prim Care Respir Med*. 2022;32(1):48. Published 2022 Nov 5. doi:10.1038/s41533-022-00314-7

Healthcare-seeking with lung cancer symptoms is a prerequisite for improving timely diagnosis of lung cancer. In this study we aimed to explore barriers towards contacting the general practitioner (GP) with lung cancer symptoms, and to analyse the impact of social inequality. The study is based on a nationwide survey with 69,060 individuals aged ≥40 years, randomly selected from the Danish population. The survey included information on lung cancer symptoms, GP contacts, barriers to healthcare-seeking and smoking status. Information about socioeconomics was obtained by linkage to Danish Registers. Descriptive statistics and multivariate logistic regression model were used to analyse the data. "Being too

busy" and "Being worried about wasting the doctor's time" were the most frequent barriers to healthcare-seeking with lung cancer symptoms. Individuals out of workforce and individuals who smoked more often reported "Being worried about what the doctor might find" and "Being too embarrassed" about the symptoms. The social inequality in barriers to healthcare-seeking with lung cancer symptoms is noticeable, which emphasises the necessity of focus on vulnerable groups at risk of postponing relevant healthcare-seeking.

Accelerating integration of tobacco use treatment in the context of lung cancer screening: Relevance and application of implementation science to achieving policy and practice
Shelley D, Wang VH, Taylor K, et al. Accelerating integration of tobacco use treatment in the context of lung cancer screening: Relevance and application of implementation science to achieving policy and practice. *Transl Behav Med*. 2022;12(11):1076-1083. doi:10.1093/tbm/ibac076
Based on the findings from the National Lung Screening Trial, the U.S. Preventive Services Task Force recommends annual low dose computed tomography (LDCT) lung cancer screening (LCS) among high-risk adults. Approximately 54% of individuals seeking LCS report current cigarette smoking. Effective smoking cessation interventions, offered at the time of LCS, enhances the health benefits of screening that are attributable to reductions in lung cancer overall and tobacco-related mortality. Considering these data, the Centers for Medicare & Medicaid Services' (CMS) 2015 decision to cover LCS with LDCT required that radiology imaging facilities make tobacco cessation interventions available for people who smoke. In February 2022, CMS reversed their 2015 coverage requirement for delivering tobacco use treatment at the time of LDCT; CMS retained the requirement for counseling during the shared decision-making visit prior to the exam. The policy change does not diminish the importance of offering high-quality tobacco cessation services in conjunction with routine LDCT for LCS. However, LCS programs face a range of barriers to implementing tobacco use treatment in their settings. As a result, implementation has lagged. Closing the "evidence to practice" gap is the focus of implementation science, a field that offers a set of rigorous methods and a systematic approach to identifying and overcoming contextual barriers to implementing evidence-based guidelines in a range of clinical settings. In this paper, we describe how implementation science frameworks and methods can be used to help guide LCS programs in their efforts to integrate tobacco use treatment and discuss policy changes needed to further facilitate the delivery of TUT as an essential component of the LCS process.

The Impact of COVID-19 on the Diagnosis and Treatment of Lung Cancer over a 2-Year Period at a Canadian Academic Center Kasymjanova G, Rizzolo A, Pepe C, et al. The Impact of COVID-19 on the Diagnosis and Treatment of Lung Cancer over a 2-Year Period at a Canadian Academic Center. *Curr Oncol*. 2022;29(11):8677-8685. Published 2022 Nov 14. doi:10.3390/curroncol29110684
Background: We have recently reported a 35% drop in new lung cancer diagnoses and a 64% drop in lung cancer surgeries during the first year of the pandemic. **Methods:** The target population was divided into three cohorts: pre-COVID-19 (2019), first year of COVID-19 (2020), and second year of COVID-19 (2021). **Results:** The number of new lung cancer diagnoses during the second year of the pandemic increased by 75%, with more than 50% being in the advanced/metastatic stage. There was a significant increase in cases with multiple extrathoracic sites of metastases during the pandemic. During the first year of the pandemic, significantly more patients were treated with radiosurgery compared to the pre-COVID-19 year. During the second year, the number of radiosurgery and surgical cases returned to pre-COVID-19 levels. No significant changes were observed in systemic chemotherapy and targeted therapy. No statistical difference was identified in the mean wait time for diagnosis and treatment during the three years of observation. However, the wait time for surgery was prolonged compared to the pre-COVID-19 cohort. **Conclusions:** The significant drop in new diagnoses of lung cancer during the first year of the pandemic was followed by an almost two-fold increase in the second year, with the increased rate of

metastatic disease with multiple extra-thoracic site metastases. Limited access to surgery resulted in the more frequent use of radiosurgery.

Transportability of Overall Survival Estimates From US to Canadian Patients With Advanced Non-Small Cell Lung Cancer With Implications for Regulatory and Health Technology Assessment

Ramagopalan SV, Popat S, Gupta A, et al. Transportability of Overall Survival Estimates From US to Canadian Patients With Advanced Non-Small Cell Lung Cancer With Implications for Regulatory and Health Technology Assessment. *JAMA Netw Open*. 2022;5(11):e2239874. Published 2022 Nov 1. doi:10.1001/jamanetworkopen.2022.39874

Importance: The external validity of survival outcomes derived from clinical practice data from US patients with advanced non-small cell lung cancer (NSCLC) is not known and is of potential importance because it may be used to support regulatory decision-making and health technology assessment outside of the US. **Objective:** To evaluate whether overall survival (OS) estimates for a selected group of patients with advanced NSCLC from a large US clinical practice database are transportable to Canadian patients receiving the same systemic therapies. **Design, setting, and participants:** This retrospective multicenter cohort study used transportability analysis to assess whether adjustment for pretreatment characteristics of eligible patient cohorts could reliably approximate OS estimated from US-based samples to Canadian populations. A total of 17 432 eligible adult patients who were diagnosed de novo with advanced NSCLC on or after January 1, 2011, were included in the analysis and followed up until September 30, 2020. Because data on race and ethnicity were available in the US database but not the Canadian database and because racial and ethnic distribution was likely to be similar between US and Canadian patients, these characteristics were not analyzed. **Exposures:** Initiation of platinum-doublet chemotherapy or pembrolizumab monotherapy as first-line systemic treatment for advanced NSCLC. **Main outcomes and measures:** OS measured from the time of initiation of the respective treatment regimen. **Results:** Among 17 432 eligible patients, 15 669 patients from the US and 1763 patients from Canada were included in the analysis. Of those, 11 863 patients (sample size-weighted estimates of mean [SD] age, 68.0 [9.3] years; 6606 [55.7%] male; 10 100 from the US and 1763 from Canada) were included in the subset of patients with complete data for baseline covariates. A total of 13 532 US patients received first-line chemotherapy, and 2137 received first-line pembrolizumab monotherapy. Of those, 8447 patients (62.4%) in the first-line chemotherapy group and 1653 patients (77.3%) in the first-line pembrolizumab group had complete data on baseline covariates for outcome model estimation. A total of 1476 Canadian patients who received first-line chemotherapy and 287 patients who received first-line pembrolizumab monotherapy were identified from the target population. After standardization to baseline patient covariates in the Canadian cohorts, transported OS estimates revealed a less than 5% mean absolute difference from the observed OS in the target population (0.56% over 60 months of follow-up in the first-line chemotherapy group and 4.54% over 30 months of follow-up in the first-line pembrolizumab group). Negative control analysis using a mismatched outcome model revealed a 6.64% discrepancy and an incompatible survival curve shape. The results were robust to assumptions of random missingness for baseline covariates, to unadjusted differences in baseline metastases and comorbidities, and to differences in the standard of care between the US and Canada related to administration of second-line anti-programmed cell death 1 ligand 1 immunotherapy for patients who initiated first-line chemotherapy. **Conclusions and relevance:** The results of this cohort study suggest that, under specific circumstances, OS estimates from US clinical practice data can be adjusted using baseline clinical characteristics to closely approximate OS in selected groups of Canadian patients with advanced NSCLC. These results may have implications for regulatory decision-making and health technology assessment in target populations outside of the US.

Annual Report to the Nation on the Status of Cancer, Part 1: National Cancer Statistics

Islami F, Ward EM, Sung H, et al. Annual Report to the Nation on the Status of Cancer, Part 1: National Cancer Statistics. *J Natl Cancer Inst*. 2021;113(12):1648-1669. doi:10.1093/jnci/djab131

Background: The American Cancer Society, Centers for Disease Control and Prevention, National Cancer Institute, and North American Association of Central Cancer Registries collaborate to provide annual updates on cancer incidence and mortality and trends by cancer type, sex, age group, and racial/ethnic group in the United States. In this report, we also examine trends in stage-specific survival for melanoma of the skin (melanoma). **Methods:** Incidence data for all cancers from 2001 through 2017 and survival data for melanoma cases diagnosed during 2001-2014 and followed-up through 2016 were obtained from the Centers for Disease Control and Prevention- and National Cancer Institute-funded population-based cancer registry programs compiled by the North American Association of Central Cancer Registries. Data on cancer deaths from 2001 to 2018 were obtained from the National Center for Health Statistics' National Vital Statistics System. Trends in age-standardized incidence and death rates and 2-year relative survival were estimated by joinpoint analysis, and trends in incidence and mortality were expressed as average annual percent change (AAPC) during the most recent 5 years (2013-2017 for incidence and 2014-2018 for mortality). **Results:** Overall cancer incidence rates (per 100 000 population) for all ages during 2013-2017 were 487.4 among males and 422.4 among females. During this period, incidence rates remained stable among males but slightly increased in females (AAPC = 0.2%, 95% confidence interval [CI] = 0.1% to 0.2%). Overall cancer death rates (per 100 000 population) during 2014-2018 were 185.5 among males and 133.5 among females. During this period, overall death rates decreased in both males (AAPC = -2.2%, 95% CI = -2.5% to -1.9%) and females (AAPC = -1.7%, 95% CI = -2.1% to -1.4%); death rates decreased for 11 of the 19 most common cancers among males and for 14 of the 20 most common cancers among females, but increased for 5 cancers in each sex. During 2014-2018, the declines in death rates accelerated for lung cancer and melanoma, slowed down for colorectal and female breast cancers, and leveled off for prostate cancer. Among children younger than age 15 years and adolescents and young adults aged 15-39 years, cancer death rates continued to decrease in contrast to the increasing incidence rates. Two-year relative survival for distant-stage skin melanoma was stable for those diagnosed during 2001-2009 but increased by 3.1% (95% CI = 2.8% to 3.5%) per year for those diagnosed during 2009-2014, with comparable trends among males and females. **Conclusions:** Cancer death rates in the United States continue to decline overall and for many cancer types, with the decline accelerated for lung cancer and melanoma. For several other major cancers, however, death rates continue to increase or previous declines in rates have slowed or ceased. Moreover, overall incidence rates continue to increase among females, children, and adolescents and young adults. These findings inform efforts related to prevention, early detection, and treatment and for broad and equitable implementation of effective interventions, especially among under resourced populations.

The Rocky Road from Preclinical Findings to Successful Targeted Therapy in Pleural Mesothelioma

Paajanen J, Bueno R, De Rienzo A. The Rocky Road from Preclinical Findings to Successful Targeted Therapy in Pleural Mesothelioma. *Int J Mol Sci*. 2022;23(21):13422. Published 2022 Nov 3. doi:10.3390/ijms232113422

Pleural mesothelioma (PM) is a rare and aggressive disease that arises from the mesothelial cells lining the pleural cavity. Approximately 80% of PM patients have a history of asbestos exposure. The long latency period of 20-40 years from the time of asbestos exposure to diagnosis, suggests that multiple somatic genetic alterations are required for the tumorigenesis of PM. The genomic landscape of PM has been characterized by inter- and intratumor heterogeneity associated with the impairment of tumor suppressor genes such as *CDKN2A*, *NF2*, and *BAP1*. Current systemic therapies have shown only limited efficacy, and none is approved for patients with relapsed PM. Advances in understanding of the molecular landscape of PM has facilitated several biomarker-driven clinical trials but so far, no predictive

biomarkers for targeted therapies are in clinical use. Recent advances in the PM genetics have provided optimism for successful molecular strategies in the future. Here, we summarize the molecular mechanism underlying PM pathogenesis and review potential therapeutic targets.

Estimation of the Number of Individuals Living With Metastatic Cancer in the United States

Gallicchio L, Devasia TP, Tonorezos E, Mollica MA, Mariotto A. Estimation of the Number of Individuals Living With Metastatic Cancer in the United States. *J Natl Cancer Inst*. 2022;114(11):1476-1483. doi:10.1093/jnci/djac158

Background: The purpose of this study was to estimate the number of individuals living with metastatic breast, prostate, lung, colorectal, or bladder cancer or metastatic melanoma in the United States using population-based data. **Methods:** A back-calculation method was used to estimate the number of individuals living with metastatic cancer for each cancer type from US cancer mortality and survival statistics from the Surveillance, Epidemiology, and End Results registries. The percentages of those living with metastatic cancer who advanced to metastatic disease from early stage cancer vs who were diagnosed with metastatic cancer de novo were calculated. One- and 5-year relative survival rates for de novo metastatic cancer were compared by year of diagnosis to assess time trends in survival. **Results:** It is estimated that, in 2018, 623 405 individuals were living with metastatic breast, prostate, lung, colorectal, or bladder cancer, or metastatic melanoma in the United States. This number is expected to increase to 693 452 in 2025. In 2018, the percentage of metastatic cancer survivors who were initially diagnosed with early stage cancer and advanced to metastatic cancer ranged from 30% for lung cancer to 72% for bladder cancer. **Conclusions:** This study demonstrates increasing numbers of individuals living with metastatic cancer of the 6 most common cancer types in the United States. This information is critical for informing the allocation of research efforts and healthcare infrastructure needed to address the needs of these individuals.

Evaluation of a National Quality Improvement Collaborative for Improving Cancer Screening

Joung RH, Mullett TW, Kurtzman SH, et al. Evaluation of a National Quality Improvement Collaborative for Improving Cancer Screening. *JAMA Netw Open*. 2022;5(11):e2242354. Published 2022 Nov 1. doi:10.1001/jamanetworkopen.2022.42354

Importance: Cancer screening deficits during the first year of the COVID-19 pandemic were found to persist into 2021. Cancer-related deaths over the next decade are projected to increase if these deficits are not addressed. **Objective:** To assess whether participation in a nationwide quality improvement (QI) collaborative, Return-to-Screening, was associated with restoration of cancer screening. **Design, setting, and participants:** Accredited cancer programs electively enrolled in this QI study. Project-specific targets were established on the basis of differences in mean monthly screening test volumes (MTVs) between representative prepandemic (September 2019 and January 2020) and pandemic (September 2020 and January 2021) periods to restore prepandemic volumes and achieve a minimum of 10% increase in MTV. Local QI teams implemented evidence-based screening interventions from June to November 2021 (intervention period), iteratively adjusting interventions according to their MTVs and target. Interrupted time series analyses was used to identify the intervention effect. Data analysis was performed from January to April 2022. **Exposures:** Collaborative QI support included provision of a Return-to-Screening plan-do-study-act protocol, evidence-based screening interventions, QI education, programmatic coordination, and calculation of screening deficits and targets. **Main outcomes and measures:** The primary outcome was the proportion of QI projects reaching target MTV and counterfactual differences in the aggregate number of screening tests across time periods. **Results:** Of 859 cancer screening QI projects (452 for breast cancer, 134 for colorectal cancer, 244 for lung cancer, and 29 for cervical cancer) conducted by 786 accredited cancer programs, 676 projects (79%) reached their target MTV. There were no hospital characteristics associated with increased likelihood of reaching target MTV except for disease

site (lung vs breast, odds ratio, 2.8; 95% CI, 1.7 to 4.7). During the preintervention period (April to May 2021), there was a decrease in the mean MTV (slope, -13.1 tests per month; 95% CI, -23.1 to -3.2 tests per month). Interventions were associated with a significant immediate (slope, 101.0 tests per month; 95% CI, 49.1 to 153.0 tests per month) and sustained (slope, 36.3 tests per month; 95% CI, 5.3 to 67.3 tests per month) increase in MTVs relative to the preintervention trends. Additional screening tests were performed during the intervention period compared with the prepandemic period (170 748 tests), the pandemic period (210 450 tests), and the preintervention period (722 427 tests). **Conclusions and relevance:** In this QI study, participation in a national Return-to-Screening collaborative with a multifaceted QI intervention was associated with improvements in cancer screening. Future collaborative QI endeavors leveraging accreditation infrastructure may help address other gaps in cancer care.

The burden and impact of chronic cough in severe disease
Emilsson ÖI. The burden and impact of chronic cough in severe disease. *Curr Opin Support Palliat Care*. 2022;16(4):183-187. doi:10.1097/SPC.0000000000000623
Purpose of review: Chronic cough is common in severe diseases, such as COPD, interstitial lung disease, lung cancer and heart failure, and has a negative effect on quality of life. In spite of this, patients with cough sometimes feel their cough is neglected by healthcare workers. This review aims to briefly describe cough mechanisms, highlight the burden chronic cough can be for the individual, and the clinical impact of chronic cough. **Recent findings:** Chronic cough is likely caused by different mechanisms in different diseases, which may have therapeutic implications. Chronic cough, in general, has a significant negative effect on quality of life, both with and without a severe comorbid disease. It can lead to social isolation, recurrent depressive episodes, lower work ability, and even conditions such as urinary incontinence. Cough may also be predictive of more frequent exacerbations among patients with COPD, and more rapid lung function decline in idiopathic pulmonary fibrosis. Cough is sometimes reported by patients to be underappreciated by healthcare. **Summary:** Chronic cough has a significant negative impact on quality of life, irrespective of diagnosis. Some differences are seen between patients with and without severe disease. Healthcare workers need to pay specific attention to cough, especially patients with severe disease.

Management of Cancer Patients in the COVID-19 Crisis Using Telemedicine: A Systematic Review
Salehi F, Mashhadi L, Khazeni K, Ebrahimi Z. Management of Cancer Patients in the COVID-19 Crisis Using Telemedicine: A Systematic Review. *Stud Health Technol Inform*. 2022;299:118-125. doi:10.3233/SHTI220969
Background: Telemedicine can provide a solution for disease management during the COVID-19 pandemic. This literature review aims to explore the role of telemedicine during the COVID-19 pandemic for management of cancer patients. **Method:** A comprehensive systematic search was conducted in PubMed, Science Direct, EMBASE, and Web of Science databases for the papers published until April 2021. Studies were included in case they had practically used telemedicine in the management of cancer patients during the COVID-19 crisis. **Results:** After screening 2614 titles and abstracts and reviewing 305 full-texts, 16 studies were found to be eligible. The results indicated that most of the patients contacted by telemedicine services mostly used to intract with patients breast cancer (n=4, 25%). The most common use of telemedicine was the provision of virtual visit services (n=10, 62.25%). Besides, communication was most frequently provided by live video conferences (n=11, 68.75%).**Conclusion:** Telemedicine can provide continued access to necessary health services in oncology care and serve as an important role in pandemic planning and response.

Association Between Cancer Center Accreditation and Compliance With Price Disclosure of Common Oncologic Surgical Procedures Zhang Y, Cerullo M, Esposito A, Golla V. Association

Between Cancer Center Accreditation and Compliance With Price Disclosure of Common Oncologic Surgical Procedures. *J Natl Compr Canc Netw*. 2022;20(11):1215-1222.e1. doi:10.6004/jnccn.2022.7057
Background: Cancer center accreditation status is predicated on several factors that measure high-value healthcare. However, price transparency, which is critical in healthcare decisions, is not a quality measure included for accreditation. We reported the rates of price disclosure of surgical procedures for 5 cancers (breast, lung, cutaneous melanoma, colon, and prostate) among hospitals ranked by the American College of Surgeon's Commission on Cancer (ACS-CoC). **Methods:** We identified nonfederal, adult, and noncritical access ACS-CoC accredited hospitals and used the commercial Turquoise Health database to perform a cross-sectional analysis of hospital price disclosures for 5 common oncologic procedures (mastectomy, lobectomy, wide local excision for cutaneous melanoma, partial colectomy, prostatectomy). Publicly available financial reporting data were used to compile facility-specific features, including bed size, teaching status, Centers for Medicare & Medicaid wage index, and patient revenues. Modified Poisson regression evaluated the association between price disclosure and ACS-CoC accreditation after adjusting for hospital financial performance. **Results:** Of 1,075 total ACS-CoC accredited hospitals, 544 (50.6%) did not disclose prices for any of the surgical procedures and only 313 (29.1%) hospitals reported prices for all 5 procedures. Of the 5 oncologic procedures, prostatectomy and lobectomy had the lowest price disclosure rates. Disclosing and nondisclosing hospitals significantly differed in ACS-CoC accreditation, ownership type, and teaching status. Hospitals that disclosed prices were more likely to receive Medicaid disproportionate share hospital payments, have lower average charge to cost ratios (4.53 vs 5.15; P<.001), and have lower net hospital margins (-2.03 vs 0.44; P=.005). After adjustment, a 1-point increase in markup was associated with a 4.8% (95% CI, 2.2%-7.4%; P<.001) higher likelihood of nondisclosure. **Conclusions:** More than half of the hospitals did not disclose prices for any of the 5 most common oncologic procedures despite ACS-CoC accreditation. It remains difficult to obtain price transparency for common oncologic procedures even at centers of excellence, signaling a discordance between quality measures visible to patients.