Caring Ambassadors Lung Cancer Program
Literature Review, November 2022

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SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

Lung Cancer Screening Choi HK, Mazzone PJ. Lung Cancer Screening. Med Clin North Am. 2022 Nov;106(6):1041-1053. doi: 10.1016/j.mcna.2022.07.007. Epub 2022 Oct 4. PMID: 36280331.
Lung cancer screening with low-dose computed tomography (LDCT) reduces lung cancer deaths by early detection. The United States Preventive Services Task Force recommends lung cancer screening with LDCT in adults of age 50 years to 80 years who have at least a 20 pack-year smoking history and are currently smoking or have quit within the past 15 years. The implementation of a lung-cancer-screening program is complex. High-quality screening requires the involvement of a multidisciplinary team. The aim of a screening program is to find balance between mortality reduction and avoiding potential harms related to false-positive findings, overdiagnosis, invasive procedures, and radiation exposure. Components and processes of a high-quality lung-cancer-screening program include the identification of eligible individuals, shared decision-making, performing and reporting LDCT results, management of screen-detected lung nodules and non-nodule findings, smoking cessation, ensuring adherence, data collection, and quality improvement.

Liquid-based rapid onsite evaluation of endobronchial ultrasound cytologies Bai S, Millis M, Wilson S, Scott M, Goulart RA, Maxfield MW, Lou F, Sood RN, Fischer AH. Liquid-based rapid onsite evaluation of endobronchial ultrasound cytologies. J Am Soc Cytopathol. 2022 Nov-Dec;11(6):375-384. doi: 10.1016/j.jasc.2022.07.004. Epub 2022 Jul 12. PMID: 36055932.
INTRODUCTION: Rapid onsite evaluation (ROSE) generally uses smears made at the site of the procedure ("smear-based ROSE"). It requires considerable time, generally 2 individuals, technical expertise, and it can be difficult to estimate material available for ancillary studies. We developed an alternative ROSE using liquid-based cytology ThinPrep with hematoxylin and eosin (H&E) stain ("liquid-based ROSE") and assessed its advantages. **MATERIALS AND METHODS**: Clinicians rinse the sample(s) into CytoRich Red and send to Pathology. A defined proportion of the needle rinse is removed for a ThinPrep stained with a rapid H&E. Adequacy and diagnosis were compared to final outcome. Total time was recorded. **RESULTS**: Among 52 liquid-based ROSE readings, 28 (53.8%) were interpreted as "adequate" with final as adequate; 17 (32.7%) were interpreted as "inadequate" with final as

inadequate; 7 (13.5%) were interpreted as "inadequate" with final as adequate. Of 23 readings provided with onsite diagnosis, 15 (65.2%) were interpreted as definitive positive or negative diagnoses; 6 (26%) were interpreted as nondiagnostic; and 2 (8.7%) were interpreted as atypical. All definitive diagnoses were concordant with final diagnoses. The time for liquid ROSE performance ranges from 6 to 22 minutes (mean: 13 minutes) and required only 1 individual. **CONCLUSIONS**: Liquid-based ROSE allows accurate adequacy determination and diagnosis, takes about 15 minutes of cytologist time, and can be performed by just 1 person. The technique produces well-preserved and stained slides, it may allow a better estimation of the total amount of material in the specimen vial and may provide a better platform for telecytology.

Advances in Multimodality Imaging in Cardio-Oncology: JACC State-of-the-Art Review
Baldassarre LA, Ganatra S, Lopez-Mattei J, Yang EH, Zaha VG, Wong TC, Ayoub C, DeCara JM, Dent S, Deswal A, Ghosh AK, Henry M, Khemka A, Leja M, Rudski L, Villarraga HR, Liu JE, Barac A, Scherrer-Crosbie M; ACC Cardio-Oncology and the ACC Imaging Councils. Advances in Multimodality Imaging in Cardio-Oncology: JACC State-of-the-Art Review. J Am Coll Cardiol. 2022 Oct 18;80(16):1560-1578. doi: 10.1016/j.jacc.2022.08.743. PMID: 36229093.
The population of patients with cancer is rapidly expanding, and the diagnosis and monitoring of cardiovascular complications greatly rely on imaging. Numerous advances in the field of cardio-oncology and imaging have occurred in recent years. This review presents updated and practical approaches for multimodality cardiovascular imaging in the cardio-oncology patient and provides recommendations for imaging to detect the myriad of adverse cardiovascular effects associated with antineoplastic therapy, such as cardiomyopathy, atherosclerosis, vascular toxicity, myocarditis, valve disease, and cardiac masses. Uniquely, we address the role of cardiovascular imaging in patients with pre-existing cardiomyopathy, pregnant patients, long-term survivors, and populations with limited resources. We also address future avenues of investigation and opportunities for artificial intelligence applications in cardio-oncology imaging. This review provides a uniform practical approach to cardiovascular imaging for patients with cancer.

Predictive Model to Guide Brain Magnetic Resonance Imaging Surveillance in Patients With Metastatic Lung Cancer: Impact on Real-World Outcomes Wu J, Ding V, Luo S, Choi E, Hellyer J, Myall N, Henry S, Wood D, Stehr H, Ji H, Nagpal S, Hayden Gephart M, Wakelee H, Neal J, Han SS. Predictive Model to Guide Brain Magnetic Resonance Imaging Surveillance in Patients With Metastatic Lung Cancer: Impact on Real-World Outcomes. JCO Precis Oncol. 2022 Oct;6:e2200220. doi: 10.1200/PO.22.00220. PMID: 36201713.
PURPOSE: Brain metastasis is common in lung cancer, and treatment of brain metastasis can lead to significant morbidity. Although early detection of brain metastasis may improve outcomes, there are no prediction models to identify high-risk patients for brain magnetic resonance imaging (MRI) surveillance. Our goal is to develop a machine learning-based clinicogenomic prediction model to estimate patient-level brain metastasis risk. **METHODS**: A penalized regression competing risk model was developed using 330 patients diagnosed with lung cancer between January 2014 and June 2019 and followed through June 2021 at Stanford HealthCare. The main outcome was time from the diagnosis of distant metastatic disease to the development of brain metastasis, death, or censoring. **RESULTS**: Among the 330 patients, 84 (25%) developed brain metastasis over 627 person-years, with a 1-year cumulative brain metastasis incidence of 10.2% (95% CI, 6.8 to 13.6). Features selected for model inclusion were histology, cancer stage, age at diagnosis, primary site, and RB1 and ALK alterations. The prediction model yielded high discrimination (area under the curve 0.75). When the cohort was stratified by risk using a 1-year risk threshold of > 14.2% (85th percentile), the high-risk group had increased 1-year cumulative incidence of brain metastasis versus the low-risk group (30.8% v 6.1%, P < .01). Of 48

high-risk patients, 24 developed brain metastasis, and of these, 12 patients had brain metastasis detected more than 7 months after last brain MRI. Patients who missed this 7-month window had larger brain metastases (58% v 33% largest diameter > 10 mm; odds ratio, 2.80, CI, 0.51 to 13) versus those who had MRIs more frequently. **CONCLUSION**: The proposed model can identify high-risk patients, who may benefit from more intensive brain MRI surveillance to reduce morbidity of subsequent treatment through early detection.

A Randomized Trial of Telephone-Based Smoking Cessation Treatment in the Lung Cancer Screening Setting Taylor KL, Williams RM, Li T, Luta G, Smith L, Davis KM, Stanton CA, Niaura R, Abrams D, Lobo T, Mandelblatt J, Jayasekera J, Meza R, Jeon J, Cao P, Anderson ED; Georgetown Lung Screening, Tobacco, and Health Trial. A Randomized Trial of Telephone-Based Smoking Cessation Treatment in the Lung Cancer Screening Setting. J Natl Cancer Inst. 2022 Oct 6;114(10):1410-1419. doi: 10.1093/jnci/djac127. PMID: 35818122; PMCID: PMC9552302.
BACKGROUND: Lung cancer mortality is reduced via low-dose computed tomography screening and treatment of early-stage disease. Evidence-based smoking cessation treatment in the lung screening setting can further reduce mortality. We report the results of a cessation trial from the National Cancer Institute's Smoking Cessation at Lung Examination collaboration.
METHODS: Eligible patients (n = 818) aged 50-80 years were randomly assigned (May 2017-January 2021) to the intensive vs minimal arms (8 vs 3 phone sessions plus 8 vs 2 weeks of nicotine patches, respectively). Bio-verified (primary) and self-reported 7-day abstinence rates were assessed at 3, 6, and 12 months post random assignment. Logistic regression analyses evaluated the effects of study arm. All statistical tests were 2-sided. **RESULTS**: Participants reported 48.0 (SD = 17.2) pack-years, and 51.6% were not ready to quit in less than 30 days. Self-reported 3-month quit rates were statistically significantly higher in the intensive vs minimal arm (14.3% vs 7.9%; odds ratio [OR] = 2.00, 95% confidence interval [CI] = 1.26 to 3.18). Bio-verified abstinence was lower but with similar relative differences between arms (9.1% vs 3.9%; OR = 2.70, 95% CI = 1.44 to 5.08). Compared with the minimal arm, the intensive arm was more effective among those with greater nicotine dependence (OR = 3.47, 95% CI = 1.55 to 7.76), normal screening results (OR = 2.58, 95% CI = 1.32 to 5.03), high engagement in counseling (OR = 3.03, 95% CI = 1.50 to 6.14), and patch use (OR = 2.81, 95% CI = 1.39 to 5.68). Abstinence rates did not differ statistically significantly between arms at 6 months (OR = 1.2, 95% CI = 0.68 to 2.11) or 12 months (OR = 1.4, 95% CI = 0.82 to 2.42). **CONCLUSIONS**: Delivering intensive telephone counseling and nicotine replacement with lung screening is an effective strategy to increase short-term smoking cessation. Methods to maintain short-term effects are needed. Even with modest quit rates, integrating cessation treatment into lung screening programs may have a large impact on tobacco-related mortality.

Prediction of malignant lymph nodes in NSCLC by machine-learning classifiers using EBUS-TBNA and PET/CT Guberina M, Herrmann K, Pöttgen C, Guberina N, Hautzel H, Gauler T, Ploenes T, Umutlu L, Wetter A, Theegarten D, Aigner C, Eberhardt WEE, Metzenmacher M, Wiesweg M, Schuler M, Karpf-Wissel R, Santiago Garcia A, Darwiche K, Stuschke M. Prediction of malignant lymph nodes in NSCLC by machine-learning classifiers using EBUS-TBNA and PET/CT. Sci Rep. 2022 Oct 20;12(1):17511. doi: 10.1038/s41598-022-21637-y. PMID: 36266403; PMCID: PMC9584941.
Accurate determination of lymph-node (LN) metastases is a prerequisite for high precision radiotherapy. The primary aim is to characterise the performance of PET/CT-based machine-learning classifiers to predict LN-involvement by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in stage-III NSCLC. Prediction models for LN-positivity based on [18F]FDG-PET/CT features were built using logistic regression and machine-learning models random forest (RF) and multilayer perceptron neural network (MLP) for stage-III NSCLC before radiochemotherapy. A total of 675 LN-stations were sampled in 180 patients. The logistic and RF models identified SUVmax, the short-axis LN-

diameter and the echelon of the considered LN among the most important parameters for EBUS-positivity. Adjusting the sensitivity of machine-learning classifiers to that of the expert-rater of 94.5%, MLP (P = 0.0061) and RF models (P = 0.038) showed lower misclassification rates (MCR) than the standard-report, weighting false positives and false negatives equally. Increasing the sensitivity of classifiers from 94.5 to 99.3% resulted in increase of MCR from 13.3/14.5 to 29.8/34.2% for MLP/RF, respectively. PET/CT-based machine-learning classifiers can achieve a high sensitivity (94.5%) to detect EBUS-positive LNs at a low misclassification rate. As the specificity decreases rapidly above that level, a combined test of a PET/CT-based MLP/RF classifier and EBUS-TBNA is recommended for radiation target volume definition.

Access to Care Limits Lung Cancer Screening Eligibility in an Urban Safety Net Hospital Dollar KR, Neutel BS, Hsia DW. Access to Care Limits Lung Cancer Screening Eligibility in an Urban Safety Net Hospital. J Prim Care Community Health. 2022 Jan-Dec;13:21501319221128701. doi: 10.1177/21501319221128701. PMID: 36200665; PMCID: PMC9549100.
PURPOSE: Lung cancer screening (LCS) results in earlier detection of malignancy and decreases mortality but requires access to care to benefit. We assessed factors associated with timing of lung cancer diagnosis in the absence of systematic LCS in an urban safety net hospital. **PATIENTS AND METHODS**: Retrospective chart review was performed of patients with pathologic diagnosis and/or staging of lung cancer at our institution between 2015 and 2018. Patient socio-demographics, disease characteristics, factors associated with access to medical care, and time point and process by which the patient accessed care were collected and analyzed. **RESULTS**: In total, 223 patients were identified with median age of 63 years and 57.8% male predominance. Racial distribution was 22.9%, 20.2%, 17.1%, and 9.4% for Black, White, Asian, and Hispanic, respectively. Stage at diagnosis was 8.1%, 4.5%, 17.0%, and 60.5% for stages I, II, III, and IV, respectively. Medicaid (59.6%) and Medicare/Medicaid (17.1%) were the most common insurance types, while 16.1% had no insurance. A majority (54.3%) had no established primary care provider (PCP), and only 17.9% had an in-network PCP. Patients without PCPs were more likely to have diagnostic evaluation initiated from Emergency Department or Urgent Care settings (95.0% vs 50.1%, P < .01) and present with later stage disease (92.7% vs 77.8%, P < .01). Of the 83 patients that met age and smoking history LCS criteria, only 33.7% (12.6% of total) also had an in-network PCP. **CONCLUSION**: Absence of established PCPs is associated with later stage presentation of lung cancer and may limit system- level benefits of LCS implementation.

Assessment of Lung Cancer Risk Among Smokers for Whom Annual Screening Is Not Recommended Faselis C, Nations JA, Morgan CJ, Antevil J, Roseman JM, Zhang S, Fonarow GC, Sheriff HM, Trachiotis GD, Allman RM, Deedwania P, Zeng-Trietler Q, Taub DD, Ahmed AA, Howard G, Ahmed A. Assessment of Lung Cancer Risk Among Smokers for Whom Annual Screening Is Not Recommended. JAMA Oncol. 2022 Oct 1;8(10):1428-1437. doi: 10.1001/jamaoncol.2022.2952. Erratum in: JAMA Oncol. 2022 Sep 1;: PMID: 35900734; PMCID: PMC9335253.
IMPORTANCE: The US Preventive Services Task Force does not recommend annual lung cancer screening with low-dose computed tomography (LDCT) for adults aged 50 to 80 years who are former smokers with 20 or more pack-years of smoking who quit 15 or more years ago or current smokers with less than 20 pack-years of smoking. **OBJECTIVE**: To determine the risk of lung cancer in older smokers for whom LDCT screening is not recommended. **DESIGN, SETTINGS, AND PARTICIPANTS**: This cohort study used the Cardiovascular Health Study (CHS) data sets obtained from the National Heart, Lung and Blood Institute, which also sponsored the study. The CHS enrolled 5888 community-dwelling individuals aged 65 years and older in the US from June 1989 to June 1993 and collected extensive baseline data on smoking history. The current analysis was restricted to 4279 individuals free of cancer who had baseline data on pack-year smoking history and duration of smoking cessation. The current

analysis was conducted from January 7, 2022, to May 25, 2022. **Exposures**: Current and prior tobacco use. **MAIN OUTCOMES AND MEASURES**: Incident lung cancer during a median (IQR) of 13.3 (7.9-18.8) years of follow-up (range, 0 to 22.6) through December 31, 2011. A Fine-Gray subdistribution hazard model was used to estimate incidence of lung cancer in the presence of competing risk of death. Cox cause-specific hazard regression models were used to estimate hazard ratios (HRs) and 95% CIs for incident lung cancer. **RESULTS**: There were 4279 CHS participants (mean [SD] age, 72.8 [5.6] years; 2450 [57.3%] women; 663 [15.5%] African American, 3585 [83.8%] White, and 31 [0.7%] of other race or ethnicity) included in the current analysis. Among the 861 nonheavy smokers (<20 pack-years), the median (IQR) pack-year smoking history was 7.6 (3.3-13.5) pack-years for the 615 former smokers with 15 or more years of smoking cessation, 10.0 (5.3-14.9) pack-years for the 146 former smokers with less than 15 years of smoking cessation, and 11.4 (7.3-14.4) pack-years for the 100 current smokers. Among the 1445 heavy smokers (20 or more pack-years), the median (IQR) pack-year smoking history was 34.8 (26.3-48.0) pack-years for the 516 former smokers with 15 or more years of smoking cessation, 48.0 (35.0-70.0) pack-years for the 497 former smokers with less than 15 years of smoking cessation, and 48.8 (31.6-57.0) pack-years for the 432 current smokers. Incident lung cancer occurred in 10 of 1973 never smokers (0.5%), 5 of 100 current smokers with less than 20 pack-years of smoking (5.0%), and 26 of 516 former smokers with 20 or more pack-years of smoking with 15 or more years of smoking cessation (5.0%). Compared with never smokers, cause-specific HRs for incident lung cancer in the 2 groups for whom LDCT is not recommended were 10.54 (95% CI, 3.60-30.83) for the current nonheavy smokers and 11.19 (95% CI, 5.40-23.21) for the former smokers with 15 or more years of smoking cessation; age, sex, and race-adjusted HRs were 10.06 (95% CI, 3.41-29.70) for the current nonheavy smokers and 10.22 (4.86-21.50) for the former smokers with 15 or more years of smoking cessation compared with never smokers. **CONCLUSIONS AND RELEVANCE**: The findings of this cohort study suggest that there is a high risk of lung cancer among smokers for whom LDCT screening is not recommended, suggesting that prediction models are needed to identify high-risk subsets of these smokers for screening.

Evidence of Racial Disparities in the Lung Cancer Screening Process: a Systematic Review and Meta-Analysis Kunitomo Y, Bade B, Gunderson CG, Akgün KM, Brackett A, Tanoue L, Bastian LA. Evidence of Racial Disparities in the Lung Cancer Screening Process: a Systematic Review and Meta-Analysis. J Gen Intern Med. 2022 Nov;37(14):3731-3738. doi: 10.1007/s11606-022-07613-2. Epub 2022 Jul 15. PMID: 35838866; PMCID: PMC9585128.

BACKGROUND: Annual lung cancer screening (LCS) with low-dose chest computed tomography for high-risk individuals reduces lung cancer mortality, with greater reduction observed in Black participants in clinical trials. While racial disparities in lung cancer mortality exist, less is known about disparities in LCS participation. We conducted a systematic review to explore LCS participation in Black compared with White patients in the USA. **METHODS**: A systematic review was conducted through a search of published studies in MEDLINE, PubMed, EMBASE, Web of Science, and Cumulative Index to Nursing and Allied-Health Literature Database, from database inception through October 2020. We included studies that examined rates of LCS participation and compared rates by race. Studies were pooled using random-effects meta-analysis. **RESULTS**: We screened 18,300 titles/abstracts; 229 studies were selected for full-text review, of which nine studies met inclusion criteria. Studies were categorized into 2 groups: studies that reported the screening rate among an LCS-eligible patient population, and studies that reported the screening rate among a patient population referred for LCS. Median LCS participation rates were 14.4% (range 1.7 to 62.6%) for eligible patient studies and 68.5% (range 62.6 to 88.8%) for referred patient studies. The meta-analyses showed screening rates were lower in the Black compared to White population among the LCS-eligible patient studies ([OR]=0.43, [95% CI: 0.25, 0.74]). However, screening rates were the same between Black and White patients in the referred patient studies (OR=0.94, [95% CI: 0.74, 1.19]). **DISCUSSION**: Black LCS-eligible patients are being screened at a lower rate than

White patients but have similar rates of participation once referred. Differences in referrals by providers may contribute to the racial disparity in LCS participation. More studies are needed to identify barriers to LCS referral and develop interventions to increase provider awareness of the importance of LCS in Black patients. Trial Registry PROSPERO; No.: CRD42020214213; URL: http://www.crd.york.ac.uk/PROSPERO.

Lung cancer screening with low-dose computed tomography: National expenditures and cost-effectiveness Zeng X, Zhou Z, Luo X, Liu Q. Lung cancer screening with low-dose computed tomography: National expenditures and cost-effectiveness. Front Public Health. 2022 Sep 29;10:977550. doi: 10.3389/fpubh.2022.977550. PMID: 36249202; PMCID: PMC9558698.
OBJECTIVE: To compare the cost-effectiveness of undertaking low-dose computed tomography (LDCT) screening for early detection of lung cancer (LC) with different frequencies within the healthcare system of China, and estimate the additional national healthcare expenditure and five-year LC mortality associated with different screening frequencies. **MATERIAL AND METHODS**: A Markov model was established using national LC epidemiological data from the Chinese Center for Disease Control and Prevention, demographic data from the Chinese Statistical Yearbook, and cost and effectiveness data mainly from the Cancer Screening Program in China. The model included thirty sex-specific screening strategies, which were classified by initial screening age (30, 35, 40, 45, and 50), and screening intervals (intervals at single time point, 1, 2, 5, 10, and 20 years). The main model outputs were incremental cost-effectiveness ratios (ICERs), additional national healthcare expenditure and five-year LC mortality. **RESULTS**: The ICERs for LDCT screening strategies vs. non-screening strategy ranged from $16,086 per quality-adjusted life-year (QALY) to $3,675,491 per QALY in the male cohort, and from $36,624 per QALY to $5,943,556 per QALY in the female cohort. The annual increment national healthcare expenditures related to LDCT screening were varied from $0.25 to $13.39 billion, with the lower cost in the cohort with older screening ages and lower screening frequencies. More frequent screening with LDCT was associated with a greater reduction in LC death: an annual LDCT screening was linked to an estimated reduction in five-year LC death by 27.27-29.07%, while a one-off screening was linked to a reduction by 5.56-5.83%. **CONCLUSION**: Under a willingness-to-pay (WTP) threshold of three times the Chinese gross domestic product (GDP) per capita (US $37,654), annual screening with an initiating age at 50 was most cost-effective in both male and female cohorts. By taking into account both the national healthcare expenditures and the effect of LDCT screening, our study results support undertaking LDCT screening annually from 50 years old in general populations.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Neoadjuvant Therapy for Patients With Non-small Cell Lung Cancer Complicated With Chest Wall Invasion Sato K, Nakamura S, Kadomatsu Y, Ueno H, Kato T, Ozeki N, Fukumoto K, Chen-Yoshikawa TF. Neoadjuvant Therapy for Patients With Non-small Cell Lung Cancer Complicated With Chest Wall Invasion. Anticancer Res. 2022 Nov;42(11):5539-5546. doi: 10.21873/anticanres.16059. PMID: 36288862.
BACKGROUND/AIM: Multidisciplinary treatment including anatomical pulmonary and chest wall resection is recommended for lung cancer complicated by chest wall invasion. The present study aimed to investigate the survival benefit and safety of preoperative therapy followed by surgery for non-small cell lung cancer with chest wall invasion. Patients and methods: Sixty-five patients who underwent surgical excision of lung cancer complicated with chest wall invasion between 2009 and 2020 were enrolled in this

study. **RESULTS**: The median age was 65 (37-81) years old, with 59 males and 6 females. Histological types included squamous cell carcinoma (n=32) and adenocarcinoma (n=21). The median tumor diameter was 5.5 cm (2.3-12.5 cm). The clinical nodal status was N0 in 49 cases and N positive in 16 cases. Of the 65 eligible patients, 5- and 10-year overall survival (OS) rates were 58.4% and 46.0%, respectively, and 5- and 10-year progression-free survival (PFS) rates were 54.2% and 41.7%, respectively. For patients receiving preoperative therapy followed by surgery (Pre-Tx), 5- and 10-year OS survival rates were 69.2% and 62.9%, and among patients receiving up-front surgery (UFS) were 48.5% and 29.1%, respectively (p=0.03). The 5- and 10-year PFS rates for pre-Tx were 65.8% and 59.2%, respectively, and 44.7% and 26.8% for UFS, respectively (p=0.02). Cox regression analysis preoperative therapy was significantly associated with OS and PFS. **CONCLUSION**: We demonstrate the survival benefit of preoperative therapy followed by surgery for patients with lung cancer and chest wall invasion.

Lobar versus sublobar resection in clinical stage IA primary lung cancer with occult N2 disease

Liou DZ, Chan M, Bhandari P, Lui NS, Backhus LM, Shrager JB, Berry MF. Lobar versus sublobar resection in clinical stage IA primary lung cancer with occult N2 disease. Eur J Cardiothorac Surg. 2022 Oct 4;62(5):ezac440. doi: 10.1093/ejcts/ezac440. PMID: 36063054.

OBJECTIVES: Sublobar resection is increasingly being utilized for early-stage lung cancers, but optimal management when final pathology shows unsuspected mediastinal nodal disease is unclear. This study tested the hypothesis that lobectomy has improved survival compared to sublobar resection for clinical stage IA tumours with occult N2 disease. **METHODS**: The use of sublobar resection and lobectomy for patients in the National Cancer Database who underwent primary surgical resection for clinical stage IA non-small-cell lung cancer with pathologic N2 disease between 2010 and 2017 was evaluated using logistic regression. Survival was assessed with Kaplan-Meier analysis, log-rank test and Cox proportional hazards model. **RESULTS**: A total of 2419 patients comprised the study cohort, including 320 sublobar resections (13.2%) and 2099 lobectomies (86.8%). Older age, female sex, smaller tumour size and treatment at an academic facility predicted the use of sublobar resection. Patients undergoing lobectomy had larger tumours (2.40 vs 2.05 cm, P < 0.001) and more lymph nodes examined (11 vs 5, P < 0.001). Adjuvant chemotherapy use was similar between the 2 groups (sublobar 79.4% vs lobectomy 77.4%, P = 0.434). Sublobar resection was not associated with worse survival compared to lobectomy in both univariate (5-year survival 46.6% vs 45.2%, P = 0.319) and multivariable Cox proportional hazards analysis (hazard ratio 0.97, P = 0.789). **CONCLUSIONS**: Clinical stage IA non-small-cell lung cancer patients with N2 disease on final pathology have similar long-term survival with either sublobar resection or lobectomy. Patients with occult N2 disease after sublobar resection may not require reoperation for completion lobectomy but should instead proceed to adjuvant chemotherapy.

Analysis of postoperative weight loss associated with prognosis after lobectomy for lung cancer

Nakada T, Tsukamoto Y, Kato D, Shibazaki T, Yabe M, Hirano J, Ohtsuka T. Analysis of postoperative weight loss associated with prognosis after lobectomy for lung cancer. Eur J Cardiothorac Surg. 2022 Oct 4;62(5):ezac479. doi: 10.1093/ejcts/ezac479. PMID: 36173323.

OBJECTIVES: Weight assessment is an easy-to-understand method of health checkup. The present study investigated the association between weight loss (WL) after lung cancer (LC) surgery and short-mid-term prognosis. **METHODS**: The data of patients who underwent radical lobectomy for primary LC were assessed between December 2017 and June 2021. Percentage weight gain or loss was determined at 3, 6 and 12 months postoperatively based on preoperative weight. The timing of decreased weight was divided into 0-3, 3-6 and 6-12 months. We also evaluated the relationship between severe WL (SWL) and prognosis. **RESULTS**: We reviewed 269 patients, of whom 187 (69.5%) showed WL within 1 year after surgery. The interquartile range for maximal WL was 2.0-8.2% (median 4.0%). Furthermore, we defined SWL as WL ≥8%. Twenty-five patients (9.3%) died: 9 from primary LC and 16 from non-LC causes.

Cancer recurrences occurred in 45 patients (16.7%). WL occurred from 6 to 12 months postoperatively was associated with poor overall survival and recurrence-free survival (P < 0.05, both). Body mass index <18.5 kg/m2 and idiopathic pulmonary fibrosis were predictive factors (P < 0.05, all). In the SWL group, overall survival, recurrence-free survival and non-cancer-specific were worse (P = 0.001, 0.005 and 0.019, respectively). Age ≥70 years and severe postoperative complications were predictive factors for SWL (P < 0.05, all). **CONCLUSIONS**: WL from 6 to 12 months postoperatively and SWL were associated with poor prognosis. Ongoing nutritional management is important to prevent life-threatening WL in patients with predictive factors.

Is Surgery Worthwhile in Locally-advanced NSCLC Patients with Persistent N2-disease After Neoadjuvant Therapy? Lococo F, Chiappetta M, Sassorossi C, Nachira D, Evangelista J, Ciavarella LP, Congedo MT, Porziella V, Boldrini L, Larici A, Bria E, Margaritora S. Is Surgery Worthwhile in Locally-advanced NSCLC Patients with Persistent N2-disease After Neoadjuvant Therapy? Rev Recent Clin Trials. 2022;17(2):103-108. doi: 10.2174/1574887117666220518102321. PMID: 35593341.
AIMS: To explore the long-term survival in lung cancer patients with persistent mediastinal lymph nodal disease after neoadjuvant followed by surgical resection and to analyse prognostic factors in this specific subset of patients. **BACKGROUND**: Surgery in non-small-cell lung cancer (NSCLC) patients with N2-disease after neoadjuvant therapy (NAD) has been debated and has been even more questioned with the advent of immunotherapy. **OBJECTIVE**: Describe long-term results of a multimodal approach in locally-advanced NSCLC patients with persistence of N2-disease and identify prognostic factors to target the strategy of care. **METHODS**: We retrospectively reviewed data of 121 consecutive Stage IIIA-N2 NSCLC patients who underwent NAD (chemoradiotherapy or chemotherapy) from 01/00 to 12/19, focusing our analysis on 37 patients with persistent N2s status after surgery. Kaplan-Meier and Cox regression analysis explored the associations between mortality and potential risk factors. **RESULTS**: The 5-year survival was 29.8%. Cox regression analysis suggested that young age (HR=0.98, C.I.95%: 0.97- 1.00; p=0.062), male sex (HR=3.8,C.I.95%:1.06-13.73;p=0.04), and adjuvant therapy (HR=6.81,C.I.95%:0.96-53.94;p=0.06) influenced long-term outcomes in these patients.
CONCLUSION: We herein observed suboptimal long-term results in this NSCLC patient subset, and, considering emerging results adopting immunotherapy following chemoradiotherapy, surgery should be carefully considered in very selected cases (young and clinically fit patients) and combined with adjuvant therapy after surgery.

Postoperative Patient-Reported Outcomes after Uniportal Video-Assisted Thoracoscopic Surgery Using the Perioperative Symptom Assessment for Lung Surgery Scale Yang D, Hong Q, Zhao C, Mu J. Postoperative Patient-Reported Outcomes after Uniportal Video-Assisted Thoracoscopic Surgery Using the Perioperative Symptom Assessment for Lung Surgery Scale. Curr Oncol. 2022;29(10):7645-7654. Published 2022 Oct 13. doi:10.3390/curroncol29100604
This study aimed to use a new special inventory for lung surgery patients to evaluate postoperative symptoms and functional status and to identify factors that may affect these after uniportal video-assisted thoracoscopic surgery (VATS). In this single-center longitudinal cohort observational study, we used a new scale, the perioperative symptom assessment for lung surgery (PSA-Lung), to evaluate the recovery from symptoms and the functional status of patients undergoing uniportal VATS. We divided patients into two groups, according to patients' symptom scores, and compared the clinical characteristics between the two groups under each item. Then, we conducted a qualitative interview regarding coughing in postoperative week 4. Exactly 104 patients were enrolled in this study. The two highest-scoring patient-reported outcome (PRO) items were "shortness of breath" and "coughing" in the fourth week after surgery. Thirty-one patients reported that "coughing" severely influenced their lives in postoperative week 4. Using the PSA-Lung inventory, we found that "shortness of breath" was the worst symptom in

postoperative week 4. Although "coughing" was not the most important symptom in the early postoperative period, it affected some patients' lives in postoperative week 4. Therefore, further research is required to determine the optimal cut-off point for coughing.

Consensus for Thoracoscopic Lower Lobectomy: Essential Components and Targets for Simulation Erwin PA, Lee AC, Ahmad U, Antonoff M, Arndt A, Backhus L, Berry M, Birdas T, Cassivi SD, Chang AC, Cooke DT, Crabtree T, DeCamp M, Donington J, Fernandez F, Force S, Gaissert H, Hofstetter W, Huang J, Kent M, Kim AW, Lin J, Martin LW, Meyerson S, Mitchell JD, Molena D, Odell D, Onaitis M, Puri V, Putnam JB, Reddy R, Schipper P, Seder CW, Shrager J, Tong B, Veeramachaneni N, Watson T, Whyte R, Ferguson MK. Consensus for Thoracoscopic Lower Lobectomy: Essential Components and Targets for Simulation. Ann Thorac Surg. 2022 Nov;114(5):1895-1901. doi: 10.1016/j.athoracsur.2021.09.033. Epub 2021 Oct 21. PMID: 34688617.

BACKGROUND: Despite demonstration of its clear benefits relative to open approaches, a video-assisted thoracic surgery technique for pulmonary lobectomy has not been universally adopted. This study aims to overcome potential barriers by establishing the essential components of the operation and determining which steps are most useful for simulation training. **METHODS**: After randomly selecting experienced thoracic surgeons to participate, an initial list of components to a lower lobectomy was distributed. Feedback was provided by the participants, and modifications were made based on anonymous responses in a Delphi process. Components were declared essential once at least 80% of participants came to an agreement. The steps were then rated based on cognitive and technical difficulty followed by listing the components most appropriate for simulation. **RESULTS**: After 3 rounds of voting 18 components were identified as essential to performance of a video-assisted thoracic surgery for lower lobectomy. The components deemed the most difficult were isolation and division of the basilar and superior segmental branches of the pulmonary artery, isolation and division of the lower lobe bronchus, and dissection of lymphovascular tissue to expose the target bronchus. The steps determined to be most amenable for simulation were isolation and division of the branches of the pulmonary artery, the lower lobe bronchus, and the inferior pulmonary vein. **CONCLUSIONS**: Using a Delphi process a list of essential components for a video-assisted thoracic surgery for lower lobectomy was established. Furthermore 3 components were identified as most appropriate for simulation-based training, providing insights for future simulation development.

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

COAST: An Open-Label, Phase II, Multidrug Platform Study of Durvalumab Alone or in Combination With Oleclumab or Monalizumab in Patients With Unresectable, Stage III Non-Small-Cell Lung Cancer Herbst RS, Majem M, Barlesi F, Carcereny E, Chu Q, Monnet I, Sanchez-Hernandez A, Dakhil S, Camidge DR, Winzer L, Soo-Hoo Y, Cooper ZA, Kumar R, Bothos J, Aggarwal C, Martinez-Marti A. COAST: An Open-Label, Phase II, Multidrug Platform Study of Durvalumab Alone or in Combination With Oleclumab or Monalizumab in Patients With Unresectable, Stage III Non-Small-Cell Lung Cancer. J Clin Oncol. 2022 Oct 10;40(29):3383-3393. doi: 10.1200/JCO.22.00227. Epub 2022 Apr 22. PMID: 35452273.

PURPOSE: Durvalumab significantly improves overall survival for patients with unresectable stage III non-small-cell lung cancer and no progression after concurrent chemoradiotherapy (cCRT). Building upon that standard of care, COAST is a phase II study of durvalumab alone or combined with the anti-CD73 monoclonal antibody oleclumab or anti-NKG2A monoclonal antibody monalizumab as consolidation therapy in this setting. **METHODS**: Patients with unresectable stage III non-small-cell lung cancer, Eastern Cooperative Oncology Group performance status 0/1, and no progression after cCRT were randomly assigned 1:1:1, ≤ 42 days post-cCRT, to durvalumab alone or combined with oleclumab or

monalizumab for up to 12 months, stratified by histology. The primary end point was investigator-assessed confirmed objective response rate (ORR; RECIST v1.1). **RESULTS**: Between January 2019 and July 2020, 189 patients were randomly assigned. At this interim analysis (data cutoff, May 17, 2021), median follow-up was 11.5 months (range, 0.4-23.4 months; all patients). Confirmed ORR was numerically higher with durvalumab plus oleclumab (30.0%; 95% CI, 18.8 to 43.2) and durvalumab plus monalizumab (35.5%; 95% CI, 23.7 to 48.7) versus durvalumab (17.9%; 95% CI, 9.6 to 29.2). Progression-free survival (PFS) was prolonged with both combinations versus durvalumab (plus oleclumab: hazard ratio, 0.44; 95% CI, 0.26 to 0.75; and plus monalizumab: hazard ratio, 0.42; 95% CI, 0.24 to 0.72), with higher 12-month PFS rates (plus oleclumab: 62.6% [95% CI, 48.1 to 74.2] and plus monalizumab: 72.7% [95% CI, 58.8 to 82.6] v durvalumab alone: 33.9% [95% CI, 21.2 to 47.1]). All-cause grade ≥ 3 treatment-emergent adverse events occurred in 40.7%, 27.9%, and 39.4% with durvalumab plus oleclumab, durvalumab plus monalizumab, and durvalumab, respectively. **CONCLUSION:** Both combinations increased ORR and prolonged PFS versus durvalumab alone. Safety was similar across arms with no new or significant safety signals identified with either combination. These data support their further evaluation in a phase III trial.

Adjuvant Atezolizumab Holds Its Own in NSCLC Adjuvant Atezolizumab Holds Its Own in NSCLC. Cancer Discov. 2022 Oct 5;12(10):2224-2225. doi: 10.1158/2159-8290.CD-NB2022-0052. PMID: 35946935.
According to new data from the phase III IMpower010 trial, adjuvant atezolizumab improves overall survival compared with best supportive care for some patients with operable non-small cell lung cancer. These results build on previous study findings, in which the immune checkpoint inhibitor, given after surgery and adjuvant chemotherapy, was shown to significantly decrease the likelihood of disease progression.

Outcomes With Local Therapy and Tyrosine Kinase Inhibition in Patients With ALK/ ROS1/ RET-Rearranged Lung Cancers Hubbeling H, Choudhury N, Flynn J, Zhang Z, Falcon C, Rusch VW, Park BJ, Ziv E, Shaverdian N, Gelblum DY, Shepherd AF, Simone CB 2nd, Wu AJ, Gomez DR, Drilon A, Rimner A. Outcomes With Local Therapy and Tyrosine Kinase Inhibition in Patients With ALK/ROS1/RET-Rearranged Lung Cancers. JCO Precis Oncol. 2022 Oct;6:e2200024. doi: 10.1200/PO.22.00024. PMID: 36201714.
PURPOSE: Local therapy prolongs progression-free survival in patients with oligometastatic non-small-cell lung cancers treated with chemotherapy. We previously reported that local therapy also prolongs survival and time to next therapy in patients on tyrosine kinase inhibitors (TKIs) for EGFR-mutant lung adenocarcinomas. Here, we investigate the role of local therapy in patients progressing on TKIs for ALK/ROS1/RET-rearranged lung adenocarcinomas. **MATERIALS AND METHODS**: Patients with advanced ALK/ROS/RET-rearranged lung adenocarcinomas who underwent radiation, surgery, or percutaneous thermal ablation from 2012 to 2020 for progression on an ALK/ROS1/RET TKI were included. Progression patterns were identified. Times from local therapy to progression, next therapy, and death were measured. **RESULTS**: Sixty-one patients with ALK (n = 37), ROS1 (n = 12), and RET (n = 12) fusions were identified. Patients received radiotherapy (92%), surgery (13%), and percutaneous thermal ablation (8%). Local therapy was administered for solitary/oligoprogressive (94%) or polyprogressive (6%) disease. For most patients (85%), local therapy addressed all progressing sites. The median times from any local therapy to subsequent progression and next systemic therapy were 6.8 months (95% CI, 5.1 to 8.1) and 10 months (95% CI, 8.4 to 15.3), respectively. Third or greater local therapy was associated with shorter time to progression and next therapy than first/second local therapies (hazard ratio, 4.97; P < .001 and hazard ratio, 2.48; P < .001). The median overall survival from first local therapy was 34

months (95% CI, 26 to not reached). **CONCLUSION**: Local therapy for progression on ALK, ROS1, or RET TKIs is associated with clinically meaningful time on continued TKI therapy beyond progression, especially earlier in the course of disease.

Schedule-Dependent Treatment Increases Chemotherapy Efficacy in Malignant Pleural Mesothelioma Karatkevich D, Deng H, Gao Y, Flint E, Peng RW, Schmid RA, Dorn P, Marti TM. Schedule-Dependent Treatment Increases Chemotherapy Efficacy in Malignant Pleural Mesothelioma. Int J Mol Sci. 2022 Oct 8;23(19):11949. doi: 10.3390/ijms231911949. PMID: 36233258; PMCID: PMC9569655.
Malignant pleural mesothelioma (MPM) is a rare but aggressive thoracic malignancy with limited treatment options. One of the standard treatments for MPM is chemotherapy, which consists of concurrent treatment with pemetrexed and cisplatin. Pemetrexed limits tumor growth by inhibiting critical metabolic enzymes involved in nucleotide synthesis. Cisplatin causes direct DNA damage, such as intra-strand and inter-strand cross-links, which are repaired by the nucleotide excision repair pathway, which depends on relatively high nucleotide levels. We hypothesized that prolonged pretreatment with pemetrexed might deplete nucleotide pools, thereby sensitizing cancer cells to subsequent cisplatin treatment. The MPM cell lines ACC-MESO-1 and NCI-H28 were treated for 72 h with pemetrexed. Three treatment schedules were evaluated by initiating 24 h of cisplatin treatment at 0 h (concomitant), 24 h, and 48 h relative to pemetrexed treatment, resulting in either concomitant administration or pemetrexed pretreatment for 24 h or 48 h, respectively. Multicolor flow cytometry was performed to detect γH2AX (phosphorylation of histone H2AX), a surrogate marker for the activation of the DNA damage response pathway. DAPI staining of DNA was used to analyze cell cycle distribution. Forward and side scatter intensity was used to distinguish subpopulations based on cellular size and granularity, respectively. Our study revealed that prolonged pemetrexed pretreatment for 48 h prior to cisplatin significantly reduced long-term cell growth. Specifically, pretreatment for 48 h with pemetrexed induced a cell cycle arrest, mainly in the G2/M phase, accumulation of persistent DNA damage, and induction of a senescence phenotype. The present study demonstrates that optimizing the treatment schedule by pretreatment with pemetrexed increases the efficacy of the pemetrexed-cisplatin combination therapy in MPM. We show that the observed benefits are associated with the persistence of treatment-induced DNA damage. **Our study suggests** that an adjustment of the treatment schedule could improve the efficacy of the standard chemotherapy regimen for MPM and might improve patient outcomes.

Intrapleural infusion of tumor cell-derived microparticles packaging methotrexate or saline combined with pemetrexed-cisplatin chemotherapy for the treatment of malignant pleural effusion in advanced non-squamous non-small cell lung cancer: A double-blind, randomized, placebo-controlled study Dong X, Huang Y, Yi T, Hu C, Gao Q, Chen Y, Zhang J, Chen J, Liu L, Meng R, Zhang S, Dai X, Fei S, Jin Y, Yin P, Hu Y, Wu G. Intrapleural infusion of tumor cell-derived microparticles packaging methotrexate or saline combined with pemetrexed-cisplatin chemotherapy for the treatment of malignant pleural effusion in advanced non-squamous non-small cell lung cancer: A double-blind, randomized, placebo-controlled study. Front Immunol. 2022 Oct 5;13:1002938. doi: 10.3389/fimmu.2022.1002938. PMID: 36275698; PMCID: PMC9580337.
BACKGROUND: Preclincal studies showed the promising efficacy of tumor cell-derived microparticles packaging methotrexate (TMPs-MTX) to treat advanced non-squamous non-small cell lung cancer (NSCLC) with malignant pleural effusion (MPE). **METHODS**: This randomized, double-blind, placebo-controlled study was conducted at six hospitals in China from 20 July 2015 to 25 April 2019. Patients newly diagnosed with non-squamous NSCLC with MPE were randomly assigned to receive TMPs-MTX (group A) or saline (group B). Patients in both groups received pemetrexed (500 mg/m2 d1) and cisplatin (75 mg/m2 in total for d1-d2). Intrapleural infusion (50 mL saline containing 5 units of TMPs-MTX per

perfusion, once every 48 hours, six total perfusions) was initiated on day 5 after pemetrexed-cisplatin chemotherapy. The primary outcome was the objective response rate (ORR) of MPE. Secondary outcomes included the ORR of target lesions, progression-free survival (PFS), overall survival (OS), toxicity, and pleural fluid properties. **RESULTS**: A total of 86 patients were enrolled in this study and randomly assigned to either group A or group B. Of these, 79 patients were evaluable for response. The ORR of MPE in group A was significantly higher than that in group B (82.50% vs. 58.97%, P = 0.0237). The ORR of target lesions was 25.64% in group A and 20.51% in group B (P = 0.5909), respectively. With a median follow-up time of 18.8 months, median PFS were 6.4 (95% CI, 4.5-12.3) months in group A and 7.3 (95% CI, 6.1-10.4) months in group B (P = 0.6893), and median OS were 19.9 (95% CI, 17.1-28.5) months and 17.5 (95% CI, 11.6-25.0) months (P = 0.4500), respectively. The incidence rates of adverse events were similar in the two groups. The most common treatment-related adverse events were chemotherapy-induced toxicities, including fever, gastrointestinal reactions, hepatic dysfunction, and leukopenia. **CONCLUSION**: Intrapleural infusion of TMPs-MTX combined with pemetrexed-cisplatin chemotherapy is safe and effective against MPE in patients with advanced non-squamous NSCLC.

Comparison of Carboplatin With Cisplatin in Small Cell Lung Cancer in US Veterans Azar I, Yazdanpanah O, Jang H, Austin A, Kim S, Chi J, Alkassis S, Saha BK, Chopra A, Neu K, Mehdi S, Mamdani H. Comparison of Carboplatin With Cisplatin in Small Cell Lung Cancer in US Veterans. JAMA Netw Open. 2022 Oct 3;5(10):e2237699. doi: 10.1001/jamanetworkopen.2022.37699. PMID: 36264573; PMCID: PMC9585434.

IMPORTANCE: The current standard of care for the treatment of small cell lung cancer (SCLC) is concurrent chemoradiation for patients with limited-stage SCLC (LS-SCLC) and chemoimmunotherapy for extensive-stage SCLC (ES-SCLC). The backbone of chemotherapy regimens in both is a platinum-etoposide doublet: cisplatin is traditionally the preferred platinum agent in the curative intent setting, whereas carboplatin is preferred in ES-SCLC because of its favorable toxicity profile. **OBJECTIVE**: To determine whether cisplatin is associated with better survival outcomes than carboplatin in treating LS-SCLC and ES-SCLC. **DESIGN, SETTING, AND PARTICIPANTS**: In this cohort study, data were compiled from the National Veterans Affairs Central Cancer Registry for patients with SCLC who received platinum-based multiagent chemotherapy between 2000 and 2020 for ES-SCLC and 2000 and 2021 for LS-SCLC. Only patients with pathologically confirmed cases of LS-SCLC who received concurrent chemoradiation and ES-SCLC who received chemotherapy were included.

MAIN OUTCOMES AND MEASURES: The primary end point was overall survival (OS). The secondary end points included OS by Eastern Cooperative Oncology Group performance status, age, and laterality. Interval-censored Weibull and Cox proportional hazard regression models were used to estimate median OS and hazard ratios (HRs), respectively. Survival curves were compared by a Wald test.

RESULTS: A total of 4408 SCLC cases were studied. Most patients were White (3589 patients [81.4%]), male (4252 [96.5%]), and non-Hispanic (4142 [94.0%]); 2262 patients (51.3%) were 60 to 69 years old, followed by 1476 patients (33.5%) aged 70 years or older, 631 patients (14.3%) aged 50 to 59 years, and 39 patients (0.9%) aged 30 to 49 years. Among 2652 patients with ES-SCLC, 2032 were treated with carboplatin-based therapy and 660 received cisplatin; the median OS was 8.45 months (95% CI, 7.75-9.20 months) for cisplatin and 8.51 months (95% CI, 8.07-8.97 months) for carboplatin (HR, 1.01; 95% CI, 0.91-1.12; P = .90). Subset analysis showed no survival difference between the 2 agents in different age or performance status groups except for patients aged 70 years and older, for whom the median OS was 6.36 months (95% CI, 5.31-7.56 months) for cisplatin and 8.47 months (95% CI, 7.79-9.19 months) for carboplatin (HR, 0.77; 95% CI, 0.61-0.96; P = .02). Multivariable analysis of performance status and age did not show a significant difference in survival between the 2 groups (HR, 0.96; 95% CI, 0.83-1.10; P = .54). Of 1756 patients with LS-SCLC, 801 received carboplatin, and 1018 received cisplatin. The median OS was 26.92 months (95% CI, 25.03-28.81 months) for cisplatin and 25.58 months (95% CI, 23.64-

27.72 months) for carboplatin (HR, 1.04; 95% CI, 0.94-1.16; P = .46). The median OS was not significantly different between 2 agents according to cancer stage (I-III), performance status, and age groups. A multivariable analysis of factors associated with OS accounting for stage (I-III), performance status, and age did not demonstrate a significant difference in survival between carboplatin and cisplatin in patients with LS-SCLC (HR, 0.995; 95% CI, 0.86-1.15; P = .95). **CONCLUSIONS AND RELEVANCE**: Cisplatin is not associated with a survival advantage over carboplatin among patients with either ES-SCLC or LS-SCLC, irrespective of performance status and age. The favorable toxicity profile of carboplatin and comparable OS support its use in both LS-SCLC and ES-SCLC in clinical practice and may allow more room for combination with novel treatment strategies in clinical trials.

What does radiomics do in PD-L1 blockade therapy of NSCLC patients? Cui R, Yang Z, Liu L. What does radiomics do in PD-L1 blockade therapy of NSCLC patients? Thorac Cancer. 2022 Oct;13(19):2669-2680. doi: 10.1111/1759-7714.14620. Epub 2022 Aug 29. PMID: 36039482; PMCID: PMC9527165.
With the in-depth understanding of programmed cell death 1 ligand 1 (PD-L1) in non-small cell lung cancer (NSCLC), PD-L1 has become a vital immunotherapy target and a significant biomarker. The clinical utility of detecting PD-L1 by immunohistochemistry or next-generation sequencing has been written into guidelines. However, the application of these methods is limited in some circumstances where the biopsy size is small or not accessible, or a dynamic monitor is needed. Radiomics can noninvasively, in real-time, and quantitatively analyze medical images to reflect deeper information about diseases. Since radiomics was proposed in 2012, it has been widely used in disease diagnosis and differential diagnosis, tumor staging and grading, gene and protein phenotype prediction, treatment plan decision-making, efficacy evaluation, and prognosis prediction. To explore the feasibility of the clinical application of radiomics in predicting PD-L1 expression, immunotherapy response, and long-term prognosis, we comprehensively reviewed and summarized recently published works in NSCLC. **In Conclusion**, radiomics is expected to be a companion to the whole immunotherapy process.

The Effect of Gefitinib on Treatment Necessity and Prognosis of NSCLC Patients with Early EGFR Mutations Song R, Cheng Y, Zheng T. The Effect of Gefitinib on Treatment Necessity and Prognosis of NSCLC Patients with Early EGFR Mutations. Contrast Media Mol Imaging. 2022 Oct 11;2022:2228744. doi: 10.1155/2022/2228744. PMID: 36304772; PMCID: PMC9578812.
OBJECTIVE: To investigate the need for and prognostic impact of gefitinib on the treatment of patients with early-stage epidermal growth factor receptor (EGFR) mutated non-small-cell lung cancer (NSCLC). **METHODS**: Clinical data of patients with stage IB-IIA non-squamous non-small-cell lung cancer admitted to our thoracic surgery department from January 2020 to January 2022 were collected, and a total of 94 cases were included, divided into 44 cases in the control group (EGFR mutation-negative) and 50 cases in the experimental group (EGFR mutation-positive (including those on medication (19 cases) and those not on medication (31 cases)) according to the outcome of EGFR mutation. To evaluate the necessity and prognostic effect of gefitinib in the treatment of NSCLC patients with early EGFR mutations. **RESULTS**: The lung cancer recurrence rate in the experimental group (66.00%) was higher than that in the control group (40.91%), and the difference was statistically significant ($\chi 2 = 5.937$, P=0.015); in the subgroup analysis of the experimental group samples, the pharmacological intervention of gefitinib had a significant effect on lung cancer recurrence ($\chi 2 = 7.797$, P=0.005), and the proportion of lung cancer recurrence in patients not taking the drug (80.65%) was significantly higher than in the drug-taking group (42.11%); the median survival time was 53.6 months using EGFR mutation type as the study factor, with a statistically significant difference in change in 5-year survival rate for EGFR mutation type ($\chi 2 = 6.095$, P=0.047) and the lowest 5-year survival rate for subjects with EGFR mutation type Exon 20 T790M. **CONCLUSION**: Patients with early gene drive positive lung adenocarcinoma are

significantly more likely to recur and metastasise and have shorter survival times in the absence of pharmacological intervention.

Comparative Clinical Outcomes Between EGFR Ex20ins and Wildtype NSCLC Treated with Immune Checkpoint Inhibitors Girard N, Minchom A, Ou SI, Gadgeel SM, Trigo J, Viteri S, Bauml JM, Londhe A, Mahadevia P, Bazhenova L. Comparative Clinical Outcomes Between EGFR Ex20ins and Wildtype NSCLC Treated with Immune Checkpoint Inhibitors. Clin Lung Cancer. 2022 Nov;23(7):571-577. doi: 10.1016/j.cllc.2022.07.007. Epub 2022 Jul 21. PMID: 36085282.
INTRODUCTION: The activity of immune checkpoint inhibitors (ICIs) in NSCLC harboring EGFR exon 20 insertion mutations (ex20ins) has not been closely examined due to the frequent exclusion of patients with EGFR mutations from large immunotherapy-based NSCLC trials. **PATIENTS AND METHODS**: A real-world, retrospective study was conducted to compare outcomes of ICI-treated patients with EGFR ex20ins and wildtype NSCLC (wt-NSCLC; defined as EGFR and ALK test negative). Patients with advanced NSCLC from the Flatiron Health database (2015-2020) were included in the analysis. Real-world time to next therapy (rwTTNT) and overall survival (rwOS), stratified by ICI initiation line of therapy, were the prespecified primary and secondary endpoints, respectively. **RESULTS**: Among 59 patients with EGFR ex20ins NSCLC and 5365 with wt-NSCLC, ICI treatment was received as first-line therapy in 25% and 39%, respectively. Patients with EGFR ex20ins had a 58% increased risk of shorter time to next-line therapy compared with wt-NSCLC (adjusted hazard ratio of 1.58 [95% confidence interval [CI], 1.2-2.1]; P = .0012). The median rwTTNT for first ICI line was 3.7 months (95% CI, 3.0-4.9) for EGFR ex20ins NSCLC compared with 5.8 months (95% CI, 5.6-6.0) for wt-NSCLC. No meaningful difference in rwOS between the groups was observed. **CONCLUSIONS**: ICI therapy may be less effective for patients with EGFR ex20ins compared with wt-NSCLC. Consistent with prior data on exon 19 deletion and L858R substitution, tumors harboring ex20ins appear to be less responsive to immune checkpoint inhibition than wt-NSCLC.

Landscape of Genomic Alterations and PD-L1 Expression in Early-Stage Non-Small-Cell Lung Cancer (NSCLC)-A Single Center, Retrospective Observational Study Stephan-Falkenau S, Streubel A, Mairinger T, Kollmeier J, Misch D, Thiel S, Bauer T, Pfannschmidt J, Hollmann M, Wessolly M, Blum TG. Landscape of Genomic Alterations and PD-L1 Expression in Early-Stage Non-Small-Cell Lung Cancer (NSCLC)-A Single Center, Retrospective Observational Study. Int J Mol Sci. 2022 Oct 19;23(20):12511. doi: 10.3390/ijms232012511. PMID: 36293366; PMCID: PMC9604339.
Precision oncology and immunotherapy have revolutionized the treatment of advanced non-small-cell lung cancer (NSCLC). Emerging studies show that targeted therapies are also beneficial for patients with driver alterations such as epidermal growth factor receptor (EGFR) mutations in early-stage NSCLC (stages I-IIIA). Furthermore, patients with elevated programmed death-ligand 1 (PD-L1) expression appear to respond favorably to adjuvant immunotherapy. To determine the frequency of genomic alterations and PD-L1 status in early-stage NSCLC, we retrospectively analyzed data from 2066 unselected, single-center patients with NSCLC diagnosed using next-generation sequencing and immunohistochemistry. Nine-hundred and sixty-two patients (46.9%) presented with early-stage NSCLC. Of these, 37.0% had genomic alterations for which targeted therapies have already been approved for advanced NSCLC. The frequencies of driver mutations in the early stages were equivalent to those in advanced stages, i.e., the rates of EGFR mutations in adenocarcinomas were 12.7% (72/567) and 12.0% (78/650) in early and advanced NSCLC, respectively (p = 0778). In addition, 46.3% of early-stage NSCLC cases were PD-L1-positive, with a tumor proportion score (TPS) of ≥1%. With comparable frequencies of driver mutations in early and advanced NSCLC and PD-L1 overexpression in nearly half of patients with early-stage NSCLC, a broad spectrum of biomarkers for adjuvant and neoadjuvant therapies is available, and several are currently being investigated in clinical trials.

The efficacy and tolerability of combining pemetrexed-based chemotherapy with gefitinib in the first-line treatment of non-small cell lung cancer with mutated EGFR: A pooled analysis of randomized clinical trials Wang BC, Zhang WX, Kuang BH, Lin GH. The efficacy and tolerability of combining pemetrexed-based chemotherapy with gefitinib in the first-line treatment of non-small cell lung cancer with mutated EGFR: A pooled analysis of randomized clinical trials. PLoS One. 2022 Oct 10;17(10):e0275919. doi: 10.1371/journal.pone.0275919. PMID: 36215289; PMCID: PMC9550038. **BACKGROUND**: Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) monotherapy is the standard of care in treating advanced non-small cell lung cancer (NSCLC). Nevertheless, whether adding pemetrexed-based chemotherapy to EGFR-TKI targeted therapy furtherly prolongs survival outcomes and improves responses remains controversial. Therefore, we conducted this pooled analysis to compare the efficacy and tolerability between gefitinib plus pemetrexed-based chemotherapy and gefitinib alone in the first-line treatment of advanced NSCLC patients with mutated EGFR. **METHODS**: We systematically searched PubMed, Web of Science, Embase, and Cochrane CENTRAL on June 23, 2022. Eligible studies were registered randomized clinical trials comparing gefitinib plus pemetrexed-based chemotherapy with gefitinib alone. The primary outcomes were overall survival (OS) and progression-free survival (PFS). Objective response rate (ORR), disease control rate (DCR), and discontinuation rate (DR) were explored as secondary outcomes. **RESULTS**: Eight studies within five randomized clinical trials were eligible. Gefitinib combined with pemetrexed-based chemotherapy significantly prolonged OS (hazard ratio [HR] 0.57, 95% confidence interval [CI] 0.37-0.89, p = 0.0125) and PFS (HR 0.52, 95% CI 0.39-0.70, p < 0.0001) versus gefitinib alone. In subgroup analysis, patients with EGFR exon 19 deletion and exon 21 L858R could benefit from the addition of pemetrexed-based chemotherapy to gefitinib in terms of PFS (EGFR exon 19 deletion: HR 0.50, 95% CI 0.34-0.75, p = 0.0008; EGFR exon 21 L858R: HR 0.46, 95% CI 0.26-0.82, p = 0.0079) but not OS. In addition, ORR was improved after the administration of gefitinib plus pemetrexed-based chemotherapy against gefitinib (odds ratio [OR] 1.91, 95% CI 1.44-2.55, p < 0.0001). Both strategies showed comparable DCRs (OR 1.46, 95% CI 0.94-2.26, p = 0.0952) and DRs (risk ratio [RR] 2.80, 95% CI 0.69-11.44, p = 0.1509). **CONCLUSION**: Compared with gefitinib alone, combining pemetrexed-based chemotherapy with gefitinib significantly improved OS and PFS in advanced EGFR-mutant NSCLC patients with acceptable tolerability. However, the accurate sub-population who could have OS benefits requires further validation.

Clinical, Pathologic, and Molecular Prognostic Factors in Patients with Early-Stage EGFR-Mutant NSCLC Jung HA, Lim J, Choi YL, Lee SH, Joung JG, Jeon YJ, Choi JW, Shin S, Cho JH, Kim HK, Choi YS, Zo JI, Shim YM, Park S, Sun JM, Ahn JS, Ahn MJ, Han J, Park WY, Kim J, Park K. Clinical, Pathologic, and Molecular Prognostic Factors in Patients with Early-Stage EGFR-Mutant NSCLC. Clin Cancer Res. 2022 Oct 3;28(19):4312-4321. doi: 10.1158/1078-0432.CCR-22-0879. PMID: 35838647. **PURPOSE**: In early-stage, EGFR mutation-positive (EGFR-M+) non-small cell lung cancer (NSCLC), surgery remains the primary treatment, without personalized adjuvant treatments. We aimed to identify risk factors for recurrence-free survival (RFS) to suggest personalized adjuvant strategies in resected early-stage EGFR-M+ NSCLC. Experimental design: From January 2008 to August 2020, a total of 2,340 patients with pathologic stage (pStage) IB-IIIA, non-squamous NSCLC underwent curative surgery. To identify clinicopathologic risk factors, 1,181 patients with pStage IB-IIIA, common EGFR-M+ NSCLC who underwent surgical resection were analyzed. To identify molecular risk factors, comprehensive genomic analysis was conducted in 56 patients with matched case-controls (pStage II and IIIA and type of EGFR mutation). **RESULTS**: Median follow-up duration was 38.8 months (0.5-156.2). Among 1,181 patients, pStage IB, II, and IIIA comprised 577 (48.9%), 331 (28.0%), and 273 (23.1%) subjects, respectively. Median RFS was 73.5 months [95% confidence interval (CI), 62.1-84.9], 48.7 months (95%

CI, 41.2-56.3), and 22.7 months (95% CI, 19.4-26.0) for pStage IB, II, and IIIA, respectively (P < 0.001). In multivariate analysis of clinicopathologic risk factors, pStage, micropapillary subtype, vascular invasion, and pleural invasion, and pathologic classification by cell of origin (type II pneumocyte-like tumor cell vs. bronchial surface epithelial cell-like tumor cell) were associated with RFS. As molecular risk factors, the non-terminal respiratory unit (non-TRU) of the RNA subtype (HR, 3.49; 95% CI, 1.72-7.09; P < 0.01) and TP53 mutation (HR, 2.50; 95% CI, 1.24-5.04; P = 0.01) were associated with poor RFS independent of pStage II or IIIA. Among the patients with recurrence, progression-free survival of EGFR-tyrosine kinase inhibitor (TKI) in those with the Apolipoprotein B mRNA Editing Catalytic Polypeptide-like (APOBEC) mutation signature was inferior compared with that of patients without this signature (8.6 vs. 28.8 months; HR, 4.16; 95% CI, 1.28-13.46; P = 0.02). **CONCLUSIONS**s: The low-risk group with TRU subtype and TP53 wild-type without clinicopathologic risk factors might not need adjuvant EGFR-TKIs. In the high-risk group, with non-TRU subtype and/or TP 53 mutation, or clinicopathologic risk factors, a novel adjuvant strategy of EGFR-TKI with others, e.g., chemotherapy or antiangiogenic agents needs to be investigated. Given the poor outcome to EGFR-TKIs after recurrence in patients with the APOBEC mutation signature, an alternative adjuvant strategy might be needed.

Ramucirumab plus atezolizumab in patients with stage IV non-small cell lung cancer previously treated with immune checkpoint inhibitors Herzog BH, Waqar SN, Devarakonda S, Ward JP, Gao F, Govindan R, Morgensztern D. Ramucirumab plus atezolizumab in patients with stage IV non-small cell lung cancer previously treated with immune checkpoint inhibitors. Lung Cancer. 2022 Nov;173:101-106. doi: 10.1016/j.lungcan.2022.09.011. Epub 2022 Sep 24. PMID: 36179540.
OBJECTIVES: The treatment options for patients with stage IV non-small cell lung cancer (NSCLC) who develop tumor progression after platinum-based chemotherapy and immune checkpoint inhibitors (ICIs) are limited. The combination of ICI with inhibitors of vascular endothelial growth receptor (VEGFR) signaling has shown promising results in previously untreated patients. Materials and **METHODS**: In this single institution phase II study, patients with advanced stage NSCLC previously treated with at least one line including ICI received ramucirumab 10 mg/kg and atezolizumab 1,200 mg intravenously every 21 days until tumor progression or intolerable toxicity. The primary endpoint was overall response rate (ORR) by the RECIST 1.1 criteria according to the investigator assessment. Secondary endpoints included clinical benefit rate (CBR), overall survival (OS), progression-free survival (PFS) and tolerability. **RESULTS**: Twenty-one patients were enrolled between June 2019 and April 2021. The median age was 67 (range 42-82), 17 (81 %) were female, and 15 (71 %) had non-squamous histology. The median number of prior systemic treatment lines and prior ICI lines were 3 (range 2-8) and 1 (range 1-3), respectively. One patient achieved a complete response for an ORR of 4.8 % while 16 (76.2 %) had stable disease with a CBR of 80.9 %. The median PFS was 3.4 months, and the median OS was 16.5 months. The most common adverse events included hypertension (86 %), proteinuria (67 %), and nausea (52 %). Grade 3 or 4 events were seen in 9 (43 %) of patients, with hypertension being the most common (33 %) of the grade 3 or 4 events. **CONCLUSIONS**: Although the primary endpoint of ORR was not met, the combination of ramucirumab plus atezolizumab was associated with a high CBR and the OS was better than expected in heavily pretreated patients. Therefore, further investigation with ICI plus VEGF inhibition is warranted.

Association between the efficacy and immune-related adverse events of pembrolizumab and chemotherapy in non-small cell lung cancer patients: a retrospective study Kurokawa K, Mitsuishi Y, Shimada N, Kawakami Y, Miura K, Miyawaki T, Asao T, Ko R, Shukuya T, Shibayama R, Nojiri S, Takahashi K. Association between the efficacy and immune-related adverse events of pembrolizumab and chemotherapy in non-small cell lung cancer patients: a retrospective study. BMC Cancer. 2022 Oct 6;22(1):1047. doi: 10.1186/s12885-022-10133-1. PMID: 36203123; PMCID: PMC9535983.

BACKGROUND: The combination of immune-checkpoint inhibitors with chemotherapy has become the standard of treatment for non-small cell lung cancer (NSCLC) patients. However, the association between therapeutic efficacy and the development of immune-related adverse events (irAEs) remains unclear in patients treated with combination therapy. We aimed to investigate the frequency of irAEs, and the association between therapeutic efficacy and the development of irAEs in patients with NSCLC. **MATERIALS AND METHODS**: We retrospectively surveyed patients with chemo-naïve advanced NSCLC who received pembrolizumab plus platinum-based chemotherapy or pembrolizumab mono-therapy at Juntendo University Hospital, Japan, between February 2017 and May 2021. **RESULTS**: Among 148 patients (median [range] age, 68 (33-85) years; 107 men [72.3%] and 41 women [27.7%]), 74 each received pembrolizumab plus chemotherapy and pembrolizumab monotherapy. IrAEs were observed in 46 (62.2%) and 41 patients (55.4%) in the combination therapy and monotherapy group, respectively. Patients with irAEs showed significantly longer progression-free survival (PFS) than those without irAEs in the combination therapy group (8.9 vs. 5.7 months; Hazard Ratio [HR], 0.53; 95% CI, 0.29-0.98; P = 0.041) and monotherapy group (11.7 vs. 5.0 months; HR, 0.40; 95% CI, 0.22-0.70; P = 0.001). In the multivariable analysis, development of irAEs was positively associated with PFS in both the groups (HR, 0.48; 95% CI, 0.26-0.89; P = 0.019 and HR, 0.38; 95% CI, 0.21-0.68; P < 0.01). In the inverse probability of treatment weighting adjusted analysis, development of irAEs was significantly associated with combination therapy (OR, 0.56; 95% CI, 0.34-0.91; P = 0.019). **CONCLUSION**: Our study demonstrated that the incidence of irAEs was associated with favorable efficacy in patients treated with pembrolizumab plus chemotherapy, as well as pembrolizumab monotherapy. Also, the addition of chemotherapy to pembrolizumab significantly increased the incidence of irAEs.

A Randomized Comparison of Nivolumab versus Nivolumab + Docetaxel for Previously Treated Advanced or Recurrent ICI-Naïve Non-Small Cell Lung Cancer: TORG1630 Taniguchi Y, Shimokawa T, Takiguchi Y, Misumi T, Nakamura Y, Kawashima Y, Furuya N, Shiraishi Y, Harada T, Tanaka H, Miura S, Uchiyama A, Nakahara Y, Tokito T, Naoki K, Bessho A, Goto Y, Seike M, Okamoto H. A Randomized Comparison of Nivolumab versus Nivolumab + Docetaxel for Previously Treated Advanced or Recurrent ICI-Naïve Non-Small Cell Lung Cancer: TORG1630. Clin Cancer Res. 2022 Oct 14;28(20):4402-4409. doi: 10.1158/1078-0432.CCR-22-1687. PMID: 35980349.
PURPOSE: The addition of cytotoxic chemotherapy to immune-checkpoint inhibitor (ICI) may enhance antitumor effects. We conducted an open-label randomized phase II/III study to evaluate nivolumab + docetaxel combination therapy in comparison with nivolumab monotherapy for previously treated ICI-naïve non-small cell lung cancer (NSCLC). **PATIENTS AND METHODS**: The primary endpoint of the phase III study was overall survival (OS), and the secondary endpoints included progression-free survival (PFS), overall response rate (ORR), and toxicity. As ICI and platinum-doublet combination chemotherapy was approved in the first-line setting during this study, patient accrual was discontinued. **RESULTS**: One hundred twenty-eight patients (each arm, n = 64) were included in the full analysis set. The median OS in nivolumab (arm A) and nivolumab + docetaxel (arm B) was 14.7 months (95% CI, 11.4-18.7) and 23.1 months (95% CI, 16.7-NR), respectively. The HR for OS was 0.63 (90% CI, 0.42-0.95; P = 0.0310). The median PFS in arms A and arm B was 3.1 months (95% CI, 2.0-3.9) and 6.7 months (95% CI, 3.8-9.4), respectively. The HR for progression was 0.58 (95% CI, 0.39-0.88; P = 0.0095). The ORR was 14.0% (95% CI, 6.3-25.8) in arm A and 41.8% (95% CI, 28.7-55.9) in arm B. Hematotoxicity and gastrointestinal adverse events were more common in arm B than in arm A. Two treatment-related deaths were observed, including one patient in arm A who died of pneumonitis and one in arm B who died of myocarditis. **CONCLUSIONS**: Despite a slightly elevated toxicity, the addition of docetaxel to nivolumab has significantly prolonged the OS and PFS of patients with previously treated ICI-naïve NSCLC.

Real-world Use of Radiation for Newly Diagnosed Brain Metastases in Patients With ALK-positive Lung Cancer Receiving First-line ALK Inhibitor Kumar S, Wang X, Pittell H, Calip GS, Weiss SE, Meyer JE, Royce TJ. Real-world Use of Radiation for Newly Diagnosed Brain Metastases in Patients With ALK-positive Lung Cancer Receiving First-line ALK Inhibitor. Int J Radiat Oncol Biol Phys. 2022 Nov 15;114(4):627-634. doi: 10.1016/j.ijrobp.2022.07.010. Epub 2022 Jul 21. PMID: 35870711.
PURPOSE: Management paradigms now allow for systemic targeted drugs before central nervous system (CNS)-directed radiation therapy (RT) in selected asymptomatic patients with non-small cell lung cancer (NSCLC) and brain metastases (BM). We aimed to quantify how novel targeted agents with improved CNS activity, such as second-generation anaplastic lymphoma kinase (ALK) inhibitors (eg, alectinib), might affect the role of CNS-directed RT. **METHODS AND MATERIALS**: This retrospective, observational, real-world, patterns-of-care study used a nationwide, electronic, health record-derived, de-identified, longitudinal database. A random sample of patients with ALK+ advanced NSCLC and BM on first-line ALK-inhibitor monotherapy between January 1, 2014 and August 31, 2019 were included. Using an index date of the first instance of BM, the outcome was brain-directed local treatment within 4 months. Trends over time were reported and tested using multivariable modified Poisson regression with robust error variance, including an indicator during or after 2017 (when alectinib was approved). **RESULTS**: Of the 352 included patients, 146 had BM. In addition, 104 patients received CNS-directed local therapy, and 42 did not. The majority of patients (89.4%) were treated with RT alone. Of those receiving RT, stereotactic radiosurgery monotherapy was the most common (53%), followed by whole brain RT alone (39%). On multivariable analysis, patients who had their first BM during or after 2017 had a decreased rate of receiving local BM treatment versus those before 2017 with an adjusted incidence rate ratio of 0.63 (95% confidence interval [CI], 0.41-0.95; P = .026). We found no change in the proportion of BM treated with whole brain RT during or after 2017 versus before (adjusted incidence rate ratio: 0.70; 95% CI: 0.24-2.06; P = .517). **CONCLUSIONS**s: We found decreasing use of CNS-directed RT in patients with NSCLC with new BM on first-line ALK inhibitors. Clinical outcomes for these patients require continued investigation, because physicians may become increasingly comfortable deferring upfront local therapy for BM in lieu of novel targeted agents with improved CNS activity.

Stereotactic Radiation for the Comprehensive Treatment of Oligometastases (SABR-COMET): Extended Long-Term Outcomes Harrow S, Palma DA, Olson R, Gaede S, Louie AV, Haasbeek C, Mulroy L, Lock M, Rodrigues GB, Yaremko BP, Schellenberg D, Ahmad B, Senthi S, Swaminath A, Kopek N, Liu M, Schlijper R, Bauman GS, Laba J, Qu XM, Warner A, Senan S. Stereotactic Radiation for the Comprehensive Treatment of Oligometastases (SABR-COMET): Extended Long-Term Outcomes. Int J Radiat Oncol Biol Phys. 2022 Nov 15;114(4):611-616. doi: 10.1016/j.ijrobp.2022.05.004. Epub 2022 May 26. PMID: 35643253.
PURPOSE: Long-term randomized data assessing the effect of ablative therapies in patients with oligometastases are lacking. The Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases (SABR-COMET) randomized phase 2 trial was originally designed with 5 years of follow-up, but the trial was amended in 2016 to extend follow-up to 10 years. Herein we report oncologic outcomes beyond 5 years. **METHODS AND MATERIALS**: Patients were eligible if they had a controlled primary tumor and 1 to 5 metastases, with all metastases amenable to SABR. Patients were randomized in a 1:2 ratio between palliative standard-of-care treatment (control arm) versus SABR to all metastases plus standard of care (SABR arm). The primary endpoint was overall survival (OS) and secondary endpoints included progression-free survival (PFS), toxicity, quality of life (using the Functional Assessment of Cancer Therapy: General [FACT-G]), and time to new metastases. **RESULTS**: Ninety-nine patients were randomized between 2012 and 2016 (n = 33 in arm 1 vs n = 66 in arm 2).

Primary tumor sites included lung (n = 18), breast (n = 18), colon (n = 18), prostate (n = 16), and other (n = 29). Eight-year OS was 27.2% in the SABR arm versus 13.6% in the control arm (hazard ratio, 0.50; 95% confidence interval, 0.30-0.84; P = .008). Eight-year PFS estimates were 21.3% versus 0.0%, respectively (hazard ratio, 0.45; 95% confidence interval, 0.28-0.72; P < .001). Rates of grade ≥ 2 acute or late toxic effects were 30.3% versus 9.1% (P = .019), with no new grade 3 to 5 toxic effects. FACT-G quality of life scores declined over time in both arms, but there were no differences in quality of life scores between arms. The use of systemic therapy overall was similar between arms, but patients in the SABR arm were less likely to require cytotoxic chemotherapy (33.3% vs 54.6%, respectively, P = .043). **CONCLUSIONS**: SABR achieved durable improvements in OS and PFS, with no new major toxicity signals with extended follow-up. A minority of patients randomized to the SABR arm (21.3%) achieved > 5 years of survival without recurrence.

Artificial Intelligence-Based Identification of Normal Chest Radiographs: A Simulation Study in a Multicenter Health Screening Cohort Yoo H, Kim EY, Kim H, Choi YR, Kim MY, Hwang SH, Kim YJ, Cho YJ, Jin KN. Artificial Intelligence-Based Identification of Normal Chest Radiographs: A Simulation Study in a Multicenter Health Screening Cohort. Korean J Radiol. 2022 Oct;23(10):1009-1018. doi: 10.3348/kjr.2022.0189. PMID: 36175002; PMCID: PMC9523233.
OBJECTIVE: This study aimed to investigate the feasibility of using artificial intelligence (AI) to identify normal chest radiography (CXR) from the worklist of radiologists in a health-screening environment. **MATERIALS AND METHODS**: This retrospective simulation study was conducted using the CXRs of 5887 adults (mean age ± standard deviation, 55.4 ± 11.8 years; male, 4329) from three health screening centers in South Korea using a commercial AI (Lunit INSIGHT CXR3, version 3.5.8.8). Three board-certified thoracic radiologists reviewed CXR images for referable thoracic abnormalities and grouped the images into those with visible referable abnormalities (identified as abnormal by at least one reader) and those with clearly visible referable abnormalities (identified as abnormal by at least two readers). With AI-based simulated exclusion of normal CXR images, the percentages of normal images sorted and abnormal images erroneously removed were analyzed. Additionally, in a random subsample of 480 patients, the ability to identify visible referable abnormalities was compared among AI-unassisted reading (i.e., all images read by human readers without AI), AI-assisted reading (i.e., all images read by human readers with AI assistance as concurrent readers), and reading with AI triage (i.e., human reading of only those rendered abnormal by AI). **RESULTS**: Of 5887 CXR images, 405 (6.9%) and 227 (3.9%) contained visible and clearly visible abnormalities, respectively. With AI-based triage, 42.9% (2354/5482) of normal CXR images were removed at the cost of erroneous removal of 3.5% (14/405) and 1.8% (4/227) of CXR images with visible and clearly visible abnormalities, respectively. In the diagnostic performance study, AI triage removed 41.6% (188/452) of normal images from the worklist without missing visible abnormalities and increased the specificity for some readers without decreasing sensitivity. **CONCLUSION**: This study suggests the feasibility of sorting and removing normal CXRs using AI with a tailored cut-off to increase efficiency and reduce the workload of radiologists.

Thoracic radiotherapy may improve the outcome of extensive stage small cell lung carcinoma patients treated with first-line immunotherapy plus chemotherapy Wu JJ, Huang JW, Hsu KH, et al. Thoracic radiotherapy may improve the outcome of extensive stage small cell lung carcinoma patients treated with first-line immunotherapy plus chemotherapy. Anticancer Drugs. 2022;33(10):e842-e849. doi:10.1097/CAD.0000000000001374
OBJECTIVE: Immunotherapy plus etoposide and platinum (EP)-based chemotherapy is the standard of care for patients with extensive stage-small cell lung carcinoma (ES-SCLC). In the era of immunotherapy, the role of thoracic radiotherapy for ES-SCLC remains unclear. **METHODS**: We retrospectively included ES-SCLC patients treated with first-line EP-based chemotherapy plus atezolizumab or durvalumab at

Taichung Veterans General Hospital to evaluate the prognostic role and safety of thoracic radiotherapy. **RESULTS**: A total of 22 patients were included. The median age was 64 years and most of them were male and smokers. Sixteen patients (72.7%) received durvalumab, while the other 6 patients (27.3%) underwent atezolizumab treatment. Among these patients, 11 (50.0%) had a history of thoracic radiotherapy. There was no significant difference in baseline characteristics between patients with and without thoracic radiotherapy. In the overall population, the objective response rate to immunotherapy plus chemotherapy was 73.7%. The progression-free survival and overall survival were 6.0 months (95% CI: 4.0-7.9) and 13.8 months (95% CI: 8.0-19.6), respectively. The overall survival was significantly longer in patients with thoracic radiotherapy (not-reached [NR] [95% CI NR-NR] vs. 9.6 months [95% CI 2.5-16.6]), respectively (P value by log-rank test <0.001). Both multivariate analysis and subgroup analysis specifically comparing patients with consolidative thoracic radiotherapy and patients with clinical benefits to systemic therapy who did not undergo thoracic radiotherapy indicated that thoracic radiotherapy improved survival. **CONCLUSION**: The real-world efficacy of EP-based chemotherapy plus atezolizumab or durvalumab was comparable with that of clinical trials. Thoracic radiotherapy may improve the outcome of ES-SCLC.

Practice radiation patterns among oncologists in the Oncology Care Model Walker B, Kavadi V, Wilfong L, Robert N. Practice radiation patterns among oncologists in the Oncology Care Model. Am J Manag Care. 2022 Oct;28(10):515-519. doi: 10.37765/ajmc.2022.89249. PMID: 36252170.
OBJECTIVES: CMS created the Oncology Care Model (OCM) to increase the delivery of cost-efficient cancer care, but in linking medical oncologist compensation to total costs of care, the model also prompted concerns about reductions in radiation therapy utilization. We compare practices that participated in the model with those that did not through its launch to estimate whether radiation therapy utilization was reduced under the OCM. **STUDY DESIGN**: Retrospective analysis of a secondary claims-based data set. **METHODS**: We used 5 years of reimbursement claims data from a large community oncology network in which approximately half of the practices participated in the OCM to measure the relative change in utilization following OCM participation compared with practices that did not participate in the OCM. We evaluated use of radiation therapy for all cancer diagnoses and, more specifically, bone metastases, lung cancer, and breast cancer to assess whether effects varied by setting using 3 quasi-experimental estimation techniques (difference-in-differences, event study, and triple differences regressions). **RESULTS**: We found no evidence of reductions in radiation therapy utilization associated with the OCM between participant and nonparticipant practices in any of the specifications or subpopulations analyzed. **CONCLUSIONS**: Despite the potential incentives for medical oncologists to reduce radiation therapy utilization, we found no evidence that such reduction occurred.

SMALL CELL LUNG CANCER - SCLC

SCLC's Treatment Arsenal Improving SCLC's Treatment Arsenal Improving. Cancer Discov. 2022 Oct 5;12(10):OF1. doi: 10.1158/2159-8290.CD-ND2022-0013. PMID: 35980130.
Although the treatment landscape for small cell lung cancer has hardly changed in decades, new possibilities are emerging. Long-term data from KEYNOTE-604 support incorporating immune checkpoint inhibition up front, as this provides durable benefit. A bispecific T-cell engager and other combination therapies also show signs of potential as second- or later-line therapies.

Endothelial activation and stress index (EASIX) as a predictive biomarker in small cell lung cancer Go SI, Park S, Kang MH, Kim HG, Kang JH, Kim JH, Lee GW. Endothelial activation and stress index (EASIX) as a predictive biomarker in small cell lung cancer. Cancer Biomark. 2022;35(2):217-225. doi: 10.3233/CBM-220032. PMID: 36120771.

BACKGROUND: Endothelial activation and insult may contribute to the aggressive clinical course of small-cell lung cancer (SCLC); however, no predictive biomarker for this pathogenesis has been identified. **OBJECTIVE**: To evaluate the clinical impact of the endothelial activation and stress index (EASIX) in SCLC. **METHODS**: In this retrospective study, the EASIX was calculated from measurements of serum lactate dehydrogenase, creatinine, and platelet levels. A total of 264 patients with SCLC treated with platinum-based chemotherapy were stratified into high and low EASIX groups. **RESULTS**: Complete and objective response rates in the limited-stage (LD) were 19.5% vs. 33.3% (P= 0.050) and 85.4% vs. 97.9% (P= 0.028) in the high and low EASIX groups, respectively. There was no significant difference in the response rate between the two groups in the extensive-stage (ED). The median overall survival was 9.8 vs. 40.5 months in LD (P< 0.001) and 7.2 vs. 11.9 months in ED (P< 0.001) in the high and low EASIX groups, respectively. In multivariate analyses, a high EASIX level was an independent prognostic factor for worse progression-free and overall survival irrespective of stage. **CONCLUSION**: EASIX may be a potential predictive biomarker of SCLC.

Inhibition of LSD1 with Bomedemstat Sensitizes Small Cell Lung Cancer to Immune Checkpoint Blockade and T-Cell Killing Hiatt JB, Sandborg H, Garrison SM, Arnold HU, Liao SY, Norton JP, Friesen TJ, Wu F, Sutherland KD, Rienhoff HY, Martins R, Houghton AM, Srivastava S, MacPherson D. Inhibition of LSD1 with Bomedemstat Sensitizes Small Cell Lung Cancer to Immune Checkpoint Blockade and T-Cell Killing. Clin Cancer Res. 2022 Oct 14;28(20):4551-4564. doi: 10.1158/1078-0432.CCR-22-1128. PMID: 35920742.

PURPOSE: The addition of immune checkpoint blockade (ICB) to platinum/etoposide chemotherapy changed the standard of care for small cell lung cancer (SCLC) treatment. However, ICB addition only modestly improved clinical outcomes, likely reflecting the high prevalence of an immunologically "cold" tumor microenvironment in SCLC, despite high mutational burden. Nevertheless, some patients clearly benefit from ICB and recent reports have associated clinical responses to ICB in SCLC with (i) decreased neuroendocrine characteristics and (ii) activation of NOTCH signaling. We previously showed that inhibition of the lysine-specific demethylase 1a (LSD1) demethylase activates NOTCH and suppresses neuroendocrine features of SCLC, leading us to investigate whether LSD1 inhibition would enhance the response to PD-1 inhibition in SCLC. **EXPERIMENTAL DESIGN**: We employed a syngeneic immunocompetent model of SCLC, derived from a genetically engineered mouse model harboring Rb1/Trp53 inactivation, to investigate combining the LSD1 inhibitor bomedemstat with anti-PD-1 therapy. In vivo experiments were complemented by cell-based studies in murine and human models. **RESULTS**: Bomedemstat potentiated responses to PD-1 inhibition in a syngeneic model of SCLC, resulting in increased CD8+ T-cell infiltration and strong tumor growth inhibition. Bomedemstat increased MHC class I expression in mouse SCLC tumor cells in vivo and augmented MHC-I induction by IFNγ and increased killing by tumor-specific T cells in cell culture. **CONCLUSIONS**: LSD1 inhibition increased MHC-I expression and enhanced responses to PD-1 inhibition in vivo, supporting a new clinical trial to combine bomedemstat with standard-of-care PD-1 axis inhibition in SCLC.

What is the effect of tumor diameter, lymph node metastases, and SUVmax value on prognosis in limited-stage small cell lung cancer? Çimen F, Aloglu M, Düzgün S, Şentürk A, Atikcan Ş, Özmen Ö. What is the effect of tumor diameter, lymph node metastases, and SUVmax value on prognosis in limited-stage small cell lung cancer? Rev Assoc Med Bras (1992). 2022 Sep;68(9):1252-1258. doi: 10.1590/1806-9282.20220325. PMID: 36228257; PMCID: PMC9575018.

OBJECTIVE: This study was designed to investigate the link between survival and prognostic factors such as tumor size, lymph node metastasis, and metabolic activity detected on positron emission tomography/computed tomography in patients with limited-stage small cell lung carcinoma. **METHODS**: Patients who were admitted to our hospital with pathological diagnosis of limited-stage small cell lung

cancer between January 2015 and December 2019 and were older than 18 years were retrospectively screened. **RESULTS**: A total of 77 patients, including 10 females and 67 males, were included in the study. While there were 39 patients over 60 years of age, 38 patients were under 60.The ratios of male patients, N stage, multiple lymph nodes, distant metastasis, brain metastasis, and prophylactic cranial irradiation in the deceased patients' group were significantly (p=0.008, p=0.000, p=0.000, p=0.000, p=0.013, p=0.000, respectively) higher than those in the living patients' group.In the univariate model, we observed that gender, smoking, T stage, N stage, multiple lymph nodes, distant metastasis, brain metastasis, liver metastasis, sequential chemotherapy, sequential radiotherapy, concurrent chemoradiotherapy, and prophylactic cranial irradiation had significant effect (p=0.049, p=0.021, p=0.022, p=0.000, p=0.000, p=0.000 p=0.003, p=0.037, p=0.029, p=0.049, p=0.000, respectively) on survival time. In the multivariate model, smoking, N stage, liver metastasis, and prophylactic cranial irradiation demonstrated significant independent effect (p=0.010, p=0.003, p=0.004, p=0.000, respectively) on survival time. **CONCLUSION**: Our findings provide useful information for better patient management, especially in terms of negative factors on the continuation of survival during and after the treatment of limited-stage small cell lung carcinoma patients.

Construction of Prognostic Risk Model for Small Cell Lung Cancer Based on Immune-Related Genes Deng F, Tao F, Xu Z, Zhou J, Gong X, Zhang R. Construction of Prognostic Risk Model for Small Cell Lung Cancer Based on Immune-Related Genes. Comput Math Methods Med. 2022 Sep 30;2022:7116080. doi: 10.1155/2022/7116080. PMID: 36245844; PMCID: PMC9554662.
Small cell lung cancer (SCLC) is a highly invasive and fatal malignancy. Research at the present stage implied that the expression of immune-related genes is associated with the prognosis in SCLC. Accordingly, it is essential to explore effective immune-related molecular markers to judge prognosis and treat SCLC. Our research obtained SCLC dataset from Gene Expression Omnibus (GEO) and subjected mRNAs in it to differential expression analysis. Differentially expressed mRNAs (DEmRNAs) were intersected with immune-related genes to yield immune-related differentially expressed genes (DEGs). The functions of these DEGs were revealed by Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses. Thereafter, we categorized 3 subtypes of immune-related DEGs via K-means clustering. Kaplan-Meier curves analyzed the effects of 3 subtypes on SCLC patients' survival. Single-sample gene set enrichment analysis (ssGSEA) and ESTIMATE validated that the activation of different immune gene subtypes differed significantly. Finally, an immune-related-7-gene assessment model was constructed by univariate-Lasso-multiple Cox regression analyses. Riskscores, Kaplan-Meier curves, receiver operating characteristic (ROC) curves, and independent prognostic analyses validated the prognostic value of the immune-related-7-gene assessment model. As suggested by GSEA, there was a prominent difference in cytokine-related pathways between high- and low-risk groups. As the analysis went further, we discovered a statistically significant difference in the expression of human leukocyte antigen (HLA) proteins and costimulatory molecules expressed on the surface of CD274, CD152, and T lymphocytes in different groups. In a word, we started with immune-related genes to construct the prognostic model for SCLC, which could effectively evaluate the clinical outcomes and offer guidance for the treatment and prognosis of SCLC patients.

Direct incorporation of patient-specific efficacy and toxicity estimates in radiation therapy plan optimization Polan DF, Epelman MA, Wu VW, Sun Y, Varsta M, Owen DR, Jarema D, Matrosic CK, Jolly S, Schonewolf CA, Schipper MJ, Matuszak MM. Direct incorporation of patient-specific efficacy and toxicity estimates in radiation therapy plan optimization. Med Phys. 2022 Oct;49(10):6279-6292. doi: 10.1002/mp.15940. Epub 2022 Sep 2. PMID: 35994026. **PURPOSE:** Current radiation therapy (RT) treatment planning relies mainly on pre-defined dose-based objectives and constraints to develop plans that aim to control disease while limiting damage to normal tissues during treatment. These objectives and

constraints are generally population-based, in that they are developed from the aggregate response of a broad patient population to radiation. However, correlations of new biologic markers and patient-specific factors to treatment efficacy and toxicity provide the opportunity to further stratify patient populations and develop a more individualized approach to RT planning. We introduce a novel intensity-modulated radiation therapy (IMRT) optimization strategy that directly incorporates patient-specific dose response models into the planning process. In this strategy, we integrate the concept of utility-based planning where the optimization objective is to maximize the predicted value of overall treatment utility, defined by the probability of efficacy (e.g., local control) minus the weighted sum of toxicity probabilities. To demonstrate the feasibility of the approach, we apply the strategy to treatment planning for non-small cell lung cancer (NSCLC) patients. **METHODS AND MATERIALS:** We developed a prioritized approach to patient-specific IMRT planning. Using a commercial treatment planning system (TPS), we calculate dose based on an influence matrix of beamlet-dose contributions to regions-of-interest. Then, outside of the TPS, we hierarchically solve two optimization problems to generate optimal beamlet weights that can then be imported back to the TPS. The first optimization problem maximizes a patient's overall plan utility subject to typical clinical dose constraints. In this process, we facilitate direct optimization of efficacy and toxicity trade-off based on individualized dose-response models. After optimal utility is determined, we solve a secondary optimization problem that minimizes a conventional dose-based objective subject to the same clinical dose constraints as the first stage but with the addition of a constraint to maintain the optimal utility from the first optimization solution. We tested this method by retrospectively generating plans for five previously treated NSCLC patients and comparing the prioritized utility plans to conventional plans optimized with only dose metric objectives. To define a plan utility function for each patient, we utilized previously published correlations of dose to local control and grade 3-5 toxicities that include patient age, stage, microRNA levels, and cytokine levels, among other clinical factors. **RESULTS:** The proposed optimization approach successfully generated RT plans for five NSCLC patients that improve overall plan utility based on personalized efficacy and toxicity models while accounting for clinical dose constraints. Prioritized utility plans demonstrated the largest average improvement in local control (16.6%) when compared to plans generated with conventional planning objectives. However, for some patients, the utility-based plans resulted in similar local control estimates with decreased estimated toxicity. **CONCLUSION:** The proposed optimization approach, where the maximization of a patient's RT plan utility is prioritized over the minimization of standardized dose metrics, has the potential to improve treatment outcomes by directly accounting for variability within a patient population. The implementation of the utility-based objective function offers an intuitive, humanized approach to biological optimization in which planning trade-offs are explicitly optimized.

Prophylactic cranial irradiation (PCI) versus active surveillance in patients with limited-stage small cell lung cancer: a retrospective, multicentre study Chen Y, Wang Y, Ren F, Huang Z, Tan B, Zhao Z, Yu X, Dong P, Yu J, Meng X. Prophylactic cranial irradiation (PCI) versus active surveillance in patients with limited-stage small cell lung cancer: a retrospective, multicentre study. Respir Res. 2022 Oct 2;23(1):274. doi: 10.1186/s12931-022-02196-2. PMID: 36184624; PMCID: PMC9526908.
BACKGROUND: The recommendation of PCI for limited-stage small cell lung cancer (LS-SCLC) is primarily based on evidence from the pre-magnetic resonance imaging (MRI) era. However, as MRI accuracy improves and stereotactic radiosurgery advances, the role of PCI for LS-SCLC has become uncertain. This study aims to compare the contemporary survival outcomes of patients with LS-SCLC treated with PCI versus active surveillance. **METHODS**: We conducted a retrospective cohort study in which 1068 patients with LS-SCLC who achieved a good response to first-line chemoradiotherapy were consecutively enrolled from 5 tertiary medical centres between June 2009 and June 2019. Of these patients, 440 received PCI, while 628 received surveillance without PCI. Propensity score matching with a 1:1 ratio was performed to balance the baseline characteristics of the two cohorts. The endpoints were

overall survival (OS) and the incidence of brain metastasis (BM). **RESULTS**: In total, 648 patients were matched. The baseline characteristics were generally well balanced. At a median follow-up of 64.5 months (range 2-190), patients who underwent PCI had a significantly lower risk for BM than those who underwent surveillance. The 3-year cumulative incidence rate of BM was 28.2% (95% CI 22.5-33.8%) in the PCI cohort and 38.5% (32.6-44.5%) in the surveillance cohort (Gray's p = 0.002). However, the lower incidence of BM in the PCI cohort did not translate into a significant extension of OS. The median OS was 35.8 months (95% CI 27.6-44.0 months) in the PCI cohort versus 32 months (26.4-37.6 months) in the surveillance cohort (HR 0.90, 95% CI 0.74-1.10, p = 0.29). Multivariable analysis showed that disease stage, chemoradiotherapy sequence, and response to chemoradiotherapy were independent prognostic factors for BM or OS. **CONCLUSIONS**: Overall, PCI reduces the risk for BM but does not substantially prolong OS compared with active surveillance. A phase 3, prospective clinical trial (NCT04829708) we initiated is currently underway, which is expected to corroborate our results.

PALLIATIVE AND SUPPORTIVE CARE

TENS Improves Cisplatin-Induced Neuropathy in Lung Cancer Patients Tomanovic Vujadinovic S, Ilic N, Selakovic I, Nedeljkovic U, Krstic N, Mujovic N, Dubljanin Raspopovic E, Jovanovic D. TENS Improves Cisplatin-Induced Neuropathy in Lung Cancer Patients. Medicina (Kaunas). 2022 Oct 6;58(10):1405. doi: 10.3390/medicina58101405. PMID: 36295566; PMCID: PMC9611034. **BACKGROUND**: Cisplatin-induced peripheral neuropathy is a common complication of cisplatin therapy, which develops in most patients with lung cancer. There are no effective preventive measures and once it occurs there is no effective therapy, except symptomatic. In this study, we aimed to assess the effect of transcutaneous electrical nerve stimulation (TENS) therapy on the pain intensity and the quality of life of patients with cisplatin-induced neuropathy. Material and **METHODS**: A prospective cohort study was performed from 2013 to 2018, at the Clinical Center of Serbia. After the initial evaluation of 106 newly diagnosed patients with lung cancer, 68 patients did not have peripheral neuropathy. These 68 patients continued in the study and started the cisplatin chemotherapy. Forty of these patients developed cisplatin-induced neuropathy, which was manifested by neuropathic symptoms and proven by ENG examination. All patients with cisplatin-induced neuropathy were treated with TENS therapy. Their neuropathic pain and quality of life were evaluated using the following questionnaires at diagnosis, after cisplatin therapy and after four weeks of TENS use: DN4, VAS scale, EORTC QLQ-C30 and FACT-L. **RESULTS**: Two thirds (68%) of the patients with cisplatin-induced neuropathy were male and the majority were smokers (70%). Adenocarcinoma was the most common (38%), followed by squamous (33%) and small-cell carcinoma (28%). The application of TENS therapy had a positive effect on reducing the neuropathic pain and increasing the quality of life for patients with painful cisplatin-induced neuropathy. The VAS and DN4 scores significantly decreased after TENS therapy, in comparison to its values after cisplatin therapy (p < 0.001). After TENS therapy, patients had significantly higher values in most of the domains of EORTC QLQ-C30 and FACT- L, in comparison with the values after cisplatin therapy (p < 0.001). **CONCLUSION**: The application of TENS therapy has a positive effect on reducing neuropathic pain and increasing the quality of life for patients with lung cancer and cisplatin-induced neuropathy.

Prevalence of anxiety and depression in people with different types of cancer or haematologic malignancies: a cross-sectional study Zeilinger EL, Oppenauer C, Knefel M, Kantor V, Schneckenreiter C, Lubowitzki S, Krammer K, Popinger C, Kitta A, Kum L, Adamidis F, Unseld M, Masel EK, Füreder T, Zöchbauer-Müller S, Bartsch R, Raderer M, Prager G, Krauth MT, Sperr WR, Porpaczy E, Staber PB, Valent P, Gaiger A. Prevalence of anxiety and depression in people with different types of cancer or

haematologic malignancies: a cross-sectional study. Epidemiol Psychiatr Sci. 2022 Oct 17;31:e74. doi: 10.1017/S2045796022000592. PMID: 36245424; PMCID: PMC9583630.
AIMS: Cancer patients often present with psychological symptoms that affect their quality of life, physical health outcomes and survival. Two of the most frequent psychiatric comorbidities are anxiety and depression. However, the prevalence of these disorders among cancer patients remains unclear, as studies frequently report varying rates. In the present study, we aimed to provide robust point estimates for the prevalence of anxiety and depression for both a mixed cancer sample and for 13 cancer types separately, considering confounding variables. **METHODS**: In a sample of 7509 cancer outpatients (51.4% female), we used the Hospital Anxiety and Depression Scale to assess rates of anxiety and depression. Applying ordinal logistic regression models, we compared the prevalence of anxiety and depression between different cancer types, controlling for age and gender. **RESULTS**: About one third of our sample showed symptoms of anxiety (35.2%) or depression (27.9%), and every sixth patient had a very likely psychiatric condition, with women being more frequently affected. Elderly patients more often showed signs of depression. The prevalence of anxiety and depression was significantly higher in lung and brain cancer patients, than in other cancer patients. Lowest depression rates were found in breast cancer patients. **CONCLUSIONS**: The prevalence of anxiety and depression is high in cancer patients. Type of cancer is an important predictor for anxiety and depressive symptoms, with lung and brain cancer patients being highly burdened. Considering a personalised medicine approach, physicians should take into account the high prevalence of psychiatric comorbidities and include psychiatric consultations in the treatment plan.

Bone mineral density, osteopenia and osteoporosis among US adults with cancer Huang JF, Tan QC, Bai H, Wang J, Bergman M, Wu Z. Bone mineral density, osteopenia and osteoporosis among US adults with cancer. QJM. 2022 Oct 25;115(10):653-660. doi: 10.1093/qjmed/hcac015. PMID: 35092293.
BACKGROUND: Bone mineral deficits are one of the most common complications in cancer survivors. However, there are no studies evaluating bone mineral density (BMD) and the prevalence of osteopenia and osteoporosis among patients with different types of cancers. **AIM**: The objective was to assess BMD and evaluate the prevalence of osteopenia and osteoporosis among US adults with cancer. **DESIGN**: A cross-section propensity score matching study. **METHODS**: We extracted data from National Health and Nutrition Examination Survey database from 2005 to 2018. We compared BMD in participants with and without cancer which was further analyzed according to cancer type. We conducted logistic regression to evaluate adjusted odds ratios of osteopenia and osteoporosis and determine risk factors for their development. **RESULTS**: We found that BMD was significantly higher in participants without cancer than cancer patients. Furthermore, the median BMD of patients with breast cancer or skin cancer (including melanoma) was significantly lower than participants without cancer. People with breast, lung, genitourinary and skin cancers were more likely to incur osteopenia/osteoporosis than those without cancer. **CONCLUSIONS**: BMD differs depending upon type in survivors. Individuals with a history of cancer have a poor understanding of osteoporosis and its risk factors. Understanding risk factors in patients with cancers identified in our study may be helpful for preventing osteoporosis and fractures and the development of screening guidelines.

COMPLEMENTARY & ALTERNATIVE THERAPY

Treatment of Lung Cancer with Orally Administered Chinese Herbal Medicine: An Evidence Map between 1970-2020 Gui YR, Zhang Y, Wang XQ, Fan BJ, Li JL, Zhang LX, Fan F, Cao KD, Zhang XG, Hou W. Treatment of Lung Cancer with Orally Administered Chinese Herbal Medicine: An Evidence Map between 1970-2020. Chin J Integr Med. 2022 Oct;28(10):930-938. doi: 10.1007/s11655-022-3465-3. Epub 2022 Mar 3. PMID: 35243583.

OBJECTIVE: Through showing the full picture of double-arm controlled clinical research and systematic review evidence in the field of orally administrated Chinese herbal medicine (CHM) for treatment of lung cancer, to provide a reference for future clinical research and to indicate a direction for future systematic reviews. **METHODS**: A comprehensive search of clinical controlled studies was performed regarding orally administered CHM treatment for lung cancer published from January 1970 to September 2020. The language was restricted to Chinese and English. Relevant data were extracted, the quality of systematic reviews was evaluated, and the research evidence was visually displayed. **RESULTS**: Randomized controlled trials were the most common type of research design. The research sample sizes were typically small. Oral CHM showed certain curative advantages in treating lung cancer. The key stages in oral CHM intervention for lung cancer are chemotherapy, radiotherapy, and late palliative treatment. The advantageous outcomes of oral CHM treatment of lung cancer are the short-term efficacy, quality of life, and adverse reactions. The perioperative stage, overall survival, pharmacoeconomic evaluation, and Chinese medicine decoctions are weak research areas. **CONCLUSIONS**: CHM has staged and therapeutic advantages in treating lung cancer. The overall methodological quality is poor, and the level of evidence requires improvement. It is necessary to carry out large-scale, standardized, and higher-quality research in the superior and weak areas of CHM treatment of lung cancer.

Acupuncture for dyspnea and breathing physiology in chronic respiratory diseases: A protocol of a systematic review and meta-analysis of randomized controlled trials Xiong C, Li Y, Li CY, Liu YF, Wei H, Fu JJ. Acupuncture for dyspnea and breathing physiology in chronic respiratory diseases: A protocol of a systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2022 Oct 14;101(41):e30909. doi: 10.1097/MD.0000000000030909. PMID: 36253986; PMCID: PMC9575781.
BACKGROUND: Dyspnea is one of the most common symptoms of chronic respiratory disease (CRD) and is closely related to increased functional disability and mortality, resulting in substantial adverse outcomes on patients and imposing great social and economic burden. Although multiple clinical trials and systematic reviews have suggested that acupuncture could be effective in treating COPD and lung cancer, little is known about its effects on dyspnea relief in patients with CRD. The present study aimed to use a systematic review approach to evaluate the effectiveness and safety of acupuncture in the treatment of dyspnea in patients with CRD. **METHODS**: We will search the following 9 databases from inception to June 30, 2022, PubMed, Web of Science, EMBASE, Cochrane Central Register of Controlled Trials, Chinese National Knowledge Infrastructure, WANFANG Database, Chinses Scientific and Technological Periodical Database, and Chinese Biomedical Database, and the Cochrane Library Database. Clinical randomized controlled trials in English or Chinese that evaluate invasive acupuncture versus control group in treatment of CRD with dyspnea will be included. The primary outcome will be dyspnea scores, breathing physiological function, and the secondary outcomes include exercise tolerance by six-minute walk distance quality of life, quality of life and adverse events. Two reviewers will independently conduct study selection, data extraction and quality assessment. The Review Manager software will be used for meta-analysis. This protocol will be carried out in accordance with the PRISMA-P guidance. **CONCLUSION**: This systematic review and meta-analysis will provide the evidence of whether acupuncture is an effective and safe intervention for CRD with dyspnea. The results will be disseminated through peer-reviewed publication.

Observation of the Curative Effect of Acupuncture for Tonifying Kidney and Removing Blood Stasis Combined with Radiofrequency Surgery in Patients with NSCLC and the Diagnostic Efficacy of Combined Detection of NTx, BGP, and CYFRA21-1 in the Occurrence of Bone Metastases Song G, Jiang T, Wang Y, Gu T, Li W. Observation of the Curative Effect of Acupuncture for Tonifying

Kidney and Removing Blood Stasis Combined with Radiofrequency Surgery in Patients with NSCLC and the Diagnostic Efficacy of Combined Detection of NTx, BGP, and CYFRA21-1 in the Occurrence of Bone Metastases. Contrast Media Mol Imaging. 2022 Sep 28;2022:8157157. doi: 10.1155/2022/8157157. PMID: 36247849; PMCID: PMC9534652.
The curative effect observation of acupuncture for tonifying kidney and removing blood stasis combined with radiofrequency surgery in patients with non-small-cell lung carcinoma (NSCLC) and the diagnostic efficacy of combined detection of NTx, BGP, and CYFRA21-1 for bone metastases are investigated. 122 NSCLC patients admitted to our hospital from January 2019 to December 2021 are selected for the examination, and the two sets of patients are randomly divided into the study set and the control set using the random number table method, with 61 cases in each set. Patients in the control set are given CT-guided percutaneous radiofrequency ablation therapy, and patients in the study set are given a combination of acupuncture therapy for tonifying the kidney and removing blood stasis on the basis of the therapy of the control set. The experimental results show that for NSCLC patients, the application of kidney-tonifying and stasis-removing acupuncture therapy combined with radiofrequency surgery can notoriously enhance the clinical therapy effect and enhance the quality of life of patients, and the detection of NTx, BGP, and CYFRA21-1 indicators can effectively predict the prognosis.

Synergy Mechanisms of Rhizoma Paridis Saponins on Non-small Cell Lung Cancer: Segmented Solid Phase Extraction, Bioactivity Screening, and Network Pharmacology Liu C, Ma Q, Du R, Chen M, Xing S, Yang Y, Rong R. Synergy Mechanisms of Rhizoma Paridis Saponins on Non-small Cell Lung Cancer: Segmented Solid Phase Extraction, Bioactivity Screening, and Network Pharmacology. Anticancer Agents Med Chem. 2022;22(20):3466-3486. doi: 10.2174/1871520622666220601090838. PMID: 35652399.
BACKGROUND: Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. Rhizoma paridis saponins (RPS), the main bioactive ingredients of Paris polyphylla Smith var. yunnanensis (PPY), have been proved to have remarkable effects on NSCLC cell lines. However, the multi-component synergistic effects and mechanisms of RPS on NSCLC have not been elucidated. **OBJECTIVE**: To decipher the multi-RPS synergistic effects and mechanisms against NSCLC based on network pharmacology combined with segmented solid-phase extraction (SPE) and bioactivity screening method. **METHODS**: Firstly, segmented SPE and cytotoxicity assays were performed to screen the RPS-enrichment fraction of PPY, and the steroidal saponins in it were identified by LC-MS/MS. Then, a network pharmacology analysis was performed to predict the potential therapeutic targets of RPS on NSCLC. Finally, viable cell counting tests and RT-qPCR were utilized to verify the synergistic effects and mechanisms of RPS. **RESULTS**: 48 potentially active compounds were identified from the 30% MeOH/EtOAc fraction of PPY (30% M/E PPY). The results of the network pharmacology analysis indicated that RPS exerted joint effects by regulating six key targets in the PI3K-AKT signaling pathway. In vitro experiments showed that due to the synergistic effects, 30% M/E PPY at 13.90 μg/mL could exert a stronger inhibitory activity on A549 cells by reducing the overexpression of six hub genes compared with the parallel control groups. **CONCLUSION**: This research elaborates on the multi-RPS synergy mechanisms against NSCLC and provides a way to develop new combination medicines for NSCLC.

MISCELLANEOUS WORKS

Lung Cancer in Women Tsai LL, Chu NQ, Blessing WA, Moonsamy P, Colson YL. Lung Cancer in Women. Ann Thorac Surg. 2022 Nov;114(5):1965-1973. doi: 10.1016/j.athoracsur.2021.09.060. Epub 2021 Nov 3. PMID: 34742731.
BACKGROUND: Lung cancer is the leading cause of cancer-related death for women in the United States. Clinical characteristics, histology, epidemiology, and treatment responses are unique for women

with lung cancer. **METHODS**: A literature search of Medline publications from 1989 to 2021 was conducted for lung cancer in women. Subsequent narrative review focused on identified differences in risk factors, diagnosis, and treatment of importance to the surgical care of these patients. **RESULTS**: Studies investigating lung cancer in which sex differences were explored demonstrated differences in risk factors, histology, and treatment response among women, with a significant postsurgical survival advantage over men (41.8 months vs 26.8 months, P = .007) and greater clinical benefit from anti-PD-1 combined with chemotherapy (hazard ratio, 0.44; 95% confidence interval, 0.25-0.76) compared with men (hazard ratio, 0.76; 95% confidence interval, 0.64-0.91). Smoking remains a dominant risk factor, and multiple clinical trials suggest lung cancer screening provides greater benefit for women. However young nonsmoking patients with lung cancer are 2-fold more likely to be female, advocating for broader sex-based screening criteria. Potential roles of genetic mutations, estrogen signaling, and infectious elements in sex-based differences in presentation, histology, prognosis, and treatment response are explored. **CONCLUSIONS**: Overall much remains unknown regarding how sex influences lung cancer risk, treatment decisions, and outcomes. However evidence of specific differences in presentation, environmental risk, molecular drivers, and mutational burden support the need to better leverage these sex-associated differences to further improve detection, diagnosis, surgical outcomes, and systemic regimens to advance the overall care strategy for women with lung cancer.

Lung Cancer Versus "Young Cancer": Is Non-Small Cell Lung Cancer in Young Patients a Different Entity? Bratova M, Brat K, Hurdalkova K, Barinova M, Drosslerova M, Kultan J, Wanke M, Koubkova L, Krejci J, Svaton M. Lung Cancer Versus "Young Cancer": Is Non-Small Cell Lung Cancer in Young Patients a Different Entity? J Adolesc Young Adult Oncol. 2022 Oct;11(5):451-458. doi: 10.1089/jayao.2021.0069. Epub 2021 Nov 2. PMID: 34726512.
PURPOSE: Aim was to analyze demographic and tumor characteristics, treatment, and survival of patients with lung cancer younger than 40 years of age (U40) compared to older subgroups (41-70 and >70 years). **METHODS**: We analyzed data of young patients diagnosed and treated in 2011-2019 in five pneumo-oncology centers in Czechia. Standard descriptive statistics, chi-squared test, Fisher exact test, and Kaplan-Meier survival analysis were used. p-Values <0.05 were considered significant. These data were compared with two control subgroups (cohort 1: 41-70 years, cohort 2: >70 years). **RESULTS**: We identified 66 patients U40, 61 with non-small cell lung cancer (NSCLC)-50.8% men, mean age 34.6 years, 54.1% nonsmokers, daily good performance status, and 82% in stage IV. Adenocarcinomas dominated, endothelial growth factor receptor (EGFR) positivity was less common than in older groups contrary to anaplastic lymphoma kinase (ALK) mutations. Median progression-free survival was 3.7 months (vs. 4.9 and 6.2 months; p = 0.006) and overall survival reached 11.7 months (vs. 22.3 and 27.3 months; p < 0.001). Young patients in stage IV and never-smokers had shorter survival than older patients. **CONCLUSION**: Patients with NSCLC U40 had significantly worse prognosis than older patients.

A global burden assessment of lung cancer attributed to residential radon exposure during 1990-2019 Shan X, Tian X, Wang B, He L, Zhang L, Xue B, Liu C, Zheng L, Yu Y, Luo B. A global burden assessment of lung cancer attributed to residential radon exposure during 1990-2019. Indoor Air. 2022 Oct;32(10):e13120. doi: 10.1111/ina.13120. PMID: 36305076.
This study aimed to explore the spatial and temporal trends of lung cancer burden attributable to residential radon exposure at the global, regional, and national levels. Based on the Global Burden of Disease Study (GBD) 2019, we collected the age-standardized mortality rate (ASMR) and age-standardized disability-adjusted life rate (ASDR) of lung cancer attributable to residential radon exposure from 1990 to 2019. The Joinpoint model was used to calculate the annual average percentage change (AAPC) to evaluate the trend of ASMR and ASDR from 1990 to 2019. The locally weighted regression

(LOESS) was used to estimate the relationship of the socio-demographic index (SDI) with ASMR and ASDR. In 2019, the global ASMR and ASDR for lung cancer attributable to residential radon exposure were 1.03 (95% CI: 0.20, 2.00) and 22.66 (95% CI: 4.49, 43.94) per 100 000 population, which were 15.6% and 23.0% lower than in 1990, respectively. According to the estimation, we found the lung cancer burden attributable to residential radon exposure declined significantly in high and high-middle SDI regions, but substantially increased in middle and low-middle SDI regions from 1990 to 2019. Across age and sex, the highest burden of lung cancer attributable to residential radon exposure was found in males and elderly groups. **In Conclusion**, the global burden of lung cancer attributable to residential radon exposure showed a declining trend from 1990 to 2019, but a relatively large increase was found in the middle SDI regions. In 2019, the burden of lung cancer attributable to residential radon exposure remained high, particularly in males, the elderly, and high-middle SDI regions compared with other groups.

From COPD to Lung Cancer: Mechanisms Linking, Diagnosis, Treatment, and Prognosis Qi C, Sun SW, Xiong XZ. From COPD to Lung Cancer: Mechanisms Linking, Diagnosis, Treatment, and Prognosis. Int J Chron Obstruct Pulmon Dis. 2022 Oct 17;17:2603-2621. doi: 10.2147/COPD.S380732. PMID: 36274992; PMCID: PMC9586171.

Many studies have proved that the pathogenesis of the chronic obstructive pulmonary disease (COPD) and lung cancer is related, and may cause and affect each other to a certain extent. In fact, the change of chronic airway obstruction will continue to have an impact on the screening, treatment, and prognosis of lung cancer. In this comprehensive review, we outlined the links and heterogeneity between COPD and lung cancer and finds that factors such as gene expression and genetic susceptibility, epigenetics, smoking, epithelial mesenchymal transformation (EMT), chronic inflammation, and oxidative stress injury may all play a role in the process. Although the relationship between these two diseases have been largely determined, the methods to prevent lung cancer in COPD patients are still limited. Early diagnosis is still the key to a better prognosis. Thus, it is necessary to establish more intuitive screening evaluation criteria and find suitable biomarkers for lung cancer screening in high-risk populations with COPD. Some studies have indicated that COPD may change the efficacy of anti-tumor therapy by affecting the response of lung cancer patients to immune checkpoint inhibitors (ICIs). And for lung cancer patients with COPD, the standardized management of COPD can improve the prognosis. The treatment of lung cancer patients with COPD is an individualized, comprehensive, and precise process. The development of new targets and new strategies of molecular targeted therapy may be the breakthrough for disease treatment in the future.

The Effect of Biomarker Use on the Speed and Duration of Clinical Trials for Cancer Drugs Mohamed L, Manjrekar S, Ng DP, Walsh A, Lopes G, Parker JL. The Effect of Biomarker Use on the Speed and Duration of Clinical Trials for Cancer Drugs. Oncologist. 2022 Oct 1;27(10):849-856. doi: 10.1093/oncolo/oyac130. PMID: 35993585; PMCID: PMC9526484.

BACKGROUND: The purpose of this study was to explore the effects biomarkers have on the duration and speed of clinical trials in oncology. **MATERIALS AND METHODS**: Clinical trial data was pooled from www.clinicaltrials.gov within the 4 cancer indications of non-small cell lung cancer, breast cancer, melanoma, and colorectal cancer. Heatmaps of clinical timelines were used to display differences in the frequency and timing of clinical trials across trials that used or did not use biomarkers, for all 4 indications. **RESULTS**: Screening of 8630 clinical trials across the 4 indications yielded 671 unique drugs corresponding to 1224 eligible trials used in our analysis. The constructed heatmaps visually represented that biomarkers did not have an effect on the time gap between trial phases for non-small cell lung cancer and melanoma but did for colorectal and breast cancer trials, reducing the speed of trial timelines. It was also observed that biomarker trials were more often concurrent over shorter periods of

time and began later in the timeline for non-small cell lung and colorectal cancers. **CONCLUSION**: The novel visualization method revealed longer gaps between trial phases, later clinical trial start times, and shorter periods of concurrently run trials for drugs that used biomarkers. The study highlights that biomarker-driven trials might impact drug approval timelines and need to be considered carefully in clinical development plan.

Traffic-related Air Pollution and Lung Cancer Incidence: The California Multiethnic Cohort Study
Cheng I, Yang J, Tseng C, Wu J, Shariff-Marco S, Park SL, Conroy SM, Inamdar PP, Fruin S, Larson T, Setiawan VW, DeRouen MC, Gomez SL, Wilkens LR, Le Marchand L, Stram DO, Samet J, Ritz B, Wu AH. Traffic-related Air Pollution and Lung Cancer Incidence: The California Multiethnic Cohort Study. Am J Respir Crit Care Med. 2022 Oct 15;206(8):1008-1018. doi: 10.1164/rccm.202107-1770OC. PMID: 35649154.
RATIONALE: Although the contribution of air pollution to lung cancer risk is well characterized, few studies have been conducted in racially, ethnically, and socioeconomically diverse populations. **OBJECTIVES**: To examine the association between traffic-related air pollution and risk of lung cancer in a racially, ethnically, and socioeconomically diverse cohort. **METHODS**: Among 97,288 California participants of the Multiethnic Cohort Study, we used Cox proportional hazards regression to examine associations between time-varying traffic-related air pollutants (gaseous and particulate matter pollutants and regional benzene) and lung cancer risk (n = 2,796 cases; average follow-up = 17 yr), adjusting for demographics, lifetime smoking, occupation, neighborhood socioeconomic status (nSES), and lifestyle factors. Subgroup analyses were conducted for race, ethnicity, nSES, and other factors. **MEASUREMENTS AND MAIN RESULTS**: Among all participants, lung cancer risk was positively associated with nitrogen oxide (hazard ratio [HR], 1.15 per 50 ppb; 95% confidence interval [CI], 0.99-1.33), nitrogen dioxide (HR, 1.12 per 20 ppb; 95% CI, 0.95-1.32), fine particulate matter with aerodynamic diameter <2.5 μm (HR, 1.20 per 10 μg/m3; 95% CI, 1.01-1.43), carbon monoxide (HR, 1.29 per 1,000 ppb; 95% CI, 0.99-1.67), and regional benzene (HR, 1.17 per 1 ppb; 95% CI, 1.02-1.34) exposures. These patterns of associations were driven by associations among African American and Latino American groups. There was no formal evidence for heterogeneity of effects by nSES (P heterogeneity > 0.21), although participants residing in low-SES neighborhoods had increased lung cancer risk associated with nitrogen oxides, and no association was observed among those in high-SES neighborhoods. **CONCLUSIONS**: These findings in a large multiethnic population reflect an association between lung cancer and the mixture of traffic-related air pollution and not a particular individual pollutant. They are consistent with the adverse effects of air pollution that have been described in less racially, ethnically, and socioeconomically diverse populations. Our results also suggest an increased risk of lung cancer among those residing in low-SES neighborhoods.

Primary Care Practitioner Perceptions on the Follow-up of Abnormal Cancer Screening Test Results Atlas SJ, Tosteson ANA, Burdick TE, Wright A, Breslau ES, Dang TH, Wint AJ, Smith RE, Harris KA, Zhou L, Haas JS. Primary Care Practitioner Perceptions on the Follow-up of Abnormal Cancer Screening Test Results. JAMA Netw Open. 2022 Sep 1;5(9):e2234194. doi: 10.1001/jamanetworkopen.2022.34194. PMID: 36173627; PMCID: PMC9523497.
IMPORTANCE: Health care systems focus on delivering routine cancer screening to eligible individuals, yet little is known about the perceptions of primary care practitioners (PCPs) about barriers to timely follow-up of abnormal results. **OBJECTIVE**: To describe PCP perceptions about factors associated with the follow-up of abnormal breast, cervical, colorectal, and lung cancer screening test results. Design, setting, and participants: Survey study of PCPs from 3 primary care practice networks in New England between February and October 2020, prior to participating in a randomized clinical trial to improve follow-up of abnormal cancer screening test results. Participants were physicians and advanced

practice clinicians from participating practices. Main outcomes and measures: Self-reported process, attitudes, knowledge, and satisfaction about the follow-up of abnormal cancer screening test results. **RESULTS**: Overall, 275 (56.7%) PCPs completed the survey (range by site, 34.9%-71.9%) with more female PCPs (61.8% [170 of 275]) and general internists (73.1% [201 of 275]); overall, 28,7% (79 of 275) were aged 40 to 49 years. Most PCPs felt responsible for managing abnormal cancer screening test results with the specific cancer type being the best factor (range, 63.6% [175 of 275] for breast to 81.1% [223 of 275] for lung; P < .001). The PCPs reported limited support for following up on overdue abnormal cancer screening test results. Standard processes such as automated reports, reminder letters, or outreach workers were infrequently reported. Major barriers to follow-up of abnormal cancer screening test results across all cancer types included limited electronic health record tools (range, 28.5% [75 of 263]-36.5%[96 of 263]), whereas 50% of PCPs felt that there were major social barriers to receiving care for abnormal cancer screening test results for colorectal cancer. Fewer than half reported being very satisfied with the process of managing abnormal cancer screening test results, with satisfaction being greatest for breast cancer (46.9% [127 of 271]) and lowest for cervical (21.8% [59 of 271]) and lung cancer (22.4% [60 of 268]). **CONCLUSIONS AND RELEVANCE**: In this survey study of PCPs, important deficiencies in systems for managing abnormal cancer screening test results were reported. These findings suggest a need for comprehensive organ-agnostic systems to promote timely follow-up of abnormal cancer screening results using a primary care-focused approach across the range of cancer screening tests.

Participation of Older Adults in Clinical Trials for New Drug Applications and Biologics License Applications From 2010 Through 2019 Lau SWJ, Huang Y, Hsieh J, Wang S, Liu Q, Slattum PW, Schwartz JB, Huang SM, Temple R. Participation of Older Adults in Clinical Trials for New Drug Applications and Biologics License Applications From 2010 Through 2019. JAMA Netw Open. 2022 Oct 3;5(10):e2236149. doi: 10.1001/jamanetworkopen.2022.36149. PMID: 36239939; PMCID: PMC9568796.

IMPORTANCE: Older age may be accompanied by changes in the pharmacokinetics or pharmacodynamics or both of medications that can result in altered safety and efficacy profiles. **OBJECTIVE**: To assess representation of older adults in clinical trials of new drug applications (NDAs) and biologics license applications (BLAs). **DESIGN, SETTING, AND PARTICIPANTS**: This cross-sectional study analyzed US Food and Drug Administration (FDA) data for NDAs and BLAs approved from 2010 through 2019. Age distribution of clinical trial participants was compared with age distribution of the US population with the disease or disorder (prevalent population). Data were from adults enrolled in registration trials for depression, heart failure, insomnia, non-small cell lung cancer (NSCLC), nonvalvular atrial fibrillation (NVAF) stroke prevention, osteoporosis, and type 2 diabetes or adults sampled from US prevalent population in community-dwelling health data. Data were analyzed from November 2020 to February 2021. **EXPOSURES**: Trial enrollment. **MAIN OUTCOMES AND MEASURES**: Representativeness of trial populations was assessed by the participation to prevalence ratio (PPR) defined as the percentage of patients by age group among clinical trial participants to the percentage of patients by age group among US prevalent population. **RESULTS**: Data from 166 clinical trials (229 558 participants) for 44 NDAs and BLAs were analyzed. The most consistent finding was the limited enrollment of the oldest age groups, namely those 75 years and above for type 2 diabetes and NSCLC, and 80 years and above for NVAF stroke prevention, insomnia, heart failure, and osteoporosis. Adults aged 60 to 74 years were enrolled in equal or greater proportion than the US prevalent population. **CONCLUSIONS AND RELEVANCE**: In this cross-sectional study, underrepresentation of the oldest adults existed during evaluation of new drugs and biologics, yet the older adults may represent significant proportions of the treatment population. Closing the representation gap between clinical trial enrollment and potential treatment populations is essential for safe and effective use of new drugs and biologics.

Trends and risk of lung cancer among people living with HIV in the USA: a population-based registry linkage study Haas CB, Engels EA, Horner MJ, Freedman ND, Luo Q, Gershman S, Qiao B, Pfeiffer RM, Shiels MS. Trends and risk of lung cancer among people living with HIV in the USA: a population-based registry linkage study. Lancet HIV. 2022 Oct;9(10):e700-e708. doi: 10.1016/S2352-3018(22)00219-3. PMID: 36179753; PMCID: PMC9641618.

BACKGROUND: Lung cancer is a common cancer in people living with HIV, but the risk of cancer in this group has not been investigated for over a decade. We investigated trends in relative and absolute risk of lung cancer among people living with HIV of various age groups in the USA. **METHODS**: In this population-based registry linkage study, we used 2001-16 data from the HIV/AIDS Cancer Match study, which links data from HIV and cancer registries from 13 regions in the USA. We included non-Hispanic White, non-Hispanic Black, and Hispanic individuals living with HIV aged 20-89 years in our study population. Average annual percentage changes in lung cancer rates were estimated with multivariable Poisson regression, and standardised incidence ratios (SIRs) and excess absolute risks were estimated comparing people living with HIV with the general US population. We used non-parametric cumulative incidence curves to estimate the 5-year cumulative incidence of lung cancer and two AIDS-defining cancers (non-Hodgkin lymphoma and Kaposi sarcoma). **FINDINGS**: There were 3426 lung cancers in 4 310 304 person-years of follow-up in our study population. Age-standardised lung cancer incidence rates in people living with HIV declined by 6% per year (95% CI -7 to -5) during 2001-16, with greater declines in the 20-29 age group (-11%, -16 to 6) than in the older age groups (eg, -3% [-6 to 1] in those aged 70-89 years). During 2013-16, the SIR of lung cancer in people living with HIV was 2·01 (95% CI 1·52 to 2·61) in those aged 40-49 years, and 1·31 (1·12 to 1·52) in those aged 60-69 years, whereas the excess absolute risk among people living with HIV was 11·87 (3·95 to 21·89) per 100 000 person-years for those aged 40-49 years and 48·23 (6·88 to 95·47) per 100 000 person-years for those aged 60-69 years. Beginning in 2011, the 5-year cumulative incidence for lung cancer (1·36%, 95% CI 1·17 to 1·53) surpassed that of Kaposi sarcoma (0·12%, 0·06 to 0·17) and non-Hodgkin lymphoma (0·45%, 0·35 to 0·56) for people living with HIV aged 60-69 years. **INTERPRETATION**: Between 2001 and 2016, the risk of lung cancer decreased for people living with HIV aged 20-69 years, but remained substantially elevated compared with the general population, probably due to a combination of smoking and immunosuppression. For people living with HIV aged 60 years and older, the risk of lung cancer exceeds that of two of the most common AIDS-defining cancers, highlighting the importance of lung cancer among the growing older population of people living with HIV.

What's Current and What's New in Mesothelioma? Leal JL, Hoang W, Xue J, Dunne B, John T, Harden S. What's Current and What's New in Mesothelioma? Clin Oncol (R Coll Radiol). 2022 Nov;34(11):771-780. doi: 10.1016/j.clon.2022.08.029. Epub 2022 Sep 22. PMID: 36155156.

Malignant mesothelioma is a rare disease with limited treatment options. In malignant pleural mesothelioma (MPM), radical trimodality approaches, including surgery, radiotherapy and systemic chemo- and immunotherapy, have been delivered in some countries but remain controversial due to a lack of randomised evidence. Even in the unresectable scenario, surgery and radiotherapy play an important role in managing pleural effusions and pain, which may optimise wellbeing and maintain performance status. From the systemic treatment point of view, the recent incorporation of anti-angiogenics and, more importantly, immunotherapy has changed the standard of care in a space where chemotherapy with platinum and pemetrexed was the only therapeutic intervention with demonstrated benefits in overall survival. Histology is essential in determining an initial treatment plan as non-epithelioid MPMs may have a higher substantial survival improvement with dual immunotherapy compared with chemotherapy, whereas chemotherapy remains an option for epithelioid MPM; however, predictive biomarkers for systemic therapy are not entirely validated to guide the selection, as a subgroup of MPM patients might

not benefit from immunotherapy. This overview approaches how the overall management of mesothelioma is evolving to incorporate the recent changes in the standards of care.

Costs Around the First Year of Diagnosis for 4 Common Cancers Among the Privately Insured Shih YT, Xu Y, Bradley C, Giordano SH, Yao J, Yabroff KR. Costs Around the First Year of Diagnosis for 4 Common Cancers Among the Privately Insured. J Natl Cancer Inst. 2022 Oct 6;114(10):1392-1399. doi: 10.1093/jnci/djac141. PMID: 36099068; PMCID: PMC9552304.
BACKGROUND: We estimated trends in total and out-of-pocket (OOP) costs around the first year of diagnosis for privately insured nonelderly adult cancer patients. **METHODS**: We constructed incident cohorts of breast, colorectal, lung, and prostate cancer patients diagnosed between 2009 and 2016 using claims data from the Health Care Cost Institute. We identified cancer-related surgery, intravenous (IV) systemic therapy, and radiation and calculated associated total and OOP costs (in 2020 US dollars). We assessed trends in health-care utilization and cost by cancer site with logistic regressions and generalized linear models, respectively. **RESULTS**: The cohorts included 105 255 breast, 23 571 colorectal, 11 321 lung, and 59 197 prostate cancer patients. For patients diagnosed between 2009 and 2016, total mean costs per patient increased from $109 544 to $140 732 for breast (29%), $151 751 to $168 730 for lung (11%) or $53 300 to $55 497 for prostate (4%) cancer were statistically significant. Increase for colorectal cancer (1%, $136 652 to $137 663) was not statistically significant (P = .09). OOP costs increased to more than 15% for all cancers, including colorectal, to more than $6000 by 2016. Use of IV systemic therapy and radiation statistically significantly increased, except for lung cancer. Cancer surgeries statistically significantly increased for breast and colorectal cancer but decreased for prostate cancer (P < .001). Total costs increased statistically significantly for nearly all treatment modalities, except for IV systemic therapy in colorectal and radiation in prostate cancer. **CONCLUSIONS**: Rising costs of cancer treatments, compounded with greater cost sharing, increased OOP costs for privately insured, nonelderly cancer patients. Policy initiatives to mitigate financial hardship should consider cost containment as well as insurance reform.

Marijuana and the Lung: Evolving Understandings Joshi M, Joshi A, Bartter T. Marijuana and the Lung: Evolving Understandings. Med Clin North Am. 2022 Nov;106(6):1093-1107. doi: 10.1016/j.mcna.2022.07.010. Epub 2022 Oct 4. PMID: 36280335.
Human beings have used marijuana products for centuries. Relatively recent data showing extensive cannabinoid receptors, particularly in the brain, help to explain the impacts of cannabinoids on symptoms/diseases, such as pain and seizures, with major nervous system components. Marijuana can cause bronchitis, but a moderate body of literature suggests that distal airway/parenchymal lung disease does not occur; marijuana does not cause chronic obstructive pulmonary disease and probably does not cause lung cancer, distinctly different from tobacco. Potentials for cognitive impairment and for damage to the developing brain are contextually important as its beneficial uses are explored.

Associations of Daily Versus Nondaily Smoking, Tobacco-Related Risk Perception, and Cancer Diagnosis Among Adults in the Population Assessment of Tobacco and Health (PATH) Study Land SR, Baker L, Bachand J, Twesten J, Kaufman AR, Reyes-Guzman CM. Associations of Daily Versus Nondaily Smoking, Tobacco-Related Risk Perception, and Cancer Diagnosis Among Adults in the Population Assessment of Tobacco and Health (PATH) Study. Nicotine Tob Res. 2022 Oct 17;24(10):1540-1547. doi: 10.1093/ntr/ntac059. PMID: 35245943; PMCID: PMC9575975.
INTRODUCTION: Nondaily smoking has become increasingly common among cigarette smokers. Our objective was to determine whether current daily versus nondaily smoking differed by tobacco-related risk perceptions (TRRPs), demographic factors, and cancer history. **METHODS**: Participants were all adults in Waves 1-3 of the longitudinal cohort Population Assessment of Tobacco and Health Study who

were current smokers at Wave 3 (N = 8307). The primary analysis was weighted logistic regression of daily versus nondaily smoking at Wave 3. TRRP measures were cigarette harm perception, worry that tobacco products will damage one's health, belief that smoking cigarettes causes [lung/bladder/mouth/liver] cancer, and nondaily cigarette harm perception (Likert-type scale). Other measures included demographic factors, other tobacco product use, minor at time of first cigarette, and cancer survivor status (yes/no). **RESULTS**: Among current smokers, daily versus nondaily smoking was significantly associated with being a minor at time of first cigarette (OR = 1.54, p < .001), TRRPs (OR = 0.83, p < .001; OR = 1.40, p < .001; and OR = 1.17, p = .009 [harm perception, worry, and nondaily cigarette harm perception, respectively]), and interaction between cancer survivor status and belief that smoking causes cancer (p < .001). TRRPs among current smokers did not differ significantly between cancer survivors and respondents without a cancer history. **CONCLUSIONS**: Respondents with lower harm perception, higher worry, and higher nondaily cigarette harm perception were more likely to be daily versus nondaily smokers. Respondents with higher belief that smoking causes cancer or who were cancer survivors were less likely to be daily (versus nondaily) smokers compared to respondents with low belief and no cancer history. **IMPLICATIONS**: This study is unique in that it examined associations of smoking cigarettes daily versus nondaily with tobacco-related risk perceptions and cancer survivorship-comparing cancer survivors to those without a cancer history. Given the increasing prevalence of nondaily smoking as compared with daily smoking in the general population, and the prognostic significance of smoking after cancer diagnosis, these findings fill a clinically important gap in the literature and provide a foundation for further research.

An EHR-automated and theory-based population health management intervention for smoking cessation in diverse low-income patients of safety-net health centers: a pilot randomized controlled trial Hitsman B, Matthews PA, Papandonatos GD, Cameron KA, Rittner SS, Mohanty N, Long T, Ackermann RT, Ramirez E, Carr J, Cordova E, Bridges C, Flowers-Carson C, Giachello AL, Hamilton A, Ciecierski CC, Simon MA. An EHR-automated and theory-based population health management intervention for smoking cessation in diverse low-income patients of safety-net health centers: a pilot randomized controlled trial. Transl Behav Med. 2022 Oct 7;12(9):892-899. doi: 10.1093/tbm/ibac026. PMID: 36205472; PMCID: PMC9540977.

This study tested the preliminary effectiveness of an electronic health record (EHR)-automated population health management (PHM) intervention for smoking cessation among adult patients of a federally qualified health center in Chicago. Participants (N = 190; 64.7% women, 82.1% African American/Black, 8.4% Hispanic/Latino) were self-identified as smokers, as documented in the EHR, who completed the baseline survey of a longitudinal "needs assessment of health behaviors to strengthen health programs and services." Four weeks later, participants were randomly assigned to the PHM intervention (N = 97) or enhanced usual care (EUC; N = 93). PHM participants were mailed a single-page self-determination theory (SDT)-informed letter that encouraged smoking cessation or reduction as an initial step. The letter also addressed low health literacy and low income. PHM participants also received automated text messages on days 1, 5, 8, 11, and 20 after the mailed letter. Two weeks after mailing, participants were called by the Illinois Tobacco Quitline. EUC participants were e-referred following a usual practice. Participants reached by the quitline were offered behavioral counseling and nicotine replacement therapy. Outcome assessments were conducted at weeks 6, 14, and 28 after the mailed letter. Primary outcomes were treatment engagement, utilization, and self-reported smoking cessation. In the PHM arm, 25.8% of participants engaged in treatment, 21.6% used treatment, and 16.3% were abstinent at 28 weeks. This contrasts with no quitline engagement among EUC participants, and a 6.4% abstinence rate. A PHM approach that can reach all patients who smoke and address unique barriers for low-income individuals may be a critical supplement to clinic-based care.