Caring Ambassadors Lung Cancer Program
Literature Review, January 2020

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Long noncoding RNA VPS9D1-AS1 augments the malignant phenotype of non-small cell lung cancer by sponging microRNA-532-3p and thereby enhancing HMGA2 expression. Han X1, Huang T1, Han J2. Aging (Albany NY). 2020 Jan 5;12(1):370-386. doi: 10.18632/aging.102628. Epub 2020 Jan 5.

We investigated the influence of the long noncoding RNA VPS9D1 antisense RNA 1 (VPS9D1-AS1) on the malignant phenotype of non-small cell lung cancer (NSCLC) cells in vitro and in vivo. We also explored the mechanisms by which VPS9D1-AS1 exerts its oncogenic action during NSCLC progression. VPS9D1-AS1 expression was upregulated in NSCLC; the extent of its upregulation significantly correlated with patients' adverse clinicopathological characteristics and shorter overall survival. When VPS9D1-AS1 was knocked down in NSCLC cells, their proliferation, colony-forming capacity, migration, and invasiveness were lower, whereas their apoptosis rate was higher, compared to the control. VPS9D1-AS1 knockdown attenuated tumor growth of NSCLC cells in vivo. Mechanistically, VPS9D1-AS1 directly interacted with microRNA-532-3p (miR-532-3p) in NSCLC cells; the impact of VPS9D1-AS1 knockdown on NSCLC cells was attenuated by miR-532-3p inhibition. Furthermore, VPS9D1-AS1 knockdown decreased the expression of high mobility group AT-hook 2 (HMGA2) in NSCLC cells via miR-532-3p sponging. Recovery of HMGA2 expression partially reversed the inhibitory effects of VPS9D1-AS1 knockdown on NSCLC cells. Thus, VPS9D1-AS1 functions as a competing endogenous RNA that positively regulates HMGA2 expression by sponging miR-532-3p in NSCLC cells, suggesting that the VPS9D1-AS1-miR-532-3p-HMGA2 pathway can be a potential diagnostic and/or therapeutic target in NSCLC.

Comprehensive Analysis of Aberrantly Expressed Profiles of lncRNAs and miRNAs with Associated ceRNA Network in Lung Adenocarcinoma and Lung Squamous Cell Carcinoma. Dong R1, Liu J2, Sun W2, Ping W3. Pathol Oncol Res. 2020 Jan 2. doi: 10.1007/s12253-019-00780-4. [Epub ahead of print]

Lung cancer (LC) continues to be the leading cause of cancer-related deaths worldwide and the prognosis remains poor worldwide. At present, the long non-coding RNAs (lncRNAs) was considered as a part of competing endogenous RNA (ceRNA) network act as natural microRNA (miRNA) sponges to regulate protein-coding gene expression. However, functional roles of lncRNA-mediated ceRNAs in LC are insufficiently understood. To classify the specific mechanism of lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC), we comprehensively compared the expression profiles of mRNAs, lncRNAs and miRNAs obtained from 509 LUAD, 473 LUSC tissues and 49 adjacent non-cancerous lung tissues, based on The Cancer Genome Atlas (TCGA). After screening for differently expressed (DE) mRNAs, DEmiRNAs, DElncRNAs and weighted gene co-expression network analysis (WGCNA) ($|\log2FC| > 2.0$ and an adjusted p value <0.05), a total of 4478 DEmRNAs, 526 DElncRNAs and 75 DEmiRNAs in LUAD, while 6237 DEmRNAs, 843 DElncRNAs and 117 DEmiRNAs in LUSC were discovered. Interaction (PPI) network analysis was performed to identify 656 nodes and 2987 edges (minimum required interaction score > 0.9), as well as 8 different protein-protein interactions. Gene ontology (GO) analysis mainly associated with cell proliferation. KEGG pathway enrichment analyses most partly associated with metabolism pathway and cytokine-cytokine receptor interaction. Finally, the dysregulated lncRNA-miRNA-ceRNA network was constructed based on correlation analyses and a total of 62 dysregulated lncRNAs, 28 DEmRNAs and 18 DEmiRNAs were involved. The most significant lncRNAs included DElncRNAs, LINC00641 and AC004947.2, miRNAs included miR-6860, miR-1285-3p, miR-767-3p and miR-7974, mRNAs included MAP3K3, FGD3 and ATP1B2. Then we analyzed and described the potential characteristics of biological function and pathological roles of the LUAD and LUSC ceRNA co-regulatory network. Our findings revealed ceRNA network will be beneficial for promoting the understanding of lncRNA-mediated ceRNA regulatory mechanisms in the pathogenesis of LUAD and LUSC.

Knockdown of circ-ABCB10 promotes sensitivity of lung cancer cells to cisplatin via miR-556-3p/AK4 axis. Wu Z1, Gong Q2, Yu Y2, Zhu J2, Li W3. BMC Pulm Med. 2020 Jan 13;20(1):10. doi: 10.1186/s12890-019-1035-z.

BACKGROUND: Due to the acquired drug resistance, the potency of cisplatin-based chemotherapy is limited in lung cancer, which is a big obstacle in clinical treatment of lung cancer. Abundant evidence has revealed that circular RNAs (circRNAs) exerted facilitating or suppressive function on the tumorigenesis of multiple cancers. The oncogenic role of circ-ABCB10 in breast cancer and clear cell renal cell carcinoma has been validated in recent researches. However, the regulatory mechanism of circ-ABCB10 and its relation to cellular sensitivity to cisplatin in lung cancer is poorly understood. **METHODS:** The expression and characteristic of circ-ABCB10 were analyzed by RT-qPCR and nucleic acid electrophoresis. CCK-8, colony formation, TUNEL and transwell assays were applied to probe the role of FOXD3-AS1 in lung cancer. The interactions of miR-556-3p with circ-ABCB10 and AK4 were testified by luciferase reporter and RIP assays. **RESULTS:** Circ-ABCB10 was markedly upregulated and featured with loop structure in lung cancer. Circ-ABCB10 depletion suppresses lung cancer progression and sensitizes lung cancer cells to cisplatin. Molecular mechanism assays manifested that circ-ABCB10 bound with miR-556-3p and negatively modulated miR-556-3p expression. Additionally, AK4 was testified to be the downstream target of miR-556-3p. More importantly, rescue assays clarified that upregulation of AK4 could reverse the cisplatin-sensitizing and tumor-suppressing effect of circ-ABCB10 knockdown on lung cancer cells. **CONCLUSIONS:** Circ-ABCB10 knockdown enhances sensitivity of lung cancer cells to cisplatin by targeting miR-556-3p/AK4 axis.

SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

Education Level Predicts Appropriate Follow-Up of Incidental Findings From Lung Cancer Screening. Kapoor S1, Deppen SA2, Paulson AB3, Haddad D4, Cook JP3, Sandler KL3. J Am Coll Radiol. 2020 Jan 10. pii: S1546-1440(19)31477-2. doi: 10.1016/j.jacr.2019.12.014. [Epub ahead of print]
PURPOSE: The aim of this study was to identify predictors of appropriate follow-up for clinically significant incidental findings (IFs) detected with low-dose CT during lung cancer screening. METHODS: Charts of 1,458 prospectively enrolled lung screening patients from January 1, 2015, to October 31, 2018, were reviewed. IFs, other than coronary artery calcification and emphysema, were identified. ACR practice guidelines defined appropriate patient follow-up. Patient demographic and social characteristics were obtained from the initial shared decision-making visit and the electronic medical record. Factors of interest included age, gender, race, education level, and insurance status. Education level was reported as high school graduate or less or education past high school. A multivariate logistic regression was estimated to assess patient factors associated with appropriate follow-up. RESULTS: One hundred thirty-eight participants (9%) with 141 actionable IFs were identified. The overall appropriate follow-up rate was 82%. The most common IFs were renal lesions (16%), dilated thoracic aorta (10%), and pulmonary fibrosis (10%). Univariate analysis of appropriate patient follow-up revealed a significant difference for education level (P = .02). A greater than high school education remained strongly associated with appropriate follow-up after controlling for other demographic factors. CONCLUSIONS: Appropriate patient follow-up of clinically significant IFs from lung cancer screening is a well-recognized avenue to improve population health. Education level is a significant independent predictor of appropriate follow-up of IFs, whether as a surrogate for low socioeconomic status or as an indication of health literacy. To address these realities, lung screening shared decision making should adapt to consider health care access and health literacy.

MicroRNA-based biomarkers for diagnosis of non-small cell lung cancer (NSCLC). Liao J1, Shen J1, Leng Q1, Qin M1, Zhan M2, Jiang F1. Thorac Cancer. 2020 Jan 28. doi: 10.1111/1759-7714.13337. [Epub ahead of print]
BACKGROUND: The development of biomarkers for the early detection of non-small cell lung cancer (NSCLC) is clinically important. We have developed miRNA biomarkers in sputum and plasma, respectively, for NSCLC. Herein, we evaluate whether integrated analysis of the miRNAs across the different types of specimens could improve the early detection of NSCLC. **METHODS:** Using reverse transcription PCR, we determined expressions of two miRNAs (miRs-31-5p and 210-3p) in sputum and three miRNAs (miRs-21-5p, 210-3p, and 486-5p) in plasma of a training cohort of 76 NSCLC patients and 72 cancer-free smokers. The results were validated in a testing cohort of 56 NSCLC patients and 55 cancer-free smokers. **RESULTS:** The panels of two sputum miRNAs and three plasma miRNAs had 65.8-75.0% sensitivities and 83.3-87.5% specificities for diagnosis of NSCLC in the training cohort. The individual sputum or plasma miRNA panel had a higher sensitivity for squamous cell carcinoma or adenocarcinoma of the lung, respectively. From the miRNAs, we optimized an integrated panel of biomarkers consisting of two sputum miRNAs (miRs-31-5p and 210-3p) and one plasma miRNA (miR-21-5p) that had higher sensitivity (85.5%) and specificity (91.7%) for diagnosis of NSCLC compared with the individual panels alone. Furthermore, the performance of the integrated panel of biomarkers was independent of histology and stage of NSCLC, and patients' age, sex, and ethnicity. The performance of the integrated panel of biomarkers was confirmed in the testing cohort. **CONCLUSIONS:** Integrating biomarkers across different body fluids would synergistically improve the early detection of NSCLC. **KEY POINTS:** Lung cancer is a heterogeneous disease and develops from complex aberrations. Integrating sputum and plasma miRNAs has higher accuracy than when they are used alone.

Unique molecular features and clinical outcomes in young patients with non-small cell lung cancer harboring ALK fusion genes. Tian P1,2, Liu Y1, Zeng H1, Tang Y3, Lizaso A4, Ye J4, Shao L4, Li Y5. J Cancer Res Clin Oncol. 2020 Jan 1. doi: 10.1007/s00432-019-03116-6. [Epub ahead of print]
PURPOSE: This study aimed to determine the molecular features and clinical outcomes of young patients with non-small cell lung cancer (NSCLC) harboring ALK fusion genes. **METHODS:** We interrogated the genomic profile of 1652 patients with lung cancer who underwent targeted next-generation sequencing to screen for candidate oncogenic drivers using histological specimens acquired from January 2016 to December 2018. **RESULTS:** ALK fusions were identified in 101 NSCLC patients, and 52 of them were diagnosed before the age of 50 years (52/367, 14.2%). Of the 52 patients with early-onset disease, 22 (42.3%) were male and 43 (82.7%) never smoked; the median patient age was 44 years (range 28-50 years). The most frequently occurring ALK fusion partner was EML4, which was identified in 80.8% (42/52) of young patients. Compared to the older patients, patients with early-onset disease were more likely to harbor EML4-ALK variant 1 (38.5% vs. 14.3%; P = 0.007). We also identified rare ALK fusions, including CHRNA7-ALK, TACR1-ALK, HIP1-ALK, DYSF-ALK and ITGAV-ALK, in patients with early-onset disease, and patients with these fusions responded well to crizotinib treatment. A statistically significant difference was observed in progression-free survival (PFS) between the young patients and older patients who received crizotinib as the first-line therapy (17.5 months vs 9.0 months, P = 0.048). However, the median PFS of young patients harboring concurrent TP53 mutations was only 6.2 months. **CONCLUSION:** Unique genetic characteristics were found in ALK-rearranged NSCLC patients with early disease onset, and these patients responded better to crizotinib and had longer PFS compared to patients with later disease onset. However, patients with concomitant TP53 mutations may not have a significant response to treatment.

Simplified molecular classification of lung adenocarcinomas based on EGFR, KRAS, and TP53 mutations. Ruiz-Cordero R1, Ma J2, Khanna A3, et al. BMC Cancer. 2020 Jan 31;20(1):83. doi: 10.1186/s12885-020-6579-z.
BACKGROUND: Gene expression profiling has consistently identified three molecular subtypes of lung adenocarcinoma that have prognostic implications. To facilitate stratification of patients with this disease into similar molecular subtypes, we developed and validated a simple, mutually exclusive classification. **METHODS:** Mutational status of EGFR, KRAS, and TP53 was used to define seven mutually exclusive molecular subtypes. A development cohort of 283 cytology specimens of lung adenocarcinoma was used to evaluate the associations between the proposed classification and clinicopathologic variables including demographic characteristics, smoking history, fluorescence in situ hybridization and molecular results. For validation and prognostic assessment, 63 of the 283 cytology specimens with available survival data were combined with a separate cohort of 428 surgical pathology specimens of lung adenocarcinoma. **RESULTS:** The proposed classification yielded significant associations between these molecular subtypes and clinical and prognostic features. We found better overall survival in patients who underwent surgery and had tumors enriched for EGFR mutations. Worse overall survival was associated with older age, stage IV disease, and tumors with co-mutations in KRAS and TP53. Interestingly, neither chemotherapy nor radiation therapy showed benefit to overall survival. **CONCLUSIONS:** The mutational status of EGFR, KRAS, and TP53 can be used to easily classify lung adenocarcinoma patients into seven subtypes that show a relationship with prognosis, especially in patients who underwent surgery, and these subtypes are similar to classifications based on more complex genomic methods reported previously.

Patient-centered Radiology Reporting for Lung Cancer Screening. Vitzthum von Eckstaedt H 5th1, Kitts AB2, Swanson C1, Hanley M1, Krishnaraj A1. J Thorac Imaging. 2020 Jan 6. doi: 10.1097/RTI.0000000000000469. [Epub ahead of print]
Medicine is slowly transitioning toward a more patient-centered approach, with patients taking a more central role in their own care. A key part of this movement has involved giving patients increased access to their medical record and imaging results via electronic health portals. However, most patients lack the knowledge to fully understand medical documents, which are generally written above their comprehension level. Radiology reports, in particular, utilize complex terminology due to radiologists' historic function as consultants to other physicians, with little direct communication to patients. As a result, typical radiology reports lack standardized formatting, and they are often inscrutable to patients. Numerous studies examining patient preference also point to a trend for more accessible radiology reports geared toward patients. Reports designed with an infographic format, combining simple pictures and standardized text, may be an ideal format that radiologists can pursue to provide patient-centered care. Our team, through feedback from patient advisory groups, developed a patient-friendly low-dose computed tomography lung cancer screening report with an infographic format that is both visually attractive and comprehensible to the average patient. The report is designed with sections including a description of low-dose computed tomography, a section on individualized patient results, the meaning of the results, and a list of the next steps in their care. We believe that this form of the report has the potential to serve as a bridge between radiologists and patients, allowing for a better patient understanding of their health and empowering patients to participate in their health and health care.

Screening Mammography Visits as Opportunities to Engage Smokers With Tobacco Cessation Services and Lung Cancer Screening. Wang GX1, Narayan AK2, Park ER3, Lehman CD2, Gorenstein JT4, Flores EJ2. Am Coll Radiol. 2020 Jan 10. pii: S1546-1440(19)31450-4. doi: 10.1016/j.jacr.2019.12.008. [Epub ahead of print]
OBJECTIVE: Tobacco use is the leading cause of preventable mortality in the United States. Screening mammography (SM) visits present opportunities for radiology practices to reduce tobacco-related morbidity and mortality. Our study evaluates implementation of a program that provides tobacco cessation service referrals and screens for lung cancer screening (LCS) eligibility among smokers presenting for SM at a community health center. **METHODS:** In 2018, two sets of questions were added to our SM patient intake questionnaire to assess (1) smoking history and (2) interest in referral to the health center-based tobacco cessation program for mailed information, telephone-based consultation, and in-person counseling. Primary outcomes were proportion of current smokers who requested a referral and of all smokers who were LCS-eligible. Bivariate logistic regression analyses compared sociodemographic characteristics of smokers who requested versus declined a referral. **RESULTS:** Of the 89.3% (1,907 of 2,136) who responded, 10.5% (201 of 1,907) were current and 29.1% (555 of 1,907) were former smokers. Of current smokers, 26.4% (53 of 201) requested referrals: mailed information by 23.9% (48 of 201), in-person counseling by 9% (18 of 201), and telephone-based consultation by 7.5% (15 of 201). No sociodemographic predictors for referral requests were identified. Of all smokers, 9.3% (70 of 756) were eligible for LCS, of which 31.4% (22 of 70) were up to date. **CONCLUSION:** One in 10 women who underwent SM at our community health center were current smokers, of which one-quarter requested tobacco cessation referrals. Among LCS-eligible smokers, one-third were up to date. SM presents opportunities for radiology practices to advance population health goals such as tobacco cessation and LCS.

Development of Decisional Values Statements for Lung Cancer Screening Among African American Smokers. Williams RM1, Beck KH2, Butler J 3rd2, Lee S2, Wang MQ2, Taylor KL3, Knott CL2. J Cancer Educ. 2020 Jan 9. doi: 10.1007/s13187-020-01687-4. [Epub ahead of print]

Lung cancer screening via low-dose computed tomography (LDCT) has been underutilized by high-risk current and former smokers since its approval in 2013. Further, lower use of other evidence-based cancer screening tests (e.g., colorectal cancer, breast cancer) has been noted among African Americans when compared with other racial and ethnic groups. Reasons for low uptake are multilayered but include the need for consideration of patients' personal values about the screening decision. The goal of the present study was to (1) identify positive and negative factors specific to lung cancer screening via LDCT and (2) develop statements to capture values about the screening test for use in a new measure of decisional values. Key informant interviews (n = 9) identified several benefits and risks of lung cancer screening that may be important to African American smokers. Based on these interviews, a pool of items with the values statements was administered to a convenience sample of 119 African Americans [aged 55-80 years, current or former smokers (who quit < 15 years), and without lung cancer]. An exploratory factor analysis revealed two components explaining 64% of the variance: cons of screening (e.g., "make you feel badly about your smoking history") and pros of screening (e.g., "lowering your risk of dying from lung cancer"). The final 12-item measure had very good internal consistency ($\alpha = 0.89$ overall; $\alpha = 0.86$ and 0.88 for subscales, respectively). This tool provides a promising values measure for lung cancer screening among African Americans and could inform future values clarification tools promoting informed and shared decision-making.

Effect of a Patient Decision Aid on Lung Cancer Screening Decision-Making by Persons Who Smoke: A Randomized Clinical Trial. Volk RJ1, Lowenstein LM1, Leal VB1, et al. JAMA Netw Open. 2020 Jan 3;3(1):e1920362. doi: 10.1001/jamanetworkopen.2019.20362.

IMPORTANCE: Lung cancer screening with low-dose computed tomography lowers lung cancer mortality but has potential harms. Current guidelines support patients receiving information about the benefits and harms of lung cancer screening during decision-making. **OBJECTIVE:** To examine the effect of a patient decision aid (PDA) about lung cancer screening compared with a standard educational material (EDU) on decision-making outcomes among smokers. **DESIGN, SETTING, AND PARTICIPANTS:** This randomized clinical trial was conducted using 13 state tobacco quitlines. Current and recent tobacco quitline clients who met age and smoking history eligibility for lung cancer screening were enrolled from March 30, 2015, to September 12, 2016, and followed up for 6 months until May 5, 2017. Data analysis was conducted between May 5, 2017, and September 30, 2018. **INTERVENTIONS:** Participants were randomized to the PDA video Lung Cancer Screening: Is It Right for Me? (n = 259) or to EDU (n = 257). **MAIN OUTCOMES AND MEASURES:** The primary outcomes were preparation for decision-making and decisional conflict measured at 1 week. Secondary outcomes included knowledge, intentions, and completion of screening within 6 months of receiving the intervention measured by patient report. **RESULTS:** Of 516 quit line clients enrolled, 370 (71.7%) were younger than 65 years, 320 (62.0%) were female, 138 (26.7%) identified as black, 47 (9.1%) did not have health insurance, and 226 (43.8%) had a high school or lower educational level. Of participants using the PDA, 153 of 227 (67.4%) were well prepared to make a screening decision compared with 108 of 224 participants (48.2%) using EDU (odds ratio [OR], 2.31; 95% CI, 1.56-3.44; P < .001). Feeling informed about their screening choice was reported by 117 of 234 participants (50.0%) using a PDA compared with 66 of 233 participants (28.3%) using EDU (OR, 2.56; 95% CI, 1.72-3.79; P < .001); 159 of 234 participants (68.0%) using a PDA compared with 110 of 232 (47.4%) participants using EDU reported being clear about their values related to the harms and benefits of screening (OR, 2.37; 95% CI, 1.60-3.51; P < .001). Participants using a PDA were more knowledgeable about lung cancer screening than participants using EDU at each follow-up assessment. Intentions to be screened and screening behaviors did not differ between groups. **CONCLUSIONS AND RELEVANCE:** In this study, a PDA delivered to clients of tobacco quit lines improved informed decision-making about lung cancer screening. Many smokers eligible for lung cancer screening can be reached through tobacco quit lines.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

The association of robotic lobectomy volume and nodal upstaging in non-small cell lung cancer. Okusanya OT1, Lutfi W2, Baker N2, et al. J Robot Surg. 2020 Jan 16. doi: 10.1007/s11701-020-01044-z. [Epub ahead of print]

Robotic lung resection for lung cancer has gained popularity over the last 10 years. As with many surgical techniques, there are improvements in outcomes associated with increased operative volume. We sought to investigate lymph-node harvest and upstaging rates for robotic lobectomies performed at hospitals with varying robotic experience. The National Cancer Data Base was queried for patients with early stage non-small cell lung cancer who received lobectomy between 2010 and 2015. Hospitals were stratified into volume categories based on the number of robotic resections performed, as a proxy for robotic experience: low at ≤ 12, low-middle 13-26, middle-high 27-52, and high volume at greater than or equal to 53. Lymph-node counts and nodal upstaging were compared among these volume categories. 8360 robotic lobectomies were performed. Mean lymph-node counts were for low, low-middle, middle-high, and high-volume robotic lobectomies were 9.8, 11.4, 12.9, and 12.6, respectively ($P < 0.001$), while nodal-upstaging rates were 10.3%, 10.2%, 12.8%, and 13.4%, respectively ($P < 0.001$). Compared to low-volume hospitals, on multivariable analysis, high-volume robotic centers had increased nodal harvest ($P < 0.001$) and nodal-upstaging rates ($P < 0.001$). Robotic lobectomies performed at high-volume hospitals have greater lymph-node harvest and upstaging than low-volume hospitals.

Feasibility and effectiveness of thoracoscopic pulmonary segmentectomy for non-small cell lung cancer. Ma M1, He F1, Lv X1, Wang X2, Dong S1, Liu C1, Zhou C1. Medicine (Baltimore). 2020 Jan;99(5):e18959. doi: 10.1097/MD.0000000000018959.

The outcomes of minimally invasive thoracoscopic pulmonary segmentectomy for non-small cell lung cancer (NSCLC) still need to be defined. This study aimed to investigate the feasibility and effectiveness of thoracoscopic pulmonary segmentectomy in patients with early peripheral NSCLC.This was a retrospective study of patients with early peripheral NSCLC admitted between January 2013 and January 2017. Patients were divided into the segmentectomy and lobectomy groups (40/group), according to the surgery they underwent. Blood loss, operation time, removal of drainage tube time, inflammatory response after operation, postoperative complications, postoperative lung function, local recurrence, and survival were compared.Blood loss and removal of drainage tube time were not significantly different between the 2 groups (all $P>.05$). Operation time in the segmentectomy group was longer than in the lobectomy group ($P<.001$). The postoperative interleukin-6, procalcitonin, and C-reactive protein changes in the segmentectomy group were significantly lower than in the lobectomy group (all $P<.001$). The pulmonary function at 2 weeks was significantly reduced in the 2 groups (all $P<.001$), but it was better in the segmentectomy group than in the lobectomy group (all $P<.05$). The 1- and 3-year local recurrence disease-free, and overall survival rates were not significantly different between the 2 groups ($P>.05$). The multivariable analysis could not identify any factor associated with local recurrence or survival (all $P>.05$). Thoracoscopic pulmonary segmentectomy and lobectomy are both acceptable for the treatment of early peripheral NSCLC, but segmentectomy was associated with lower postoperative inflammation and better postoperative pulmonary function than lobectomy.

A prospective study examining the impact of uniportal video-assisted thoracic surgery on the short-term quality of life in patients with lung cancer. Xu GW1, Xie MR1, Wu HR1, Xiong R1, Li CW1, Xu SB1, Xu MQ1, Li T1. Thorac Cancer. 2020 Jan 22. doi: 10.1111/1759-7714.13305. [Epub ahead of print]
BACKGROUND: The aim of this study was to evaluate the effect of uniportal and three-portal VATS in lung cancer patients on the postoperative short-term quality of life (QOL). **METHODS:** A single-center, prospective, nonrandomized study was performed on patients who underwent uniportal or three-portal video-assisted thoracoscopic surgery (VATS) lobectomy and systemic mediastinal lymph node dissection. QOL was measured before surgery at baseline and at one, two, four, and eight weeks after the operation. The measured data of normal distribution were indicated by the mean ± standard deviation, the independent sample t-test was used among the groups, and the $\chi 2$ test was used to compare the counting. Non-normal distribution of the measurement data was carried out using the Mann-Whitney test. **RESULTS:** Preoperative functional areas, symptom areas and overall health scores were similar in the two groups. The physical, role, emotional and social functions and overall health status of the uniportal group were significantly higher than those of the three-portal group in postoperative time. The score of symptom field was higher in one week after operation, the score of two, four and eight weeks decreased gradually, but it was still above the preoperative level, and the fatigue and pain of the uniportal group were significantly lower than that of the three-portal group. **CONCLUSION:** The advantages of uniportal VATS include a shorter hospital stay, more rapid recovery and superior cosmetic results compared to three-portal VATS. Additionally, uniportal VATS is superior to three-portal thoracoscopic surgery in terms of the immediate postoperative short-term QOL.

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

Nab-paclitaxel in older patients with non-small cell lung cancer who have developed disease progression after platinum-based doublet chemotherapy. Weiss JM1, Pennell N2, Deal AM1, et al. Cancer. 2020 Jan 14. doi: 10.1002/cncr.32573. [Epub ahead of print]
BACKGROUND: The selection of later-line treatment for older patients with AJCC (version 7) stage IV non-small cell lung cancer (NSCLC) remains controversial. Nanoparticle albumin-bound (nab)-paclitaxel is approved with carboplatin for the first-line treatment of patients with NSCLC and subgroup analysis of phase 3 data has suggested superior survival in older patients. **METHODS:** The authors conducted a phase 2 study of nab-paclitaxel in 42 patients aged ≥70 years who had been treated previously with a platinum doublet regimen; patients also could have received a PD-1 inhibitor. The primary endpoint of the current study was grade 3 to 5 toxicity (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [version 4.0]). In addition to response rate, progression-free survival (PFS), and overall survival (OS), geriatric assessments also were performed before and during treatment, associations between baseline sarcopenia and outcomes were explored, and changes in T lymphocyte p16 before and during treatment were measured. The authors also performed a retrospective subgroup analysis of 19 older patients who were treated with nab-paclitaxel as part of a larger, randomized, phase 2 study; data were not combined. **RESULTS:** The rate of grade 3 to 5 toxicities was 33.7%. The most common grade 3 to 5 toxicities were decreased white blood cell count (11.9%), neutropenia (9.5%), and fatigue (11.9%). The response rate was 34.2% (2.6% complete response rate and 31.6% partial response rate). The median PFS was 5.2 months and the median OS was 9.3 months. Adverse prognostic factors were common: 42% of patients were frail and 39% of patients were prefrail, whereas 21% had an Eastern Cooperative Oncology Group performance status of 2 and 27% were sarcopenic. Only frailty was found to be predictive of inferior survival. A subgroup analysis of 19 older patients treated with nab-paclitaxel alone in a prior trial demonstrated a response rate of 15.8%, a PFS of 4.2 months, and an OS of 13.6 months. **CONCLUSIONS:** Fit and prefrail older patients with stage IV NSCLC should be considered for treatment with nab-paclitaxel after disease progression with doublet chemotherapy.

Lung Stereotactic Body Radiotherapy and Concurrent Immunotherapy: A Multi-Center Safety and Toxicity Analysis. Tian S1, Switchenko JM2, Buchwald ZS1, et al. Int J Radiat Oncol Biol Phys. 2020 Jan 23. pii: S0360-3016(19)34548-1. doi: 10.1016/j.ijrobp.2019.12.030. [Epub ahead of print]
BACKGROUND: Radical treatment of metastases with stereotactic body radiotherapy (SBRT) is commonly implemented in patients receiving concurrent immune checkpoint inhibition (ICI), despite limited safety and toxicity data. The purpose of this study was to evaluate the safety and tolerability of lung SBRT with concurrent ICI. **METHODS:** Records from a single academic institution were reviewed to identify patients treated with lung SBRT and concurrent (within 30 days) ICI; a contemporaneous cohort receiving lung SBRT alone was included for reference. Treatment-related adverse-effects (AE) occurring within 30 days (acute) and 180 days (subacute) of SBRT were evaluated. **RESULTS:** 117 patients were included; 54 received SBRT with concurrent ICI (56 courses, 69 target lesions) and 63 received SBRT alone (68 courses, 79 lesions). Median follow-up was 9.2 months in the SBRT+ICI cohort. 67.9% received ICI monotherapy, 17.9% ICI/chemotherapy, and 14.3% ICI/ICI combinations. 25% received ICI between SBRT fractions; 42.9% received ICI both before and after SBRT. The risk of grade 3 (G3) pneumonitis was higher in the SBRT+ICI vs SBRT alone cohort (10.7% vs 0%, $p<0.01$); while any-grade pneumonitis was similar (33.9% vs 27.9%, SBRT+ICI vs SBRT, $p=0.47$). The risk of any-grade pneumonitis appeared elevated with ICI/ICI combinations (62.5% vs 29.2%). Receipt of ICI, PTV volume and lobes involved by SBRT were linked to high-grade pneumonitis. Subacute G3+ AEs occurred in 26.8% of SBRT+ICI and 2.9% of SBRT-alone patients. **CONCLUSIONS:** Concurrent lung SBRT+ICI overall is safe. Given the clinically meaningful risk of pneumonitis, closer monitoring should be considered for SBRT+ICI patients, especially those receiving RT with ICI/ICI combinations.

Tumor Analyses Reveal Squamous Transformation and Off-Target Alterations As Early Resistance Mechanisms to First-line Osimertinib in EGFR-Mutant Lung Cancer. Schoenfeld AJ1, Chan JM1, Kubota D2, et al. Clin Cancer Res. 2020 Jan 7. pii: clincanres.3563.2019. doi: 10.1158/1078-0432.CCR-19-3563. [Epub ahead of print]
PURPOSE: Patterns of resistance to first-line osimertinib are not well-established and have primarily been evaluated using plasma assays which cannot detect histologic transformation and have differential sensitivity for copy number changes and chromosomal rearrangements. **EXPERIMENTAL DESIGN:** To characterize mechanisms of resistance to osimertinib, patients with metastatic EGFR-mutant lung cancers who received osimertinib at Memorial Sloan Kettering and had next-generation sequencing performed on tumor tissue before osimertinib initiation and after progression were identified. **RESULTS:** Among 62 patients who met eligibility critieria, histologic transformation, primarily squamous transformation, was identified in 15% of first-line osimertinib cases and 14% of later-line cases. Nineteen percent (5/27) of patients treated with first-line osimertinib had off-target genetic resistance (2 MET amplification, 1 KRAS mutation, 1 RET fusion, and 1 BRAF fusion) whereas 4% (1/27) had an acquired EGFR mutation (EGFR G724S). Patients with squamous transformation exhibited considerable genomic complexity; acquired PIK3CA mutation, chromosome 3q amplification and FGF amplification were all seen. Patients with transformation had shorter time on osimertinib and shorter survival compared to patients with on-target resistance. Initial EGFR sensitizing mutation, time on osimertinib treatment and line of therapy also influenced resistance mechanism that emerged. The compound mutation EGFR S768 + V769L and the mutation MET H1094Y were identified and validated as resistance mechanisms with potential treatment options. **CONCLUSION:** Histologic transformation and other off-target molecular alterations are frequent early emerging resistance mechanisms to osimertinib and are associated with poor clinical outcomes.

Cost-effectiveness of pembrolizumab for advanced non-small cell lung cancer patients with varying comorbidity burden. Criss SD1, Palazzo L1, Watson TR1, Paquette AM1, Sigel K2, Wisnivesky J2,3, Kong CY1,4.

OBJECTIVES: While previous cost-effectiveness studies on pembrolizumab in stage IV non-small cell lung cancer (NSCLC) have found these regimens to be cost-effective, their reliance on randomized controlled trial (RCT) data with strict inclusion criteria limits generalizability to patients with comorbidities. We estimated the cost-effectiveness of first-line pembrolizumab for patients with various comorbidities. **MATERIALS AND METHODS:** In our base case analysis, we studied pembrolizumab plus chemotherapy (pembrolizumab combination therapy) versus chemotherapy alone. In a secondary analysis, we considered only patients with PD-L1 expression of at least 50% (PD-L1-high) and evaluated pembrolizumab monotherapy, pembrolizumab combination therapy, and chemotherapy alone. Microsimulation models were developed for the base case and the PD-L1-high analyses. To estimate outcomes of patients with differing comorbidities, we combined survival data from patients with few or no comorbidities from the RCTs with estimates from the general population obtained from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. Comorbidity burden level was divided into three groups based on the Charlson score (equal to 0, 1, or 2+); patients with various other specific comorbidities were also analyzed. Incremental cost-effectiveness ratios (ICER) were compared to a willingness-to-pay (WTP) threshold of $100,000/quality-adjusted life-year (QALY). **RESULTS:** In the Charlson 0, Charlson 1, and Charlson 2+ patient populations, estimated ICERs for pembrolizumab combination therapy in the base case model were $173,919/QALY, $175,165/QALY, and $181,777/QALY, respectively, compared to chemotherapy. In the PD-L1-high model, the Charlson 0, Charlson 1, and Charlson 2+ patients had ICERs of $147,406/QALY, $149,026/QALY, and $154,521/QALY with pembrolizumab combination therapy versus chemotherapy. Pembrolizumab monotherapy was weakly dominated for each comorbidity group in the PD-L1-high model. **CONCLUSION:** For patients with stage IV NSCLC and varying comorbidity burden, first-line treatment with pembrolizumab does not represent a cost-effective strategy compared to chemotherapy. Resources should be focused on collecting immunotherapy survival data for more representative NSCLC patient populations.

The value of immunotherapy for survivors of stage IV non-small cell lung cancer: patient perspectives on quality of life. Park R1, Shaw JW2, Korn A3, McAuliffe J3. J Cancer Surviv. 2020 Jan 16. doi: 10.1007/s11764-020-00853-3. [Epub ahead of print]

PURPOSE: The aim of this study was to examine what personally mattered to 24 patients who received immuno-oncology (IO) therapy for stage IV non-small cell lung cancer (NSCLC), as well as their families and friends, to understand how they evaluated their cancer treatments and the determinants of the quality of life (QoL) of long-term survivors. **METHODS:** Ethnographic research was conducted with 24 patients who had responded to IO (pembrolizumab, nivolumab, atezolizumab, or durvalumab) for stage IV NSCLC, and their families and friends, evenly split among field sites in Denmark, the USA, and the UK. Data were collected using in-depth qualitative interviews, written exercises, and participant observation. Data analysis methods included interpretative phenomenological analysis, coding, and the development of grounded theory. Researchers spent 2 days with participants in their homes and accompanied them on health-related outings. **RESULTS:** Our findings reveal that long-term survivors on IO experienced their journey in two phases: one in which their cancer had taken over their lives mentally, physically, and spiritually, and another in which their cancer consumed only a part of their everyday lives. Patients who survived longer than their initial prognosis existed in a limbo state in which they were able to achieve some semblance of normalcy in spite of being identified as having a terminal condition. This limbo state impacted their life priorities, decision-making, experience of patient support, and health information-seeking behaviors, all of which shaped their definitions and experience of QoL. **CONCLUSIONS:** The

results of this study, which identify the specific challenges of living in limbo, where patients are able to reclaim a portion of their pre-cancer lives while continuing to wrestle with a terminal prognosis, may inform how cancer research can more effectively define and measure the QoL impacts of IO treatments. Also, they may identify approaches that the cancer community can use to support the needs of patients living in a limbo state. These experiences may not be adequately understood by the cancer community or captured by existing QoL measures, which were designed prior to the emergence of IO and without sufficient incorporation of contextual, patient-driven experience. **IMPLICATIONS FOR CANCER SURVIVORS:** Increased awareness of the specific experiences that come with long-term survival on IO may direct how resources should be spent for cancer support for patients and their families. Expanding how QoL is evaluated based on patients' lived experiences of IO can reflect a more accurate depiction of the treatment's benefits and harms.

Smokers or non-smokers: who benefits more from immune checkpoint inhibitors in treatment of malignancies? An up-to-date meta-analysis. Mo J1, Hu X2, Gu L3, Chen B4, Khadaroo PA5, Shen Z1, Dong L6, Lv Y1, Chitumba MN7, Liu J8. V

BACKGROUND: Immune checkpoint inhibitors, which are a milestone in anti-cancer therapy, have been applied in the treatment of multiple malignancies. Real-world data have suggested that smoking status may be associated with the efficacy of anti-PD-1/PD-L1 therapy. Hereby, to evaluate "smoking benefit or not", we included numerous high-quality randomized controlled clinical trials (RCTs) without any restriction on category. **METHODS:** A systematic search of online database was performed from July 2010 to July 2019. Eligible studies included phase II/III RCTs comparing PD-1/PD-L1 inhibitors with chemotherapy in the treatment of multiple carcinomas and contained subgroup analysis of smoking status. Then, related hazard ratios (HRs) with 95% confidence intervals (CIs) of overall survival (OS) were pooled. **RESULTS:** In the initial meta-analysis, compared with chemotherapy, the OS of non-smokers (HR, 0.81; 95% CI, 0.67-0.98) and smokers (HR, 0.77; 95% CI, 0.71-0.83) were significantly prolonged with PD-1/PD-L1 inhibitors. Outcomes from subgroup analysis showed that in anti-PD-1/PD-L1 monotherapy groups, non-smokers showed no significant improvement in OS (HR, 0.94; 95% CI, 0.83-1.06), while the OS of smokers was significantly prolonged (HR, 0.79; 95% CI, 0.74-0.85); in groups of PD-1/PD-L1 inhibitors combined with chemotherapy, the OS of non-smokers (HR, 0.45; 95% CI, 0.28-0.71) and smokers (HR, 0.72; 95% CI, 0.61-0.85) were significantly prolonged. Combined ipilimumab and chemotherapy showed no significance in both groups. **CONCLUSION:** Smokers benefit from either anti-PD-1/PD-L1 monotherapy or the combined regimen compared with chemotherapy. Considering cost-effectiveness, monotherapy was recommended to smokers. For non-smokers, only the combined regimen was feasible in non-small cell lung cancer.

Patterns of care for older patients with stage IV non-small cell lung cancer in the immunotherapy era. Kehl KL1, Hassett MJ1, Schrag D1. Cancer Med. 2020 Jan 27. doi: 10.1002/cam4.2854. [Epub ahead of print]

BACKGROUND: Historically, older patients with advanced lung cancer have often received no systemic treatment. Immunotherapy has improved outcomes in clinical trials, but its dissemination and implementation at the population level is not well-understood. **METHODS:** A retrospective cohort study of patients with stage IV non-small cell lung cancer (NSCLC) diagnosed age 66 or older from 2012 to 2015 was conducted using SEER-Medicare. Treatment patterns within one year of diagnosis were ascertained. Outcomes included delivery of (a) any systemic therapy; (b) any second-line infusional therapy, following first-line infusional therapy; and (c) any second-line immunotherapy, following first-line infusional therapy. Trends in care patterns associated with second-line immunotherapy approvals in 2015 were assessed using generalized additive models. Sociodemographic and clinical predictors of treatment were explored using logistic regression. **RESULTS:** Among 10 303 patients, 5173 (50.2%)

received first-line systemic therapy, with little change between the years 2012 (47.5%) and 2015 (50.3%). Among 3943 patients completing first-line infusional therapy, the proportion starting second-line infusional treatment remained stable from 2012 (30.5%) through 2014 (32.9%), before increasing in 2015 (42.4%) concurrent with second-line immunotherapy approvals. Factors associated with decreased utilization of any therapy included age, black race, Medicaid eligibility, residence in a high-poverty area, nonadenocarcinoma histology, and comorbidity; factors associated with increased utilization of any therapy included Asian race and Hispanic ethnicity. Among patients who received first-line infusional therapy, factors associated with decreased utilization of second-line infusional therapy included age, Medicaid eligibility, nonadenocarcinoma histology, and comorbidity; Asian race was associated with increased utilization of second-line infusional therapy. **CONCLUSION:** United States Food and Drug Administration (FDA) approvals of immunotherapy for the second-line treatment of advanced NSCLC in 2015 were associated with increased rates of any second-line treatment, but disparities based on social determinants of health persisted.

Overcoming acquired resistance of epidermal growth factor receptor-mutant non-small-cell lung cancer cells to osimertinib by combining osimertinib with the histone deacetylase inhibitor panobinostat (LBH589). Zhang H1,2, Qian G2, Zong D2, Fan S1, Owonikoko TK2, Ramalingam SS2, Sun SY2. Cancer. 2020 Jan 30. doi: 10.1002/cncr.32744. [Epub ahead of print]
BACKGROUND: The major clinical obstacle that limits the long-term benefits of treatment with osimertinib (AZD9291) in patients with epidermal growth factor receptor-mutant non-small-cell lung cancer is the development of acquired resistance. Therefore, effective strategies that can overcome acquired resistance to osimertinib are urgently needed. The authors' current efforts in this direction have identified LBH589 (panobinostat), a clinically used histone deacetylase inhibitor, as a potential agent in overcoming osimertinib resistance. **METHODS:** Cell growth and apoptosis in vitro were evaluated by measuring cell numbers and colony formation and by detecting annexin V-positive cells and protein cleavage, respectively. Drug effects on tumor growth in vivo were assessed with xenografts in nude mice. Alterations of tested proteins in cells were monitored with Western blot analysis. Gene knockout was achieved using the CRISPR/Cas9 technique. **RESULTS:** The combination of LBH589 and osimertinib synergistically decreased the survival of different osimertinib-resistant cell lines, including those harboring C797S mutations, with greater inhibition of cell colony formation and growth. The combination enhanced the induction of apoptosis in osimertinib-resistant cells. Importantly, the combination effectively inhibited the growth of osimertinib-resistant xenograft tumors in nude mice. Mechanistically, the combination of LBH589 and osimertinib enhanced the elevation of Bim in osimertinib-resistant cells. Knockout of Bim in osimertinib-resistant cells substantially attenuated or abolished apoptosis enhanced by the LBH589 and osimertinib combination. These results collectively support a critical role of Bim elevation in the induction of apoptosis of osimertinib-resistant cells for this combination.
CONCLUSIONS: The current findings provide strong preclinical evidence in support of the potential for LBH589 to overcome osimertinib resistance in the clinic.

Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Neuroendocrine Tumors: Results From the Phase 2 KEYNOTE-158 Study. Strosberg JR1, Mizuno N2, Doi T3, et al. Clin Cancer Res. 2020 Jan 24. pii: clincanres.3014.2019. doi: 10.1158/1078-0432.CCR-19-3014. [Epub ahead of print]
PURPOSE: KEYNOTE-158 (ClinicalTrials.gov identifier: NCT02628067) investigated the efficacy and safety of pembrolizumab across multiple cancers. We present results from patients with previously treated advanced well-differentiated neuroendocrine tumors (NETs). **PATIENTS AND METHODS:** Pembrolizumab 200 mg was administered every 3 weeks for 2 years or until progression, intolerable toxicity, or physician/patient decision. Tumor imaging was performed every 9 weeks for the first year,

and then every 12 weeks. Endpoints included objective response rate (ORR) per RECIST v1.1 by independent central radiologic review (primary) and duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety (secondary). **RESULTS:** One-hundred-seven patients with NETs of the lung, appendix, small intestine, colon, rectum, or pancreas were treated. Median age was 59.0 years (range, 29-80), 44.9% had ECOG performance status 1, 40.2% had received ≥3 prior therapies for advanced disease and 15.9% had PD-L1-positive tumors (combined positive score ≥1). Median follow-up was 24.2 months (range, 0.6-33.4). ORR was 3.7% (95% CI, 1.0-9.3), with 0 complete responses and 4 partial responses (3 pancreatic and 1 rectal) all in patients with PD-L1-negative tumors. Median DOR was not reached, with 1 of 4 responses ongoing after ≥21 months follow-up. Median PFS was 4.1 months (95% CI, 3.5-5.4); the 6-month PFS rate was 39.3%. Median OS was 24.2 months (95% CI, 15.8-32.5). Treatment-related adverse events (AEs) occurred in 75.7% of patients, 21.5% of whom had grade 3-5 AEs. **CONCLUSION:** Pembrolizumab monotherapy showed limited antitumor activity and manageable safety in patients with previously treated advanced well-differentiated NETs.

Measuring Tumor Mutational Burden Using Whole-Exome Sequencing. Vilimas T1. Methods Mol Biol. 2020;2055:63-91. doi: 10.1007/978-1-4939-9773-2_3.
Cancer immunotherapy, particularly a class of antibodies targeting the CTLA4 and PD-1/PD-L1 negative regulators of immune response (collectively called the immune checkpoint), is one of the most promising approaches for cancer treatment and the use of immune checkpoint inhibitors (ICI) has demonstrated remarkable success in several types of cancer. In studies of unselected patient populations, it was shown that melanoma, non small cell lung cancer (NSCLC), renal cell carcinoma and urothelial carcinoma patients treated with CTLA-4, PD-1 or PD-L1 inhibitors had an improved objective response and overall survival relative to chemotherapy or historical trends, and several ICIs have been approved for the treatment of these and other indications.More recently, several groups found that response to ICI therapy strongly correlates with a high burden of single nucleotide variant (SNV) mutations in the tumor genome, termed tumor mutational burden (TMB), usually expressed as the number of nonsynonymous single nucleotide variants per megabase of sequenced genome. These studies showed that TMB is a promising predictive biomarker for ICI response in melanoma, urothelial carcinoma and a subset of NSCLC patients. High TMB relates to ICI response via the production of increased numbers of novel, mutant peptide antigens (neoantigens), resulting in enhanced recognition and killing of neoantigen-presenting tumor cells by cytotoxic CD8+ T cells. In this chapter I describe the current best-practice methods for measuring TMB in tumor specimens using whole-exome sequencing (WES).

Association of age with differences in immune related adverse events and survival of patients with advanced nonsmall cell lung cancer receiving pembrolizumab or nivolumab. Ksienski D1, Wai ES2, Croteau NS3, et al. J Geriatr Oncol. 2020 Jan 11. pii: S1879-4068(19)30406-0. doi: 10.1016/j.jgo.2020.01.006. [Epub ahead of print]
OBJECTIVES: To explore the association of age with development of immune related adverse events (irAE) and survival in patients with advanced nonsmall cell lung cancer (aNSCLC) receiving programmed cell death 1 antibodies (PD-1 Ab) outside of clinical trials. **METHODS:** A multicenter retrospective study of PD-1 Ab prescription for patients with aNSCLC between 06/2015-11/2018 at BC Cancer. Multivariable (MVA) logistic regression identified baseline variables associated with irAE manifested within 3 months of PD-1 Ab initiation. Overall survival (OS) analyzed in a propensity-score matched cohort and survival outcomes compared between age groups by stratified log-rank. Six-week landmark analysis was performed and OS compared between patients with interrupted versus continuous treatment by log-rank. **RESULTS:** Of 527 patients, 40.6% were age ≤ 64 years, 40.6% were 65-74 years, and 18.8% were ≥ 75 years. In MVA, ECOG performance status 2/3 (p = .034), squamous histology (p = .031), and nivolumab therapy (vs. pembrolizumab, p = .012) were associated with increased odds of irAE

by 3 months of treatment. Across age groups no difference existed in any grade irAE (p = .98), hospitalization (p = 1.0), or corticosteroids use (p = .51). The propensity score-matched survival analysis comprised 77 patients from each age group; all covariates were balanced. OS did not differ significantly by age in the matched cohort (p = .17). Treatment interruption due to irAE at 6 weeks was more common in patient ≥75 years (vs. <75, p = .055) and correlated with lower OS (p = .002). **CONCLUSION:** In this cohort of patients with a NSCLC treated in routine clinical practice with PD-1 Ab, immune-toxicity and observed survival were similar amongst age groups.

Imaging of Novel Oncologic Treatments in Lung Cancer Part 1: Systemic Therapies. Halpenny D1, O'Dwyer E, Girshman J, Ginsberg MS. J Thorac Imaging. 2020 Jan;35(1):26-36. doi: 10.1097/RTI.0000000000000451.
Thoracic tumors are a leading cause of cancer-related morbidity and mortality. In recent years, developments in oncologic treatments for these tumors have ushered in an era of targeted therapy, and, in many cases, these novel treatments have replaced conventional strategies to become standard therapeutic options, particularly in those with lung cancer. Targeted medical therapies for lung cancer now include angiogenesis inhibitors, tyrosine kinase inhibitors, and immunotherapeutic agents. Several novel ablative therapies have also gained widespread acceptance as alternatives to conventional surgical options in appropriately selected patients. Tumors treated with targeted medical therapies can respond to treatment differently when compared with conventional therapies. For example, pseudoprogression is a well-described phenomenon in patients receiving checkpoint inhibitor immunotherapy in which an initial increase in tumor burden is followed by a decrease in tumor burden and sometimes partial or complete response, while the frequent cavitating responses seen when antiangiogenic agents are used can be difficult to quantify using existing response assessment criteria. In some cases, novel response assessment criteria are needed to adequately capture response. In addition, numerous treatment-related side effects have been described, which are important to recognize, both to ensure appropriate treatment and to avoid misclassification as worsening tumor. Imaging plays a vital role in the assessment of patients receiving targeted medical therapy, and it is essential that thoracic radiologists are familiar with the rationale underpinning these treatments and the expected posttherapy findings.

A Phase II Trial of Albumin-Bound Paclitaxel and Gemcitabine in Patients with Newly Diagnosed Stage IV Squamous Cell Lung Cancers. Paik PK1, Kim RK2, Ahn L3, et al. Clin Cancer Res. 2020 Jan 9. pii: clincanres.3060.2019. doi: 10.1158/1078-0432.CCR-19-3060. [Epub ahead of print]
PURPOSE: Gemcitabine and albumin-bound paclitaxel (ABP) exhibit synergistic anti-tumor efficacy, with ABP serving to increase the intratumoral gemcitabine concentration. Both drugs are active in squamous cell lung cancers (SQCLCs) and are conventional partners for carboplatin. We hypothesized that combining gemcitabine and ABP would enhance the anti-tumor activity in patients with advanced SQCLCs. **EXPERIMENTAL DESIGN:** This was a Simon two-stage, open-label, single-arm, multicenter phase II study that enrolled patients between August 1, 2015 and June 1, 2018. We enrolled 37 patients with chemotherapy-naïve, PD-L1 low/unknown advanced stage IV SQCLC. Patients were administered weekly intravenous gemcitabine (1000 mg/m2) plus ABP (100 mg/m2) in a 3 week on, 1 week off schedule during Stage 1 and a 2 week on, 1 week off schedule in Stage 2. The primary endpoint was best objective response rate (ORR). Next-generation sequencing by MSK-IMPACT was used to calculate tumor mutation burden and genome doubling and assess somatic variants for correlations with efficacy. **RESULTS:** Thirty-two patients were evaluable for response assessment. The study satisfied its primary endpoint, with confirmed partial responses in 18 of 32 patients and a complete response in 1 patient (ORR 59%, 95% CI 42% to 74%). Median progression-free survival (PFS), a secondary endpoint, was 7.5 (95% CI 6.7 to 10.5) months. There were no unexpected toxicities. **CONCLUSIONS:** Gemcitabine plus ABP was a safe, tolerable, and effective first-line therapy for patients with

chemotherapy-naïve SQCLCs, with an ORR and median PFS substantially higher than carboplatin doublet regimens and efficacy comparable to carboplatin plus taxane plus pembrolizumab.

NSCLC - RADIOTHERAPY

Impact of contouring variability on oncological PET radiomics features in the lung. Yang F1, Simpson G2, Young L3, Ford J4, Dogan N4, Wang L4. Sci Rep. 2020 Jan 15;10(1):369. doi: 10.1038/s41598-019-57171-7.
Radiomics features extracted from oncological PET images are currently under intense scrutiny within the context of risk stratification for a variety of cancers. However, the lack of robustness assessment poses problems for their application across institutions and for broader patient populations. The objective of the current study was to examine the extent to which radiomics parameters from oncological PET vary in response to manual contouring variability in lung cancer. Imaging data employed in the study consisted of 26 PET scans with lesions in the lung being created through the use of an anthropomorphic phantom in conjunction with Monte Carlo simulations. From each of the simulated lesions, 25 radiomics features related to the gray-level co-occurrence matrices (GLCOM), gray-level size zone matrices (GLSZM), and gray-level neighborhood difference matrices (GLNDM) were extracted from ground truth contour and from manual contours provided by 10 raters in regard to four intensity discretization schemes with number of gray levels of 32, 64, 128, and 256, respectively. The impact of interrater variability in tumor delineation upon the agreement between raters on radiomics features was examined via interclass correlation and leave-p-out assessment. Only weak and moderate correlations were found between segmentation accuracy as measured by the Dice coefficient and percent feature error from ground truth for the vast majority of the features being examined. GLNDM-based texture parameters emerged as the top performing category of radiomcs features in terms of robustness against contouring variability for discretization schemes engaging number of gray levels of 32, 64, and 128 while GLCOM-based parameters stood out for discretization scheme engaging 256 gray levels. How and to what extent interrater reliability of radiomics features vary in response to the number of raters were largely feature-dependent. It was concluded that impact of contouring variability on PET-based radiomics features is present to varying degrees and could be experienced as a barrier to convey PET-based radiomics research to clinical relevance.

CT Densitometry and Morphology of Radiofrequency-Ablated Stage IA Non-Small Cell Lung Cancer: Results from the American College of Surgeons Oncology Group Z4033 (Alliance) Trial. Alexander ES1, Xiong L2, Baird GL3, Fernando H4, Dupuy DE5. J Vasc Interv Radiol. 2020 Feb;31(2):286-293. doi: 10.1016/j.jvir.2019.09.010. Epub 2020 Jan 3.
PURPOSE: To evaluate tumor and ablation zone morphology and densitometry related to tumor recurrence in participants with Stage IA non-small cell lung cancer undergoing radiofrequency ablation in a prospective, multicenter trial. **MATERIALS AND METHODS:** Forty-five participants (median 76 years old; 25 women; 20 men) from 16 sites were followed for 2 years (December 2006 to November 2010) with computed tomography (CT) densitometry. Imaging findings before and after ablation were recorded, including maximum CT attenuation (in Hounsfield units) at precontrast and 45-, 90-, 180-, and 300-s postcontrast. **RESULTS:** Every 1-cm increase in the largest axial diameter of the ablation zone at 3-months' follow-up compared to the index tumor reduced the odds of 2-year recurrence by 52% (P = .02). A 1-cm difference performed the best (sensitivity, 0.56; specificity, 0.93; positive likelihood ratio of 8). CT densitometry precontrast and at 45 seconds showed significantly different enhancement patterns in a comparison among pretreated lung cancer (delta = +61.2 HU), tumor recurrence (delta = +57 HU), and treated tumor/ablation zone (delta [change in attenuation] = +16.9 HU), (P < .0001). Densitometry from 45 to 300 s was also different among pretreated tumor (delta = -6.8 HU), recurrence (delta = -11.2 HU),

and treated tumor (delta = +12.1 HU; P = .01). Untreated and residual tumor demonstrated washout, whereas treated tumor demonstrated increased attenuation. **CONCLUSIONS:** An ablation zone ≥1 cm larger than the initial tumor, based on 3-month follow-up imaging, is recommended to decrease odds of recurrence. CT densitometry can delineate tumor versus treatment zones.

Predictors of Distant Recurrence Following Stereotactic Body Radiation Therapy for Stage I Non-Small Cell Lung Cancer. Wong JK1, Shaikh T1, DeMora L2, Zhang E1, Borghaei H3, Hayes SB1, Kumar S1, Meyer JE1, Hallman MA1. Am J Clin Oncol. 2020 Jan 7. doi: 10.1097/COC.0000000000000662. [Epub ahead of print]
OBJECTIVE: The objective of this study was to characterize patients at an increased risk of distant metastasis (DM) following stereotactic body radiation therapy (SBRT) for stage I non-small cell lung cancer (NSCLC). **MATERIALS AND METHODS:** We identified patients undergoing SBRT for stage I NSCLC between 2005 and 2016. Patients with a prior lung cancer diagnosis, receiving a biological effective dose <100 Gy, or receiving chemotherapy were excluded. Patients underwent pretreatment staging and were classified according to the American Joint Committee for Cancer (AJCC) 8th edition staging. The primary endpoint was DM. The Kaplan-Meier method and the Cox proportional hazards model were used for survival analysis and to identify predictors of DM. **RESULTS:** A total of 174 patients were included, with a median age 75 years (range, 49 to 96 y) and a median follow-up of 24 months (range, 3 to 123 mo). The 2- and 4-year cumulative incidences of DM were 14.2% and 19.1%, respectively. Patients who developed DM had worse overall survival versus patients developing a locoregional recurrence (P=0.023). On multivariable analysis, having stage IB disease (hazard ratio: 2.95; 95% confidence interval: 1.06-8.23; P=0.039) or a lower/middle lobe tumor (hazard ratio: 2.67; 95% confidence interval: 1.07-6.69; P=0.036) was associated with increased risk of DM. The 2-year cumulative incidences of DM were 10.9% and 35.7% (P=0.002) for patients with stage IA versus IB tumors, respectively, and 11.3% and 19.7% (P=0.049) for patients with upper lobe versus lower/middle lobe tumors, respectively. **CONCLUSIONS:** Patients with stage IB disease or lower/middle lobe tumors may have an increased risk of DM following SBRT. Randomized controlled trials are needed to further identify patients who may benefit from adjuvant systemic therapy after SBRT for stage I NSCLC.

Evaluating Positron Emission Tomography-Based Functional Imaging Changes in the Heart After Chemo-Radiation for Patients With Lung Cancer. Vinogradskiy Y1, Diot Q2, Jones B2, et al. Int J Radiat Oncol Biol Phys. 2020 Jan 23. pii: S0360-3016(19)34526-2. doi: 10.1016/j.ijrobp.2019.12.013. [Epub ahead of print]
PURPOSE: Studies have noted a link between radiation dose to the heart and overall survival (OS) for patients with lung cancer treated with chemoradiation. The purpose of this study was to characterize pre- to posttreatment cardiac metabolic changes using fluorodeoxyglucose/positron emission tomography (FDG-PET) images and to evaluate whether changes in cardiac metabolism predict for OS. **METHODS AND MATERIALS:** Thirty-nine patients enrolled in a functional avoidance prospective study who had undergone pre- and postchemoradiation FDG-PET imaging were evaluated. For each patient, the pretreatment and posttreatment PET/CTs were rigidly registered to the planning CT, dose, and structure set. PET-based metabolic dose-response was assessed by comparing pretreatment to posttreatment mean standardized uptake values (SUVmean) in the heart as a function of dose-bin. OS analysis was performed by comparing SUVmean changes for patients who were alive or had died at last follow-up and by using a multivariate model to assess whether pre- to posttreatment SUVmean changes were a predictor of OS. **RESULTS:** The dose-response curve revealed increasing changes in SUV as a function of cardiac dose with an average SUVmean increase of 1.7% per 10 Gy. Patients were followed for a median of 437 days (range, 201-1131 days). SUVmean change was significantly predictive of OS on multivariate analysis with a hazard ratio of 0.541 (95% confidence intervals, 0.312-0.937). Patients alive at follow-up had an

average increase of 17.2% in cardiac SUVmean while patients that died had an average decrease in SUVmean decrease of 13.5% (P = .048). **CONCLUSIONS:** Our data demonstrated that posttreatment SUV changes in the heart were significant indicators of dose-response and predictors of OS. The present work is hypothesis generating and must be validated in an independent cohort. If validated, our data show the potential for cardiac metabolic changes to be an early predictor for clinical outcomes.

Impact of Patient Stage and Disease Characteristics on the proposed Radiation Oncology Alternative Payment Model (RO-APM) at a Large Academic Cancer Center.
Waddle MR1, Stross WC1, Vallow LA1, et al. Int J Radiat Oncol Biol Phys. 2020 Jan 27. pii: S0360-3016(19)34525-0. doi: 10.1016/j.ijrobp.2019.12.012. [Epub ahead of print]
BACKGROUND: The proposed Radiation Oncology Alternative Payment Model (RO-APM) released on July 10, 2019 represents a dramatic shift from fee-for-service (FFS) reimbursement in radiation therapy (RT). This study compares historical revenue at our institution to the RO-APM and quantifies the impact that disease characteristics may have on reimbursement. **MATERIALS/METHODS:** FFS Medicare reimbursements were determined for patients undergoing RT at Our Institution from 2015-2016. Disease categories and payment episodes were defined as per the RO-APM. Average RT episode reimbursements were reported for each disease site, except for lymphoma and metastases, and stratified by stage and disease subcategory. Comparisons with RO-APM reimbursements were made via descriptive statistics. **RESULTS:** A total of 2,098 patients were identified of which1,866 (89%) were categorized per the RO-APM, and 840 (45%) of those over the age of 65 years. Breast (33%), head and neck (HN) (14%), prostate (11%) cancer were most common. RO-APM base rate reimbursements and sensitivity analysis range were lower than historical reimbursement for bladder (-40%), cervical (-34%), lung (-28%), uterine (-26%), colorectal (-24%), upper gastrointestinal (-24%), HN (-23%), pancreatic (-20%), prostate (-16%), CNS (-13%), anal (-10%), and higher for liver (+24%) and breast (+36%). Historical reimbursement varied with stage (Stage III vs. Stage I) for breast (+57%, $p<0.01$), uterine (+53%, $p=0.01$), lung (+50%, $p<0.01$), HN (+24%, $p=0.01$), and prostate (+13%, $p=0.01$). Overall, for patients over 65 the RO-APM resulted in a -9% reduction in total RT reimbursement compared with historical FFS (-2%, -15%, and -27% for high, mid, and low adjusted RO-APM rates). **CONCLUSIONS:** Our findings indicate that the RO-APM will result in significant reductions in reimbursement at our center, particularly for cancers more common in underserved populations. Practices that care for socioeconomically disadvantaged populations may face significant reductions in revenue which could further reduce access for this vulnerable population.

Response and outcomes after anti-CTLA4 versus anti-PD1 combined with stereotactic body radiation therapy for metastatic non-small cell lung cancer: retrospective analysis of two single-institution prospective trials. Chen D#1, Menon H#2, Verma V3, et al. J Immunother Cancer. 2020 Jan;8(1). pii: e000492. doi: 10.1136/jitc-2019-000492.
BACKGROUND: This study compared response rates and outcomes of combined radiotherapy and immunotherapy (iRT) based on the type of checkpoint inhibitor (anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) vs antiprogrammed death-1 (PD1)) for metastatic non-small cell lung cancer (mNSCLC). **METHODS:** We retrospectively reviewed two prospective trials of radiation combined with anti-CTLA4 or anti-PD1 for patients with mNSCLC. Patients undergoing non-salvage stereotactic body radiation therapy (SBRT) to lung sites were selected from both trials and grouped by the immunotherapeutic compound received. Endpoints included in-field and out-of-field response rates, and overall response rate (complete or partial response) (all by response evaluation criteria in solid tumors). Progression-free survival (PFS) and overall survival (OS) were estimated with the Kaplan-Meier method. **RESULTS:** Median follow-up times for the 33 patients (n=17 SBRT+anti-CTLA4, n=16 SBRT+anti-PD1) were 19.6 and 19.9 months. Response rates for out-of-field lesions were similar between anti-PD1

(37%) and anti-CTLA4 (24%) (p=0.054). However, global response rates for all lesions were 24% anti-CTLA4 vs 56% anti-PD1 (p=0.194). The PFS was 76% for anti-CTLA4 vs 94% anti-PD1 at 3 months, 52% vs 87% at 6 months, 31% vs 80% at 12 months, and 23% vs 63% at 18 months (p=0.02). Respective OS values were 76% vs 87% at 6 months, 47% vs 80% at 12 months, and 39% vs 66% at 18 months (p=0.08). **CONCLUSIONS:** Both anti-CTLA4 and anti-PD1 agents prompt a similar degree of in-field and out-of-field responses after iRT, although the global response rate and PFS were statistically higher in the anti-PD1 cohort. Further dedicated study and biological mechanistic assessment is required.

SMALL CELL LUNG CANCER - SCLC

The impact of quantitative CT-based tumor volumetric features on the outcomes of patients with limited stage small cell lung cancer. Kamran SC1,2, Coroller T3,4, Milani N4, et al. Radiat Oncol. 2020 Jan 14;15(1):14. doi: 10.1186/s13014-020-1460-4.
INTRODUCTION: Limited stage small cell lung cancer (LS-SCLC) has a poor prognosis. Additional prognostic markers are needed for risk-stratification and treatment intensification. This study compares quantitative CT-based volumetric tumor measurements versus International Association for the Study of Lung Cancer (IASLC) TNM staging to predict outcomes. **MATERIALS & METHODS:** A cohort of 105 patients diagnosed with LS-SCLC and treated with chemoradiation (CRT) from 2000 to 2013 were analyzed retrospectively. Patients were staged by the Union for International Cancer Control (UICC) TNM Classification, 8th edition. Tumor volumes and diameters were extracted from radiation planning CT imaging. Univariable and multivariable models were used to analyze relationships between CT features and overall survival (OS), locoregional recurrence (LRR), in-field LRR, any progression, and distant metastasis (DM). **RESULTS:** Median follow-up was 21.3 months. Two-year outcomes were as follows: 38% LRR, 31% in-field LRR, 52% DM, 62% any progression, and 47% OS (median survival 16.5 months). On univariable analysis, UICC T-stage and N-stage were not associated with any clinical outcome. UICC overall stage was only statistically associated with in-field LRR. One imaging feature (3D maximum tumor diameter) was found to be significantly associated with LRR (HR 1.10, p = 0.003), in-field LRR (HR 1.10, p = 0.007), DM (HR 1.10, p = 0.02), any progression (HR 1.10, p = 0.008), and OS (HR 1.10, p = 0.03). On multivariable analysis, this feature remained significantly associated with all outcomes. **CONCLUSION:** For LS-SCLC, quantitative CT-based volumetric tumor measurements were significantly associated with outcomes after CRT and may be better predictors of outcome than TNM stage.

A Meta-Analysis of the Efficacy and Toxicity of Twice-Daily vs. Once-Daily Concurrent Chemoradiotherapy for Limited-Stage Small Cell Lung Cancer Based on Randomized Controlled Trials. Wu Q1,2, Xiong Y1,2, Zhang S2,3, Chen X2,3, Yi F3, Wei Y1, Zhang W1. Front Oncol. 2020 Jan 8;9:1460. doi: 10.3389/fonc.2019.01460. eCollection 2019.
BACKGROUND: Currently, the accepted standard management of limited-stage small cell lung cancer (SCLC) is concurrent chemoradiotherapy (CCRT), but the frequency of radiotherapy is controversial. Therefore, this meta-analysis, which compared the efficacy and toxicity between twice-daily (BID) and once-daily (OD) CCRT, was performed to help clinicians make better decisions. **METHODS:** Relevant randomized controlled trials (RCTs) were collected by searching the PubMed, Ovid MEDLINE, Embase, ScienceDirect, Web of Science, the Cochrane Library, Scopus and Google Scholar databases to assess antitumor effects (overall survival, OS; progression-free survival, PFS; overall response rate, ORR) and toxicity (adverse effects, AEs). **Results:** We screened 1499 articles and included 5 RCTs including 1421 patients. We found that BID CCRT improved OS (hazard ratio, HR = 0.88, 95% confidence interval, CI 0.78-0.99, p = 0.03), the 1-year OS rate (OSR-1y, risk ratio, RR = 1.07, 95%CI 1.01-1.13, p = 0.03), and OSR-4y (RR = 1.22, 95%CI 1.03-1.43, p = 0.02), with better trends in OSR-2y, OSR-3y, and OSR-5y,

compared to OD CCRT. In addition, BID CCRT had a higher complete response (CR, RR = 1.31, 95%CI 1.01-1.70, p = 0.04) than OD CCRT. PFS (HR = 0.92, 95%CI 0.79-1.07, p = 0.29), annual PFS rate, ORR (RR = 0.99, 95%CI 0.93-1.05, p = 0.72), and AEs for all grades (RR = 1.00, 95%CI 0.98-1.01, p = 0.57), and grades 3-5 (RR = 1.02, 95%CI 0.95-1.09, p = 0.60) were similar between the two arms. **CONCLUSIONS:** BID CCRT appears to be better than OD CCRT for limited-stage SCLC, with better antitumor effects (OS, OSR, and CR) and similar AEs. However, the high levels of AEs in both arms should be taken as a sign of caution. More large sample and high-quality RCTs need to be conducted to confirm our conclusions.

Nivolumab for the treatment of small cell lung cancer. Simeone E1, Grimaldi AM1, Festino L1, Trojaniello C1, Vitale MG1, Vanella V1, Curvietto M1, Ascierto PA1. Expert Rev Respir Med. 2020 Jan;14(1):5-13. doi: 10.1080/17476348.2020.1681977. Epub 2019 Oct 29.
INTRODUCTION: Treatment of extensive-stage SCLC is still a challenge but immunotherapy with checkpoint inhibitors is showing promising results. Nivolumab alone or in combination with ipilimumab has demonstrated a benefit in terms of response and survival in patients with pre-treated extensive-stage disease and has been approved as third-line therapy after failure of chemotherapy. However, data from two phase III trials with nivolumab are negative. In the first trial, nivolumab was administered as a single agent compared to second-line chemotherapy, while in the second it was given alone or in combination with ipilimumab as maintenance treatment after platinum-based chemotherapy. **AREAS COVERED:** Our review focuses on the role of immunotherapy, and in particular nivolumab, in the treatment of SCLC, describing the results of the main trials and its future perspectives, with reference to clinical trials with other checkpoint inhibitors. **EXPERT OPINION:** The future of nivolumab in the treatment of SCLC needs to be clarified with further clinical trials, in which improved patient selection and a more specific setting and/or timepoint of the disease may be identified.

PALLIATIVE AND SUPPORTIVE CARE

Aprepitant for Cough Suppression in Advanced Lung Cancer: A Randomized Trial. Noronha V1, Bhattacharjee A2, Patil VM1, et al. Chest. 2020 Jan 17. pii: S0012-3692(20)30032-5. doi: 10.1016/j.chest.2019.11.048. [Epub ahead of print]
BACKGROUND: Although cough is a common and distressing symptom in lung cancer patients, there is almost no evidence to guide management. Aprepitant, a centrally acting neurokinin-1 inhibitor, significantly decreased cough frequency in a pilot study. **METHODS:** Patients with advanced lung cancer and cough lasting over two weeks despite a cough suppressant, were randomized 1:1 to aprepitant 125 mg orally on day one then 80 mg orally on days two to seven with physician's choice of antitussive; or to physician's choice of antitussive alone. Evaluation was at baseline and on days three, seven, nine and twelve. Primary endpoint was subjective cough improvement on day nine, measured by the Visual Analog Scale (VAS) and Manchester Cough in Lung Cancer Scale (MCLCS). Secondary endpoints included quality of life (QoL) as measured by the EORTC QLQ-C30 and QLQ-LC13 and toxicity. **RESULTS:** Between 2017 and 2018, 128 patients were randomized. Median baseline cough duration was 90 days. Mean VAS scores (in mm) at baseline and day nine were 68 and 39 in the aprepitant arm and 62 and 49 in the control arm respectively, P<0.001; Mean MCLCS scores at baseline and day nine were 33 and 23 in aprepitant arm and 30 and 25 in control arm, P<0.001. Overall QoL was not significantly different between the two arms, however aprepitant led to a significant improvement in the cough-specific QoL domain, P=0.017. Aprepitant did not increase severe adverse events. **CONCLUSIONS:** Aprepitant led to a significant improvement in cough in advanced lung cancer, without increasing severe side-effects.

Determining the prevalence and severity of cancer cachexia in advanced non-small cell lung cancer and its relationship with chemotherapy outcomes. White R1,2, Weekes CE3, Grant R4, Baldwin C5, Ahmed H4. Support Care Cancer. 2020 Jan 8. doi: 10.1007/s00520-019-05259-1. [Epub ahead of print]
PURPOSE: Cancer cachexia (CC) is a syndrome characterised by an ongoing loss of skeletal muscle mass associated with reduced tolerance to treatment. This study explored the prevalence and severity of CC in advanced non-small cell lung cancer (NSCLC) patients and determined its relationship with chemotherapy outcomes. **METHODS:** CC was classified into a four-stage model: no cachexia, pre-cachexia (PC), cachexia and refractory cachexia (RC) with categorisation determined from biochemical and body composition and performance assessment. Associations between the stage of cachexia and chemotherapy outcomes including radiological response, the number of chemotherapy cycles completed nd the number of cycles delayed or dose reduced were explored. **RESULTS:** Twenty-four patients were included with 4 (18%) classified as having no cachexia, 4 (18%) PC, 3 (14%) cachexia (13.6%), and 11 (50%) RC. No association was observed between the stage of cachexia and the radiological response to chemotherapy number of cycles delayed or the number of cycle's dose reduced; however, there was an association with the number of cycles completed ($p = 0.030$). An association between C-reactive protein (CRP) and the number of chemotherapy cycles completed ($p = 0.044$) and the number of dose reductions ($p = 0.044$) was also identified. **CONCLUSIONS:** Limited conclusions can be drawn given the small sample size. However, the majority of patients presented with some degree of cachexia at diagnosis. A relationship was identified between the increasing severity of cachexia and a lower number of chemotherapy cycles completed, as well as between CRP and the number of chemotherapy cycles completed and the number of dose reductions required, and therefore warrants further exploration in larger studies.

A cross sectional study to determine the prevalence of cough and its impact in patients with lung cancer: a patient unmet need. Harle A1,2, Molassiotis A3, Buffin O4,5, Burnham J4,6, Smith J7,8, Yorke J4,9, Blackhall FH10,11. BMC Cancer. 2020 Jan 6;20(1):9. doi: 10.1186/s12885-019-6451-1.
BACKGROUND: There is absence of literature related to cough prevalence and its characteristics in lung cancer patients, with information deriving only from broader symptoms occurrence studies. The aims of this study were to provide a snapshot of the prevalence of all-cause-cough in lung cancer patients and to characterise cough in terms of its impact and severity. **METHODS:** A cross-sectional study recruiting consecutive lung cancer patients over a pre-defined period of time and using cough-specific validated tools in a tertiary referral centre in the UK, including a cough severity VAS and the Manchester Cough in Lung Cancer scale (MCLCS). **RESULTS:** Data was collected from 202 patients. All-cause cough prevalence was 57% (through VAS) both in the screened ($N = 223$) and research ($N = 202$) population or 67% (through the MCLCS), and cough severity was moderate at a mean of 32 mm (in a 100 mm VAS). Age, sex, smoking status, lung cancer histology, stage and comorbidities were not associated with cough prevalence. The only variable associated with lower cough reports was being 'on anticancer treatment'; fewer patients on treatment reported a cough (40%) compared to those off treatment (54%) ($p = 0.04$). The impact of cough (as measured by MCLCS) was also significant (mean score = 22). About 18% of patients felt moderate/severe distress from their cough and about 15% often or always reported disturbed sleep due to coughing. Half the patients felt their cough warranted treatment. **CONCLUSIONS:** Cough is a common symptom in lung cancer with considerable impact on patients' lives. Cough presence and severity should regularly be assessed in clinical practice. There is an urgent need to focus on developing more potent antitussive treatments and improve the management of this complex and distressing symptom.

Preoperative Anxiety and Intraoperative Nociception in Patients Undergoing Thoracic Surgery.

Takenaka S1, Hirose M2. J Surg Res. 2020 Jan 6;249:13-17. doi: 10.1016/j.jss.2019.12.017. [Epub ahead of print]
BACKGROUND: Preoperative anxiety is a common psychological state in cancer patients before surgery, inducing stress responses after surgery. Associations between preoperative anxiety and intraoperative nociception, however, have not been evaluated well. In the present study, we investigated the relationship in patients with lung cancer undergoing thoracic surgery. **MATERIALS AND METHODS:** In this prospective study, 27 adult patients were enrolled. Intraoperative nociception during surgery was calculated as mean values of the nociceptive response (NR) throughout surgery. Associations between intraoperative nociception and preoperative patient characteristics including anxiety in addition to intraoperative variables were analyzed using univariate and multivariate regression analyses. **RESULTS:** Multiple linear regression analysis revealed that mean NR values during surgery showed a negative correlation with preoperative anxiety ($\beta = -0.353$; $P = 0.041$) after adjustment for body mass index, depression, and total amount of fentanyl used during surgery. Body mass index was a confounder positively associated with mean NR during surgery. **CONCLUSIONS:** Intraoperative nociception is likely associated with preoperative patient characteristics, having an inverse relationship with preoperative anxiety.

The association of physical function and quality of life on physical activity for non-small cell lung cancer survivors. Yoo JS1,2, Yang HC3, Lee JM3, Kim MS3, Park EC4, Chung SH5. Support Care Cancer. 2020 Jan 25. doi: 10.1007/s00520-020-05302-6. [Epub ahead of print]
PURPOSE: Our study aimed to assess the association between physical function and quality of life (QOL) with physical activity among non-small cell lung cancer (NSCLC) survivors. **METHODS:** Participants were 92 NSCLC survivors. Physical activity was assessed by a self-report with physiatrist's interview and the Korean version of the short form of the International Physical Activity Questionnaire (IPAQ-SF). All participants were required to perform three standardized fitness tests. The Korean version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) was used to assess QOL. Factors associated with physical functioning and QOL were determined using multiple linear regression. **RESULTS:** A significant correlation between metabolic equivalent task minutes per week (MET-min/wk) and aerobic fitness was found ($r = 0.277$, $p = 0.008$). Factors associated with aerobic fitness include gender, age, and MET-min/wk. The meeting physical activity guideline group was also a factor associated with aerobic fitness. In the QOL aspect, a significant correlation between MET-min/wk and some QOL score was found. The meeting physical activity guideline group was a factor associated with QOL (global health status, physical function, and role function), not total MET-min/wk. **CONCLUSIONS:** Increased physical activity was associated with higher aerobic fitness and QOL. Engagement in physical activity that met physical activity guidelines was a factor related to aerobic fitness and better QOL in some domains. To improve aspects of aerobic fitness and QOL, we may consider the pattern of physical activity, including regular participation and intensity, rather than total physical activity including basal activity.

COMPLEMENTARY & ALTERNATIVE THERAPY

Efficacy and safety of Jianpishengsui for chemotherapy-related fatigue in patients with non-small cell lung cancer: study protocol for a randomized placebo-controlled clinical trial. Xiao Z1, Hu L2, Lin J1, Lu L3, Huang X1, Zhu X4, Teo C5, Lin L6. Trials. 2020 Jan 16;21(1):94. doi: 10.1186/s13063-019-3982-3.
BACKGROUND: Chemotherapy-related fatigue (CRF) is a common symptom in non-small cell lung cancer (NSCLC) patients. A Chinese herbal formula cream for oral application, called Jianpishengsui (JPSS), is extensively used in the First Affiliated Hospital of Guangzhou University of Chinese Medicine

as an internal preparation for CRF and is associated with a promising response. Due to the lack of high-quality clinical evidence, a randomized placebo-controlled trial is required to assess the efficacy and safety of JPSS. **METHODS/DESIGN:** The efficacy and safety of JPSS herbal formula cream will be evaluated through a prospective, randomized, placebo-controlled trial conducted in the First Affiliated Hospital of Guangzhou University of Chinese Medicine. NSCLC patients with CRF will be randomized into two groups at a ratio of 1:1. Each group will receive either 15 g of the oral JPSS herbal formula cream or placebo twice a day from day 6 to day 20 during two courses of paclitaxel + platinum/docetaxel + platinum/pemetrexed + platinum (TP/DP/AP) chemotherapy. The primary endpoint is the difference in the degree of fatigue between baseline (the day before the start of the intervention) and day 42, which will be assessed by the Revised Piper Fatigue Scale score. The secondary endpoints are quality of life (measured by the 43-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer C43), Eastern Cooperative Oncology Group Performance Status, and Traditional Chinese Medicine syndrome score. The toxicity of the treatments will also be evaluated at the same time. All outcomes will be measured at baseline, day 6, day 21, and day 42 of the treatment. **DISCUSSION:** This randomized trial will investigate the efficacy and safety of JPSS applied for CRF in patients with NSCLC. **TRIAL REGISTRATION:** Chinese Clinical Trial Registry, ChiCTR1900023451. Registered on 28 May 2019.

Recent advances in natural therapeutic approaches for the treatment of cancer. Wang XJ1, Chen JY2, Fu LQ1, Yan MJ3. J Chemother. 2020 Jan 13:1-13. doi: 10.1080/1120009X.2019.1707417. [Epub ahead of print]

Plants and natural compounds have been widely recognized to have potential for the prevention of cancer progression and as complementary or standalone treatments for cancer patients. The major benefits of natural compounds are their reduced toxicity compared to more aggressive and widely utilized cancer treatment approaches. Preclinical studies have led to the discovery of a number of natural anticancer compounds, including preparations of Vitex negundo L., green tea, mandarin peel oil, ursolic acid, curcumin and resveratrol. Although the in vitro data highlights the potential of these natural alternatives, their benefits in clinical cancer treatment remain less conclusive. In this review, we will discuss some of the recent advances in natural anticancer treatment discovery for the four most prominent global cancers, namely, breast, lung, prostate and skin metastases. As the exploration of natural therapeutics continues to expand, these substances have the potential to be utilized as preventative strategies and complimentary therapeutics. In some cases, they may have sufficient anti-tumor and anti-carcinogenic properties to function as standalone cancer treatments.

Potential of Thai Herbal Extracts on Lung Cancer Treatment by Inducing Apoptosis and Synergizing Chemotherapy. Poofery J1, Khaw-On P1, Subhawa S1, et al. Molecules. 2020 Jan 6;25(1). pii: E231. doi: 10.3390/molecules25010231.

The incidence of lung cancer has increased while the mortality rate has continued to remain high. Effective treatment of this disease is the key to survival. Therefore, this study is a necessity in continuing research into new effective treatments. In this study we determined the effects of three different Thai herbs on lung cancer. Bridelia ovata, Croton oblongifolius, and Erythrophleum succirubrum were extracted by ethyl acetate and 50% ethanol. The cytotoxicity was tested with A549 lung cancer cell line. We found four effective extracts that exhibited toxic effects on A549 cells. These extracts included ethyl acetate extracts of B. ovata (BEA), C. oblongifolius (CEA), and E. succirubrum (EEA), and an ethanolic extract of E. succirubrum (EE). Moreover, these effective extracts were tested in combination with chemotherapeutic drugs. An effective synergism of these treatments was found specifically through a combination of BEA with methotrexate, EE with methotrexate, and EE with etoposide. Apoptotic cell death was induced in A549 cells by these effective extracts via the mitochondria-mediated pathway.

Additionally, we established primary lung cancer and normal epithelial cells from lung tissue of lung cancer patients. The cytotoxicity results showed that EE had significant potential to be used for lung cancer treatment. In conclusion, the four effective extracts possessed anticancer effects on lung cancer. The most effective extract was found to be E. succirubrum (EE).

MISCELLANEOUS WORKS

Use of High-Cost Cancer Treatments in Academic and Nonacademic Practice. Mitchell AP1,2,3, Kinlaw AC3,4, Peacock-Hinton S5, Dusetzina SB6,7, Sanoff HK2,8, Lund JL5,8. Oncologist. 2020 Jan;25(1):46-54. doi: 10.1634/theoncologist.2019-0338. Epub 2019 Oct 14.
BACKGROUND: Academic physicians, such as those affiliated with National Cancer Institute (NCI)-designated Comprehensive Cancer Centers, may have different practice patterns regarding the use of high-cost cancer drugs than nonacademic physicians. **MATERIALS AND METHODS:** For this cohort study, we linked cancer registry, administrative, and demographic data for patients with newly diagnosed cancer in North Carolina from 2004 to 2011. We selected cancer types with multiple U.S. Food and Drug Administration-approved, National Comprehensive Cancer Network-recommended treatment options and large differences in reimbursement between higher-priced and lower-priced options (stage IV colorectal, stage IV lung, and stage II-IV head-and-neck cancers). We assessed whether provider's practice setting-NCI-designated Comprehensive Cancer Center ("NCI") versus other location ("non-NCI")-was associated with use of higher-cost treatment options. We used inverse probability of exposure weighting to control for patient characteristics. **RESULTS:** Of 800 eligible patients, 79.6% were treated in non-NCI settings. Patients treated in non-NCI settings were more likely to receive high-cost treatment than patients treated in NCI settings (36.0% vs. 23.2%), with an unadjusted prevalence difference of 12.7% (95% confidence interval [CI], 5.1%-20.0%). After controlling for potential confounding factors, non-NCI patients remained more likely to receive high-cost treatment, although the strength of association was attenuated (adjusted prevalence difference, 9.6%; 95% CI -0.1%-18.7%). Exploratory analyses suggested potential heterogeneity across cancer type and insurance status. **CONCLUSION:** Use of higher-cost cancer treatments may be more common in non-NCI than NCI settings. This may reflect differential implementation of clinical evidence, local practice variation, or possibly a response to the reimbursement incentives presented by chemotherapy billing. **IMPLICATIONS FOR PRACTICE:** Oncology care delivery and practice patterns may vary between care settings. By comparing otherwise similar patients treated in National Cancer Institute (NCI)-designated Comprehensive Cancer Centers with those treated elsewhere, this study suggests that patients may be more likely to receive treatment with certain expensive cancer drugs if treated in the non-NCI setting. These practice differences may result in differences in patient costs and outcomes as a result of where they receive treatment.

Network-Based Matching of Patients and Targeted Therapies for Precision Oncology. Liu Q1, Ha MJ, Bhattacharyya R, Garmire L, Baladandayuthapani V. Pac Symp Biocomput. 2020;25:623-634.
The extensive acquisition of high-throughput molecular profiling data across model systems (human tumors and cancer cell lines) and drug sensitivity data, makes precision oncology possible - allowing clinicians to match the right drug to the right patient. Current supervised models for drug sensitivity prediction, often use cell lines as exemplars of patient tumors and for model training. However, these models are limited in their ability to accurately predict drug sensitivity of individual cancer patients to a large set of drugs, given the paucity of patient drug sensitivity data used for testing and high variability across different drugs. To address these challenges, we developed a multilayer network-based approach to impute individual patients' responses to a large set of drugs. This approach considers the triplet of patients, cell lines and drugs as one inter-connected holistic system. We first use the omics profiles to construct a patient-cell line network and determine best matching cell lines for patient tumors based on

robust measures of network similarity. Subsequently, these results are used to impute the "missing link" between each individual patient and each drug, called Personalized Imputed Drug Sensitivity Score (PIDS-Score), which can be construed as a measure of the therapeutic potential of a drug or therapy. We applied our method to two subtypes of lung cancer patients, matched these patients with cancer cell lines derived from 19 tissue types based on their functional proteomics profiles, and computed their PIDS-Scores to 251 drugs and experimental compounds. We identified the best representative cell lines that conserve lung cancer biology and molecular targets. The PIDS-Score based top sensitive drugs for the entire patient cohort as well as individual patients are highly related to lung cancer in terms of their targets, and their PIDS-Scores are significantly associated with patient clinical outcomes. These findings provide evidence that our method is useful to narrow the scope of possible effective patient-drug matchings for implementing evidence-based personalized medicine strategies.

A Smartphone App Designed to Help Cancer Patients Stop Smoking: Results From a Pilot Randomized Trial on Feasibility, Acceptability, and Effectiveness. Bricker JB1,2, Watson NL1, Heffner JL1, Sullivan B1, Mull K1, Kwon D1,2, Westmaas JL3, Ostroff J4. JMIR Form Res. 2020 Jan 17;4(1):e16652. doi: 10.2196/16652.

BACKGROUND: Persistent smoking after a cancer diagnosis predicts worse treatment outcomes and mortality, but access to effective smoking cessation interventions is limited. Smartphone apps can address this problem by providing a highly accessible, low-cost smoking cessation intervention designed for patients with a recent cancer diagnosis. **OBJECTIVE:** This study aimed to summarize our development process and report the trial design, feasibility, participant acceptability, preliminary effectiveness, and impact on processes of change (eg, cancer stigma) of the first-known smoking cessation smartphone app targeted for cancer patients. **METHODS:** We used an agile, user-centered design framework to develop a fully automated smartphone app called Quit2Heal that provided skills training and stories from cancer survivors focusing on coping with internalized shame, cancer stigma, depression, and anxiety as core triggers of smoking. Quit2Heal was compared with the National Cancer Institute's QuitGuide, a widely used stop smoking app for the general population, in a pilot double-blinded randomized trial with a 2-month follow-up period. Participants were 59 adult smokers diagnosed with cancer within the past 12 months and recruited through 2 cancer center care networks and social media over a 12-month period. The most common types of cancer diagnosed were lung (21/59, 36%) and breast (10/59, 17%) cancers. The 2-month follow-up survey retention rate was 92% (54/59) and did not differ by study arm (P=.15). **RESULTS:** Compared with QuitGuide participants, Quit2Heal participants were more satisfied with their assigned app (90% [19/21] for Quit2Heal vs 65% [17/26] for QuitGuide; P=.047) and were more likely to report that the app assigned to them was made for someone like them (86% [18/21] for Quit2Heal vs 62% [16/26] for QuitGuide; P=.04). Quit2Heal participants opened their app a greater number of times during the 2-month trial period, although this difference was not statistically significant (mean 10.0, SD 14.40 for Quit2Heal vs mean 6.1, SD 5.3 for QuitGuide; P=.33). Self-reported 30-day point prevalence quit rates at the 2-month follow-up were 20% (5/25) for Quit2Heal versus 7% (2/29) for QuitGuide (odds ratio 5.16, 95% CI 0.71-37.29; P=.10). Quit2Heal participants also showed greater improvement in internalized shame, cancer stigma, depression, and anxiety, although these were not statistically significant (all P>.05). **CONCLUSIONS:** In a pilot randomized trial with a high short-term retention rate, Quit2Heal showed promising acceptability and effectiveness for helping cancer patients stop smoking. Testing in a full-scale randomized controlled trial with a longer follow-up period and a larger sample size is required to test the effectiveness, mediators, and moderators of this promising digital cessation intervention.

Follow-Up of the Libby, Montana Screening Cohort: A 17-Year Mortality Study. Larson TC1, Williamson L, Antao VC. J Occup Environ Med. 2020 Jan;62(1):e1-e6. doi: 10.1097/JOM.0000000000001760.

OBJECTIVE: To evaluate mortality patterns among participants in a community-based screening program for asbestos-related disease. **METHODS:** We calculated standardized mortality ratios (SMRs) and stratified results by exposure group (three occupational exposure groups, household contacts and residents without occupational asbestos exposure) and by radiographic abnormality presence. **RESULTS:** All-cause mortality (15.8%; 1,429/8,043) was statistically lower than expected. Asbestosis was statistically elevated in all exposure groups. Lung cancer was moderately associated with vermiculite miner/miller employment. Mesothelioma was elevated in that same exposure group and among residents. Systemic autoimmune disease mortality was also elevated. Radiographic parenchymal abnormalities were associated with lung cancer mortality. **CONCLUSION:** In addition to asbestos-related mortality in occupational exposure groups, this initial follow-up of this cohort also shows elevated mortality for some asbestos-related causes in non-occupational exposure groups.

Improving Clinical Trial Participant Prescreening With Artificial Intelligence (AI): A Comparison of the Results of AI-Assisted vs Standard Methods in 3 Oncology Trials. Calaprice-Whitty D1, Galil K2, Salloum W2, Zariv A2, Jimenez B2. Ther Innov Regul Sci. 2020 Jan;54(1):69-74. doi: 10.1007/s43441-019-00030-4. Epub 2020 Jan 6.

BACKGROUND: Delays in clinical trial enrollment and difficulties enrolling representative samples continue to vex sponsors, sites, and patient populations. Here we investigated use of an artificial intelligence-powered technology, Mendel.ai, as a means of overcoming bottlenecks and potential biases associated with standard patient prescreening processes in an oncology setting. **METHODS:** Mendel.ai was applied retroactively to 2 completed oncology studies (1 breast, 1 lung), and 1 study that failed to enroll (lung), at the Comprehensive Blood and Cancer Center, allowing direct comparison between results achieved using standard prescreening practices and results achieved with Mendel.ai. Outcome variables included the number of patients identified as potentially eligible and the elapsed time between eligibility and identification. **RESULTS:** For each trial that enrolled, use of Mendel.ai resulted in a 24% to 50% increase over standard practices in the number of patients correctly identified as potentially eligible. No patients correctly identified by standard practices were missed by Mendel.ai. For the nonenrolling trial, both approaches failed to identify suitable patients. An average of 19 days for breast and 263 days for lung cancer patients elapsed between actual patient eligibility (based on clinical chart information) and identification when the standard prescreening practice was used. In contrast, ascertainment of potential eligibility using Mendel.ai took minutes. **CONCLUSIONS:** This study suggests that augmentation of human resources with artificial intelligence could yield sizable improvements over standard practices in several aspects of the patient prescreening process, as well as in approaches to feasibility, site selection, and trial selection.

COPD and lung cancer incidence in the Women's Health Initiative Observational Study: A brief report. Nagasaka M1, Lehman A2, Chlebowski R3, et al. Lung Cancer. 2020 Jan 7;141:78-81. doi: 10.1016/j.lungcan.2020.01.006. [Epub ahead of print]

OBJECTIVES: Lung cancer is the leading cause of cancer mortality in both men and women in the United States. COPD is associated with lung cancer independently of cigarette smoking, but remains understudied in women. Utilizing data from the Women's Health Initiative Observational Study (WHI-OS), this report investigates the association between COPD and development of lung cancer, with a focus on ethnicity and cancer subtype. **MATERIALS AND METHODS:** The WHI-OS, part of the larger Women's Health Initiative (WHI), is comprised of postmenopausal women between ages 50 and 79 years old at enrollment. Self-administered questionnaires were utilized to gather baseline demographic, socioeconomic, and behavioral information from participants. For this analysis, COPD status was determined at study entry (baseline) and on annual survey (incident). Information on the primary outcome of interest, diagnosis of lung cancer, was also collected annually. **RESULTS AND CONCLUSION:** Of

the 92,789 women examined, 1,536 developed lung cancer. Overall, women with COPD were 1.64 times more likely to develop lung cancer than those without COPD, after adjusting for smoking status and intensity, ethnicity, education, body mass index, and income (HR = 1.64, 95 % CI: 1.43, 1.89). The relationship between COPD and lung cancer was not found to be significantly different between ethnic groups (p-value = 0.697). The associations between COPD and lung cancer was similar across subtypes (HR range 1.31-2.16), after adjusting for smoking status and intensity. COPD increases risk of lung cancer in women, thus they may benefit from more intensive surveillance compared to similar women without COPD.

Lung Cancer Stigma: Does Smoking History Matter? Williamson TJ1, Kwon DM1, Riley KE2, Shen MJ3, Hamann HA4,5, Ostroff JS1. Ann Behav Med. 2020 Jan 14. pii: kaz063. doi: 10.1093/abm/kaz063. [Epub ahead of print]
BACKGROUND: Lung cancer patients commonly report stigma, often attributing it to the well-established association of smoking as the leading preventable cause. Theory and research suggest that patients' smoking history may differentiate patients' experience of lung cancer stigma. However, there is inconsistent evidence whether lung cancer stigma varies by patients' smoking history, owing to limitations in the literature. **PURPOSE:** This study examined differences in lung cancer patients' reported experience of lung cancer stigma by smoking history. **METHOD:** Participants (N = 266, 63.9% female) were men and women with lung cancer who completed a validated, multidimensional questionnaire measuring lung cancer stigma. Multivariable regression models characterized relationships between smoking history (currently, formerly, and never smoked) and lung cancer stigma, controlling for psychological and sociodemographic covariates. **RESULTS:** Participants who currently smoked reported significantly higher total, internalized, and perceived lung cancer stigma compared to those who formerly or never smoked (all $p < .05$). Participants who formerly smoked reported significantly higher total and internalized stigma compared to those who never smoked ($p < .001$). Participants reported similar levels of constrained disclosure, regardless of smoking history ($p = .630$). **CONCLUSIONS:** Total, internalized, and perceived stigma vary meaningfully by lung cancer patients' smoking history. Patients who smoke at diagnosis are at risk for experiencing high levels of stigma and could benefit from psychosocial support. Regardless of smoking history, patients reported similar levels of discomfort in sharing information about their lung cancer diagnosis with others. Future studies should test relationships between health-related stigma and associated health behaviors in other stigmatized groups.

Financial toxicity in lung cancer: an assessment of magnitude, perception, and impact on quality of life. Hazell SZ1, Fu W2, et al. Ann Oncol. 2020 Jan;31(1):96-102. doi: 10.1016/j.annonc.2019.10.006.
BACKGROUND: Advances in lung cancer therapy have resulted in improved clinical outcomes. Unfortunately, advances can come at a financial cost to patients and their families that poses a significant risk to overall quality of life (QoL). Financial distress has been shown to be associated with increased symptom burden and decreased treatment compliance but the magnitude of financial distress is not well characterized in lung cancer populations. **PATIENTS AND METHODS:** Patients with stage II-IV newly diagnosed lung cancer and starting first-line therapy were recruited at a tertiary academic institution between July 2018 and April 2019. The comprehensive score for financial toxicity (COST) was used to assess financial toxicity and the Functional Assessment of Cancer Therapy-Lung (FACT-L) was used to assess QoL. Associations between financial toxicity and baseline variables were assessed using multivariable linear regression and correlations were assessed using the Pearson correlation.
RESULTS: In this study, 143 consecutive patients were approached and 91.6% agreed to participate (N = 131). The median age was 65 years (35-90); 52.7% were male (n = 69), and 75.6% were white (n = 99). The inability to afford basic necessities and having <1 month of savings was associated with increased

financial toxicity (P < 0.001) after adjusting for other factors such as age, race, insurance, and income. There was also a trend toward increased financial toxicity among those who were employed but on sick leave (P = 0.06). Increased financial toxicity was correlated with a decrease in QoL (correlation coefficient 0.41, P < 0.001). Patients' anticipated out-of-pocket (OOP) expenses for the upcoming 6 months ranged from $0 to $50 000 (median $2150). However, there was no correlation between anticipated OOP expenses and either financial toxicity or QoL. **CONCLUSIONS:** These data identify key factors for identifying at-risk patients and builds a framework for exploring the benefit of financial counseling interventions, which may improve QoL and oncologic outcomes.

Mortality in a cohort of US firefighters from San Francisco, Chicago and Philadelphia: an update. Pinkerton L1, Bertke SJ1, Yiin J2, Dahm M1, Kubale T3, Hales T4, Purdue M5, Beaumont JJ6, Daniels R7. Occup Environ Med. 2020 Feb;77(2):84-93. doi: 10.1136/oemed-2019-105962. Epub 2020 Jan 2.
OBJECTIVES: To update the mortality experience of a previously studied cohort of 29 992 US urban career firefighters compared with the US general population and examine exposure-response relationships within the cohort. **METHODS:** Vital status was updated through 2016 adding 7 years of follow-up. Cohort mortality compared with the US population was evaluated via life table analyses. Full risk-sets, matched on attained age, race, birthdate and fire department were created and analysed using the Cox proportional hazards regression to examine exposure-response associations between select mortality outcomes and exposure surrogates (exposed-days, fire-runs and fire-hours). Models were adjusted for a potential bias from healthy worker survivor effects by including a categorical variable for employment duration. **RESULTS:** Compared with the US population, mortality from all cancers, mesothelioma, non-Hodgkin's lymphoma (NHL) and cancers of the oesophagus, intestine, rectum, lung and kidney were modestly elevated. Positive exposure-response relationships were observed for deaths from lung cancer, leukaemia and chronic obstructive pulmonary disease (COPD). **CONCLUSIONS:** This update confirms previous findings of excess mortality from all cancers and several site-specific cancers as well as positive exposure-response relations for lung cancer and leukaemia. New findings include excess NHL mortality compared with the general population and a positive exposure-response relationship for COPD. However, there was no evidence of an association between any quantitative exposure measure and NHL.

Association of Physician Peer Influence With Subsequent Physician Adoption and Use of Bevacizumab. Keating NL1,2, O'Malley AJ3, Onnela JP4, Gray SW5, Landon BE1,6. JAMA Netw Open. 2020 Jan 3;3(1):e1918586. doi: 10.1001/jamanetworkopen.2019.18586.
IMPORTANCE: Understanding adoption of new cancer therapies may help identify opportunities to increase use for high-value indications. **OBJECTIVE:** To determine whether use of bevacizumab in 2005 to 2006 by oncologists' peers was associated with greater bevacizumab use among oncologists in 2007 to 2010. **DESIGN, SETTING, AND PARTICIPANTS:** This cohort study of physicians and their patients took place in 51 randomly selected hospital referral regions in the United States. Participants were 44 012 fee-for-service Medicare beneficiaries aged 65 years or older with cancers of the colorectum, lung, breast, kidney, brain, or ovary treated by 3261 oncologists in 2005 to 2010 and assigned to one of 252 communities. Data were analyzed in 2017 to 2018. **EXPOSURES:** Among patients treated with chemotherapy during 2007 to 2010 by an oncologist who had not treated patients with bevacizumab in 2005 to 2006, models assessed the association of bevacizumab use with rates of bevacizumab use in their physician's community of connected physicians in 2005 to 2006. Models adjusted for patient and physician characteristics and physician, practice, and community random effects. **MAIN OUTCOMES AND MEASURES:** Receipt of bevacizumab. **RESULTS:** A total of 34 750 patients (14 126 [40.6%] aged ≥75 years; 21 321 [61.4%] female) with cancers of the colorectum, lung, breast, kidney, brain, and ovary were treated with chemotherapy in 2005 to 2006 in the 51 hospital referral regions. Among 9262 patients treated in 2007 to 2010 by 829 physicians whose patients did not use bevacizumab in 2005 to

2006, 3654 (39.5%) were aged 75 years or older and 6227 (67.2%) were female. The rate of bevacizumab use relative to other chemotherapy in 2007 to 2010 by tertile of use (bevacizumab for <4.4%, 4.4%-6.2%, and >6.2% of all patients receiving chemotherapy) among their physician's peers in 2005 to 2006 was 10.0%, 9.5%, and 13.6%, respectively. After adjustment, use of bevacizumab in 2007 to 2010 was greater among physicians in communities with the highest rates of bevacizumab use in 2005 to 2006 compared with those whose peers were in the lowest tertile of bevacizumab use in 2005 to 2006 (adjusted odds ratio, 1.64; 95% CI, 1.20-2.25). **CONCLUSIONS AND RELEVANCE:** This study found that an increase in oncologists' adoption and use of bevacizumab in the years after its approval was associated with their peer physicians being earlier adopters. As organizations seek to provide better care at lower costs, interventions that leverage physician ties may help to promote adoption of high-value use of new cancer treatments and deimplementation of low-value therapies.