Caring Ambassadors Lung Cancer Program
Literature Review, March 2018

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Epithelial-mesenchymal transition leads to NK cell-mediated metastasis-specific immuno-surveillance in lung cancer. Chockley PJ1,2, Chen J1, Chen G3, Beer DG3, Standiford TJ1, Keshamouni VG1. J Clin Invest. 2018 Feb 26. pii: 97611. doi: 10.1172/JCI97611. [Epub ahead of print]
During epithelial-mesenchymal transition (EMT) epithelial cancer cells transdifferentiate into highly motile, invasive, mesenchymal-like cells, giving rise to disseminating tumor cells. Few of these disseminated cells successfully metastasize. Immune cells and inflammation in the tumor microenvironment were shown to drive EMT, but few studies investigated the consequences of EMT for tumor immunosurveillance. In addition to initiating metastasis, we demonstrate that EMT confers increased susceptibility to natural killer (NK) cells and contributes, in part, to the inefficiency of the metastatic process. Depletion of NK cells allowed spontaneous metastasis without affecting primary tumor growth. EMT-induced modulation of E-cadherin and cell adhesion molecule 1 (CADM1) mediated increased susceptibility to NK cytotoxicity. Higher CADM1 expression correlates with improved patient survival in 2 lung and 1 breast adenocarcinoma patient cohorts and decreased metastasis. Our observations reveal a novel NK-mediated, metastasis-specific immunosurveillance in lung cancer and present a window of opportunity for preventing metastasis by boosting NK cell activity.

Inflammatory Gene Polymorphisms in Lung Cancer Susceptibility. Eaton KD1, Romine PE2, Goodman GE3, Thornquist MD3, Barnett MJ3, Petersdorf EW4. J Thorac Oncol. 2018 Feb 2. pii: S1556-0864(18)30090-X. doi: 10.1016/j.jtho.2018.01.022. [Epub ahead of print]
INTRODUCTION: Chronic inflammation has been implicated in carcinogenesis, with increasing evidence of its role in lung cancer. We aim to evaluate the role of genetic polymorphisms in inflammation-related genes in the risk for developing lung cancer. **METHODS:** Using a nested case-control study design, 625 cases and 625 well-matched controls were selected from participants in the CARET study, a large, prospective lung cancer chemoprevention trial. The association between lung cancer incidence and survival and 23 polymorphisms descriptive of 11 inflammation-related genes (interferon γ, IL-10, IL-1α, IL-1β, IL-2, IL-4R, IL-4, IL-6, PTGS2 (COX-2), TGF-β1, and TNFα) was evaluated. **RESULTS:** Of the 23 polymorphisms, two were associated with risk for lung cancer.

Compared to individuals with the wild type (CC) variant, individuals carrying the minor allele variants of the IL-1β-511C>T promoter polymorphism (rs16944) (CT and TT) had decreased odds of lung cancer (OR = 0.74 [95% CI 0.58 - 0.94] and OR = 0.71 [95% CI 0.50 - 1.01], respectively, p = 0.03). Similar results were observed for the IL-1β-1464 C>G promoter polymorphism (rs1143623), with presence of the minor variants CG and CC having decreased odds of lung cancer (OR=0.75[95% CI 0.59-0.95] and OR=0.69[95% CI 0.46-1.03], respectively, p=0.03). Survival was not influenced by genotype. **CONCLUSIONS:** This study provides further evidence that IL-1β promoter polymorphisms may modulate the risk for developing lung cancer.

MAGE-A gene expression in peripheral blood serves as a poor prognostic marker for patients with lung cancer. Gu L1, Sang M1,2, Yin D1, Liu F1, Wu Y1, Liu S1, Huang W1, Shan B1,2. Thorac Cancer. 2018 Feb 12. doi: 10.1111/1759-7714.12571. [Epub ahead of print]
BACKGROUND: MAGE-A genes belong to the cancer/testis antigens family. The prognostic significance of MAGE-A expression in the peripheral blood of patients with lung cancer is unknown. Therefore, this study evaluated the expression and possible prognostic significance of MAGE-A in the peripheral blood of patients with lung cancer. **METHODS:** In this study, we detected MAGE-A gene expression in the peripheral blood of 150 patients with lung cancer and 30 healthy donors using multiplex semi-nested PCR and analyzed their correlation with clinicopathological risk factors. **RESULTS:** MAGE-A expression was associated with factors indicating poor prognosis. The expression of MAGE-A and each individual MAGE-A gene were also associated with low overall survival in patients with lung cancer. **CONCLUSION:** The expression of MAGE-A genes in peripheral blood may act as a poor prognostic marker in patients with lung cancer.

2-anilino-4-amino-5-aroylthiazole-type compound AS7128 inhibits lung cancer growth through decreased iASPP and p53 interaction. Cheng HW1, Chein RJ2, Cheng TJ3, et al. Cancer Sci. 2018 Mar;109(3):832-842. doi: 10.1111/cas.13489. Epub 2018 Feb 6.
Lung cancer is the leading cause of cancer-related death worldwide. Thus, developing novel therapeutic agents has become critical for lung cancer treatment. In this study, compound AS7128 was selected from a 2-million entry chemical library screening and identified as a candidate drug against non-small cell lung cancer in vitro and in vivo. Further investigation indicated that AS7128 could induce cell apoptosis and cell cycle arrest, especially in the mitosis stage. In addition, we also found that iASPP, an oncogenic protein that functionally inhibits p53, might be associated with AS7128 through mass identification. Further exploration indicated that AS7128 treatment could restore the transactivation ability of p53 and, thus, increase the expressions of its downstream target genes, which are related to cell cycle arrest and apoptosis. This occurs through disruption of the interactions between p53 and iASPP in cells. Taken together, AS7128 could bind to iASPP, disrupt the interaction between iASPP and p53, and result in cell cycle arrest and apoptosis. These findings may provide new insight for using iASPP as a therapeutic target for non-small cell lung cancer treatment.

SCREENING, DIAGNOSIS AND STAGING

Assessment of Plasma Proteomics Biomarker's Ability to Distinguish Benign From Malignant Lung Nodules: Results of the PANOPTIC (PulmonAry NOdule Plasma proTeomIc Classifier) trial. Silvestri GA1, Tanner NT2, Kearney P3, et al. Chest. 2018 Feb 26. pii: S0012-3692(18)30307-6. doi: 10.1016/j.chest.2018.02.012. [Epub ahead of print]
BACKGROUND: Lung nodules are a diagnostic challenge with an estimated yearly incidence of 1.6 million in the United States. This study evaluated the accuracy of an integrated proteomic classifier in identifying benign nodules in patients with a pretest probability of malignancy (pCA) ≤50%.

METHODS: A prospective multicenter observational trial of 685 patients with 8-30 mm lung nodules. Multiple reaction monitoring mass spectrometry measured the relative abundance of two plasma proteins, LG3BP and C163A. Results were integrated with a clinical risk prediction model to identify likely benign nodules. Sensitivity, specificity and negative predictive value were calculated. Estimates of potential changes in invasive testing had the integrated classifier results been available and acted upon were made. **RESULTS:** A subgroup of 178 patients with a clinician assessed pCA≤50% had a 16% prevalence of lung cancer. The integrated classifier demonstrated a sensitivity of 97% (CI 82%-100%), a specificity of 44% (CI 36%-52%) and a negative predictive value (NPV) of 98% (CI 92%-100%) in distinguishing benign from malignant nodules. The classifier performed better than positron emission tomography (PET), validated lung nodule risk models, and physician cancer probability estimates ($p<0.001$). If the integrated classifier results were used to direct care, 40% fewer procedures would be performed on benign nodules while 3% of malignant nodules would be misclassified. **CONCLUSIONS:** When used in patients with lung nodules with a pCA≤50%, the integrated classifier accurately identifies benign lung nodules with good performance characteristics. If used in clinical practice, invasive procedures could be reduced by diverting benign nodules to surveillance.

Developing and testing a brief clinic-based lung cancer screening decision aid for primary care settings. McDonnell KK1, Strayer SM2, Sercy E3,4, Campbell C1, Friedman DB4,5, Cartmell KB6, Eberth JM3,4. Health Expect. 2018 Feb 23. doi: 10.1111/hex.12675. [Epub ahead of print]
BACKGROUND: Cancer screening-related decisions require patients to evaluate complex medical information in short time frames, often with primary care providers (PCPs) they do not know. PCPs play an essential role in facilitating comprehensive shared decision making (SDM). **OBJECTIVE:** To develop and test a decision aid (DA) and SDM strategy for PCPs and high-risk patients. **DESIGN:** The DA was tested with 20 dyads. Each dyad consisted of one PCP and one patient eligible for screening. A prospective, one-group, mixed-method study design measured fidelity, patient values, screening intention, acceptability and satisfaction. **RESULTS:** Four PCPs and 20 patients were recruited from an urban academic medical centre. Most patients were female (n = 14, 70%), most had completed high school (n = 15, 75%), and their average age was 65 years old. Half were African American. Patients and PCPs rated the DA as helpful, easy to read and use and acceptable in terms of time frame (observed t = 11.6 minutes, SD 2.7). Most patients (n = 16, 80%) indicated their intent to be screened. PCPs recommended screening for most patients (n = 17, 85%). **CONCLUSIONS:** Evidence supports the value of lung cancer screening with LDCT for select high-risk patients. Guidelines endorse engaging patients and their PCPs in SDM discussions. Our findings suggest that using a brief, interactive, plain-language, culturally sensitive, theory-based DA and SDM strategy is feasible, acceptable and may be essential to effectively translate and sustain the adoption of LDCT screening recommendations into the clinic setting.

Demographic, psychosocial, and behavioral associations with cancer screening among a homeless population. Williams LB1, McCall A2, Looney SW3, Joshua T1, Tingen MS4. Public Health Nurs. 2018 Feb 23. doi: 10.1111/phn.12391. [Epub ahead of print]
BACKGROUND: Although cancer incidence and mortality is declining, cancer remains among the leading causes of death in the United States. Research shows that cancer morbidity and mortality can be reduced by early detection. Yet, both cancer risks and screening behavior remain understudied in the homeless population. **METHODS:** Researchers conducted a cross-sectional survey of homeless individuals (n = 201). The analysis describes the demographic, psychosocial, and behavioral associations with cancer screenings and knowledge of the lung cancer screening recommendation. **RESULTS:** Participants' mean age was 51.7 years (SD 13.6); the group was largely African American (77.3%) and male (67.9%). Among women, the breast and cervical cancer screening rates were 46.5% and 85.1%. Among men the prostate cancer screening rate was 34.2%. Among all participants, the colon cancer

screening rate was 44%. Cancer risk behaviors were high. Lung cancer screening knowledge was low (23.0%). Some cancer screening behaviors were associated with age, income, health status, obesity, tobacco use, and physical activity. **DISCUSSION:** Despite higher cancer risk behaviors, knowledge and general participation rates for cancer screenings were below national benchmarks. **CONCLUSION:** To improve cancer survival among disparate populations, sustained community outreach is necessary to increase awareness of screening recommendations, identify high-risk individuals, and navigate them to resources.

Patient and Clinician Perspectives on Shared Decision-making in Early Adopting Lung Cancer Screening Programs: a Qualitative Study. Wiener RS1,2, Koppelman E3,4, Bolton R3,5, Lasser KE4,6, Borrelli B7, Au DH8,9, Slatore CG10,11, Clark JA3,4, Kathuria H12. J Gen Intern Med. 2018 Feb 21. doi: 10.1007/s11606-018-4350-9. [Epub ahead of print]
BACKGROUND: Guidelines recommend, and Medicare requires, shared decision-making between patients and clinicians before referring individuals at high risk of lung cancer for chest CT screening. However, little is known about the extent to which shared decision-making about lung cancer screening is achieved in real-world settings. **OBJECTIVE:** To characterize patient and clinician impressions of early experiences with communication and decision-making about lung cancer screening and perceived barriers to achieving shared decision-making. **DESIGN:** Qualitative study entailing semi-structured interviews and focus groups. **PARTICIPANTS:** We enrolled 36 clinicians who refer patients for lung cancer screening and 49 patients who had undergone lung cancer screening in the prior year. Participants were recruited from lung cancer screening programs at four hospitals (three Veterans Health Administration, one urban safety net). **APPROACH:** Using content analysis, we analyzed transcripts to characterize communication and decision-making about lung cancer screening. Our analysis focused on the recommended components of shared decision-making (information sharing, deliberation, and decision aid use) and barriers to achieving shared decision-making. **KEY RESULTS:** Clinicians varied in the information shared with patients, and did not consistently incorporate decision aids. Clinicians believed they explained the rationale and gave some (often purposely limited) information about the trade-offs of lung cancer screening. By contrast, some patients reported receiving little information about screening or its trade-offs and did not realize the CT was intended as a screening test for lung cancer. Clinicians and patients alike did not perceive that significant deliberation typically occurred. Clinicians perceived insufficient time, competing priorities, difficulty accessing decision aids, limited patient comprehension, and anticipated patient emotions as barriers to realizing shared decision-making. **CONCLUSIONS:** Due to multiple perceived barriers, patient-clinician conversations about lung cancer screening may fall short of guideline-recommended shared decision-making supported by a decision aid. Consequently, patients may be left uncertain about lung cancer screening's rationale, trade-offs, and process.

Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update. Kalemkerian GP1, Narula N1, Kennedy EB1, et al. J Clin Oncol. 2018 Feb 5:JCO2017767293. doi: 10.1200/JCO.2017.76.7293. [Epub ahead of print]
PURPOSE: In response to advances in the field, the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) recently updated their recommendations for molecular testing for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors. ASCO has a policy and set of procedures for endorsing clinical practice guidelines that have been developed by other professional organizations. **METHODS:** The molecular testing guideline was reviewed for developmental rigor by

methodologists. Then an ASCO Expert Panel reviewed the content and the recommendations. **RESULTS:** The ASCO Expert Panel determined that the recommendations from the CAP/IASLC/AMP molecular testing guideline are clear, thorough, and based upon the most relevant scientific evidence. ASCO endorsed the guideline with minor modifications. **RECOMMENDATIONS:** This update clarifies that any sample with adequate cellularity and preservation may be tested and that analytical methods must be able to detect mutation in a sample with as little as 20% cancer cells. It strongly recommends against evaluating epidermal growth factor receptor (EGFR) expression by immunohistochemistry for selection of patients for EGFR-targeted therapy. New for 2018 are recommendations for stand-alone ROS1 testing with additional confirmation testing in all patients with advanced lung adenocarcinoma, and RET, ERBB2 (HER2), KRAS, and MET testing as part of larger panels. ASCO also recommends stand-alone BRAF testing in patients with advanced lung adenocarcinoma. Recommendations are also provided for testing methods for lung cancers that have a nonadenocarcinoma non-small-cell component, for patients with targetable mutations who have relapsed on targeted therapy, and for testing the presence of circulating cell-free DNA. Additional information is available at www.asco.org/thoracic-cancer-guidelines and www.asco.org/guidelineswiki.

Screening for Lung Cancer: CHEST Guideline and Expert Panel Report.
Mazzone PJ1, Silvestri GA2, Patel S3, Kanne JP4, Kinsinger LS5, Wiener RS6, Soo Hoo G7, Detterbeck FC8. Chest. 2018 Feb 17. pii: S0012-3692(18)30094-1. doi: 10.1016/j.chest.2018.01.016. [Epub ahead of print]
BACKGROUND: Low-dose chest CT screening for lung cancer has become a standard of care in the United States in the past few years, in large part due to the results of the National Lung Screening Trial. The benefit and harms of low-dose chest CT screening differ in both frequency and magnitude. The translation of a favorable balance of benefit and harms into practice can be difficult. Here, we update the evidence base for the benefit, harms, and implementation of low radiation dose chest CT screening. We use the updated evidence base to provide recommendations where the evidence allows, and statements based on experience and expert consensus where it does not. **METHODS:** Approved panelists developed key questions using the PICO (population, intervention, comparator, and outcome) format to address the benefit and harms of low-dose CT screening, as well as key areas of program implementation. A systematic literature review was conducted by using MEDLINE via PubMed, Embase, and the Cochrane Library. Reference lists from relevant retrievals were searched, and additional papers were added. The quality of the evidence was assessed for each critical or important outcome of interest using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach. Important clinical questions were addressed based on the evidence developed from the systematic literature review. Graded recommendations and ungraded statements were drafted, voted on, and revised until consensus was reached. **RESULTS:** The systematic literature review identified 59 studies that informed the response to the 12 PICO questions that were developed. Key clinical questions were addressed resulting in six graded recommendations and nine ungraded consensus based statements. **CONCLUSIONS:** Evidence suggests that low-dose CT screening for lung cancer results in a favorable but tenuous balance of benefit and harms. The selection of screen-eligible patients, the quality of imaging and image interpretation, the management of screen-detected findings, and the effectiveness of smoking cessation interventions can affect this balance. Additional research is needed to optimize the approach to low-dose CT screening.

Computer-aided diagnosis of lung cancer: the effect of training data sets on classification accuracy of lung nodules. Gong J1, Liu JY, Sun XW, Zheng B, Nie SD. Phys Med Biol. 2018 Feb 5;63(3):035036. doi: 10.1088/1361-6560/aaa610.
This study aims to develop a computer-aided diagnosis (CADx) scheme for classification between malignant and benign lung nodules, and also assess whether CADx performance changes in detecting

nodules associated with early and advanced stage lung cancer. The study involves 243 biopsy-confirmed pulmonary nodules. Among them, 76 are benign, 81 are stage I and 86 are stage III malignant nodules. The cases are separated into three data sets involving: (1) all nodules, (2) benign and stage I malignant nodules, and (3) benign and stage III malignant nodules. A CADx scheme is applied to segment lung nodules depicted on computed tomography images and we initially computed 66 3D image features. Then, three machine learning models namely, a support vector machine, naïve Bayes classifier and linear discriminant analysis, are separately trained and tested by using three data sets and a leave-one-case-out cross-validation method embedded with a Relief-F feature selection algorithm. When separately using three data sets to train and test three classifiers, the average areas under receiver operating characteristic curves (AUC) are 0.94, 0.90 and 0.99, respectively. When using the classifiers trained using data sets with all nodules, average AUC values are 0.88 and 0.99 for detecting early and advanced stage nodules, respectively. AUC values computed from three classifiers trained using the same data set are consistent without statistically significant difference ($p > 0.05$). This study demonstrates (1) the feasibility of applying a CADx scheme to accurately distinguish between benign and malignant lung nodules, and (2) a positive trend between CADx performance and cancer progression stage. Thus, in order to increase CADx performance in detecting subtle and early cancer, training data sets should include more diverse early stage cancer cases.

Challenges Implementing Lung Cancer Screening in Federally Qualified Health Centers. Zeliadt SB1, Hoffman RM2, Birkby G3, Eberth JM4, Brenner AT5, Reuland DS6, Flocke SA7. Am J Prev Med. 2018 Feb 8. pii: S0749-3797(18)30001-1. doi: 10.1016/j.amepre.2018.01.001. [Epub ahead of print]
INTRODUCTION: The purpose of this study is to identify issues faced by Federally Qualified Health Centers (FQHCs) in implementing lung cancer screening in low-resource settings. **METHODS:** Medical directors of 258 FQHCs serving communities with tobacco use prevalence above the median of all 1,202 FQHCs nationally were sampled to participate in a web-based survey. Data were collected between August and October 2016. Data analysis was completed in June 2017. **RESULTS:** There were 112 (43%) FQHC medical directors or surrogates who responded to the 2016 survey. Overall, 41% of respondents were aware of a lung cancer screening program within 30 miles of their system's largest clinic. Although 43% reported that some providers in their system offer screening, it was typically at a very low volume (less than ten/month). Although FQHCs are required to collect tobacco use data, only 13% indicated that these data can identify patients eligible for screening. Many FQHCs reported important patient financial barriers for screening, including lack of insurance (72%), preauthorization requirements (58%), and out-of-pocket cost burdens for follow-up procedures (73%). Only 51% indicated having adequate access to specialty providers to manage abnormal findings, and few reported that leadership had either committed resources to lung cancer screening (12%) or prioritized lung cancer screening (12%). **CONCLUSIONS:** FQHCs and other safety-net clinics, which predominantly serve low-socioeconomic populations with high proportions of smokers eligible for lung cancer screening, face significant economic and resource challenges to implementing lung cancer screening. Although these vulnerable patients are at increased risk for lung cancer, reducing patient financial burdens and appropriately managing abnormal findings are critical to ensure that offering screening does not inadvertently lead to harm and increase disparities.

Regional lymph node sampling in lung carcinoma: a single institutional and national database comparison. Bosch DE1, Farjah F2, Wood DE2, Schmidt RA3. Hum Pathol. 2018 Feb 12. pii: S0046-8177(18)30042-X. doi: 10.1016/j.humpath.2018.02.002. [Epub ahead of print]
Assessing regional lymph node metastasis is a key component of lung carcinoma staging and prognostication. Recent guidelines have suggested a quality metric of 10 total regional lymph nodes sampled with each stage I-II primary lung carcinoma resection. However, the extent of mediastinal lymph node sampling remains controversial. We assessed factors contributing to regional lymph node counts and

effect on overall patient survival in an institutional cohort of 888 cases and the Surveillance, Epidemiology, and End Results (SEER) national cancer registry (10 856 cases). The distribution of total lymph node counts in lobectomy and pneumonectomy cases was variable with median 10, interquartile range 7-14. Multiple clinical and pathologic factors correlated to total regional node counts. Total lymph node counts ≥10 in the institutional cohort did not correlate to significant differences in overall survival as compared to node counts <10 (P = .38). In the SEER database, although 0 regional lymph nodes reported correlated to reduced overall survival (hazard ratio 1.47, P < .01), no significant difference was detected for 1-9 versus ≥10 nodes (P = .8). **In conclusion,** lymph node counts for primary lung carcinoma are driven by surgical, pathological, and biological variability. We find no evidence for a meaningful quality metric of 10 total regional lymph nodes at the institutional and national registry levels.

The impact of EGFR mutations on the incidence and survival of stages I to III NSCLC patients with subsequent brain metastasis. Chang WY1,2, Wu YL3, Su PL1, Yang SC1, Lin CC1,2, Su WC1,2. PLoS One. 2018 Feb 15;13(2):e0192161. doi: 10.1371/journal.pone.0192161. eCollection 2018.
Previous studies have demonstrated the association between EGFR mutations and distant metastasis. However, the association for subsequent brain metastasis (BM) in stages I-III non-small cell lung cancer (NSCLC) patients remains inconclusive. We conducted a retrospective analysis to clarify the impact of EGFR mutations on the incidence of BM and associated survival in patients with stage I-III NSCLC. A total of 491 patients screened for EGFR mutations were retrospectively enrolled. Brain MRI or CT was used to detect the BM. Cumulative incidence of subsequent BM and overall survival (OS) after diagnosis of BM were estimated by the Kaplan-Meier method and compared using log-rank test. We performed Cox proportional hazard regression for predictors of subsequent BM and determinants of OS after BM. The cumulative incidence of BM seemed higher in patients harboring EGFR mutations than those without EGFR mutations although it did not reach statistical significance (hazard ratio [HR] = 1.75, 95% confidence interval [CI] = 0.73~1.81). After adjusting possible confounders, including age, smoking, stage, and tumor size, EGFR mutation became one of the predictors for subsequent BM (HR = 1.89, 95% CI = 1.12~3.17, p = 0.017). Though there was no statistical difference in survival after BM between patients with EGFR mutations and wild-type EGFR (median survival: 17.8 vs. 12.2 months, HR = 0.79, 95% CI = 0.45-1.40), patients with EGFR 19 deletion (Del) tended to have a longer survival after BM than the non-EGFR 19 Del group (median survival: 29.4 vs. 14.3 months, HR 0.58, 95% CI = 0.32-1.09, p = 0.089). In conclusion, our data suggested EGFR mutation to be one of the predictors for subsequent BM in stage I-III patients. Given the small sample size, more studies are warranted to corroborate our results.

Implementation of Digital Awareness Strategies to Engage Patients and Providers in a Lung Cancer Screening Program: Retrospective Study. Jessup DL#1, Glover Iv M#1,2, Daye D1, Banzi L1, Jones P1, Choy G1, Shepard JO1, Flores EJ1. J Med Internet Res. 2018 Feb 15;20(2):e52. doi: 10.2196/jmir.8932.
BACKGROUND: Lung cancer is the leading cause of cancer-related deaths in the United States. Despite mandated insurance coverage for eligible patients, lung cancer screening rates remain low. Digital platforms, including social media, provide a potentially valuable tool to enhance health promotion and patient engagement related to lung cancer screening (LCS). **OBJECTIVE:** The aim was to assess the effectiveness of LCS digital awareness campaigns on utilization of low-dose computed tomography (LDCT) and visits to institutional online educational content. **METHODS:** A pay-per-click campaign utilizing Google and Facebook targeted adults aged 55 years and older and caregivers aged 18 years and older (eg, spouses, adult children) with LCS content during a 20-week intervention period from May to September 2016. A concurrent pay-per-click campaign using LinkedIn and Twitter targeted health care providers with LCS content. Geographic target radius was within 60 miles of an academic medical center. Social media data included aggregate demographics and click-through rates (CTRs). Primary outcome

measures were visits to institutional Web pages and scheduled LDCT exams. Study period was 20 weeks before, during, and after the digital awareness campaigns. **RESULTS:** Weekly visits to the institutional LCS Web pages were significantly higher during the digital awareness campaigns compared to the 20-week period prior to implementation (mean 823.9, SD 905.8 vs mean 51, SD 22.3, P=.001). The patient digital awareness campaign surpassed industry standard CTRs on Google (5.85%, 1108/18,955 vs 1.8%) and Facebook (2.59%, 47,750/1,846,070 vs 0.8%). The provider digital awareness campaign surpassed industry standard CTR on LinkedIn (1.1%, 630/57,079 vs 0.3%) but not Twitter (0.19%, 1139/587,133 vs 0.25%). Mean scheduled LDCT exam volumes per week before, during, and after the digital awareness campaigns were 17.4 (SD 7.5), 20.4 (SD 5.4), and 26.2 (SD 6.4), respectively, with the difference between the mean number of scheduled exams after the digital awareness campaigns and the number of exams scheduled before and after the digital awareness campaigns being statistically significant (P<.001). **CONCLUSIONS:** Implementation of the LCS digital awareness campaigns was associated with increased visits to institutional educational Web pages and scheduled LDCT exams. Digital platforms are an important tool to enhance health promotion activities and engagement with patients and providers.

Liquid biopsy and its role in an advanced clinical trial for lung cancer. Johann DJ Jr1, Steliga M2, Shin IJ1, et al. Exp Biol Med (Maywood). 2018 Feb;243(3):262-271. doi: 10.1177/1535370217750087. Liquid biopsy methodologies, for the purpose of plasma genotyping of cell-free DNA (cfDNA) of solid tumors, are a new class of novel molecular assays. Such assays are rapidly entering the clinical sphere of research-based monitoring in translational oncology, especially for thoracic malignancies. Potential applications for these blood-based cfDNA assays include: (i) initial diagnosis, (ii) response to therapy and follow-up, (iii) tumor evolution, and (iv) minimal residual disease evaluation. Precision medicine will benefit from cutting-edge molecular diagnostics, especially regarding treatment decisions in the adjuvant setting, where avoiding over-treatment and unnecessary toxicity are paramount. The use of innovative genetic analysis techniques on individual patient tumor samples is being pursued in several advanced clinical trials. Rather than using a categorical treatment plan, the next critical step of therapeutic decision making is providing the "right" cancer therapy for an individual patient, including correct dose and timeframe based on the molecular analysis of the tumor in question. Per the 21st Century Cures Act, innovative clinical trials are integral for biomarker and drug development. This will include advanced clinical trials utilizing: (i) innovative assays, (ii) molecular profiling with cutting-edge bioinformatics, and (iii) clinically relevant animal or tissue models. In this paper, a mini-review addresses state-of-the-art liquid biopsy approaches. Additionally, an on-going advanced clinical trial for lung cancer with novelty through synergizing liquid biopsies, co-clinical trials, and advanced bioinformatics is also presented. Impact statement Liquid biopsy technology is providing a new source for cancer biomarkers, and adds new dimensions in advanced clinical trials. Utilizing a non-invasive routine blood draw, the liquid biopsy provides abilities to address perplexing issues of tumor tissue heterogeneity by identifying mutations in both primary and metastatic lesions. Regarding the assessment of response to cancer therapy, the liquid biopsy is not ready to replace medical imaging, but adds critical new information; for instance, through a temporal assessment of quantitative circulating tumor DNA (ctDNA) assay results, and importantly, the ability to monitor for signs of resistance, via emerging clones. Adjuvant therapy may soon be considered based on a quantitative cfDNA assay. As sensitivity and specificity of the technology continue to progress, cancer screening and prevention will improve and save countless lives by finding the cancer early, so that a routine surgery may be all that is required for a definitive cure.

Quantitative PET/CT in clinical practice: assessing the agreement of PET tumor indices using different clinical reading platforms. Mhlanga JC1,2, Chirindel A1, Lodge MA1, Wahl RL1,2, Subramaniam RM1,3,4,5,6,7. Nucl Med Commun. 2018 Feb;39(2):154-160. doi: 10.1097/MNM.0000000000000786.

OBJECTIVE: The aim of this study was to determine whether various fluorine-18-fluorodeoxyglucose PET/CT-derived parameters used in oncology vary significantly depending on the interpretation software systems used in clinical practice for multiple human solid tumors. **PATIENTS AND METHODS:** A total of 120 fluorine-18-fluorodeoxyglucose PET/CT studies carried out in patients with pancreatic, lung, colorectal, and head and neck cancers were evaluated retrospectively on two different vendor software platforms including Mirada and MIMVista. Regions of interest were placed on the liver to determine the liver mean standardized uptake value at lean body mass (SUL) and on each tumor to determine the SULmax, SULpeak. Total lesion glycolysis (TLG) and metabolic tumor volume (MTV) were determined using fixed thresholds of 50% of SULmax and SULpeak. Inter-reader, intersystem intraclass correlations, systematic bias, and variability reflected by the 95% limits of agreement, and precision were determined. **RESULTS:** There was excellent inter-reader reliability between the readers and the two software systems, with intraclass correlations more than 0.9 for all PET metrics, with P values less than 0.0001. The bias and SD on Bland-Altman analysis between the two software platforms for tumor SULmax, SULpeak, Max50MTV, and Peak50MTV, respectively, for Reader 1 were -1.52±2.24, 0.80±3.67, -0.80±13.01, and -4.49±20.6. For Reader 2, the biases were -1.62±1.95, 0.18±3.60, -0.27±4.64, and -3.13±8.30. The precision between the two systems was better for SULmax and SULpeak, with less variance observed, than for volume-based metrics such as Max50MTV and Peak50MTV or TLG. **CONCLUSION:** Excellent correlation has been found between two tested software reading platforms for all PET-derived metrics in a dual-reader analysis. Overall, the SULmax and SULpeak values had less bias and better precision compared with the MTV and TLG.

Features of Chronic Obstructive Pulmonary Disease as Predictors of Lung Cancer. Carr LL1, Jacobson S2, Lynch DA3, et al. Chest. 2018 Feb 13. pii: S0012-3692(18)30254-X. doi: 10.1016/j.chest.2018.01.049. [Epub ahead of print]
BACKGROUND: Lung cancer is a leading cause of death and hospitalization for patients with chronic obstructive lung disease, (COPD); a detailed understanding of which clinical features of COPD increase risk is needed. **METHODS:** To identify clinical and imaging features of smokers, with and without COPD, that are associated with an increased risk of lung cancer, we performed a nested case-control study of COPDGene subjects with and without lung cancer, age 45-80, who smoked at least 10-pack years. Baseline evaluation included: spirometry, high-resolution chest CT, and respiratory questionnaires. New lung cancer diagnoses were identified over eight years of longitudinal follow-up. Lung cancer cases were matched 1:4 with control subjects for age, race, gender, and smoking history. Multiple logistic regressions were used to determine features predictive of lung cancer. **RESULTS:** Features associated with a future risk of lung cancer included: decreased FEV1/FVC (Odds Ratio (OR) 1.28 per 10% decrease, 95%CI 1.12- 1.46), visual severity of emphysema (OR 2.31, none-trace vs mild-advanced, 95%CI 1.41-3.86), and respiratory exacerbations prior to study entry (OR 1.39 per increased events, 0, 1, > 2, 95%CI 1.04-1.85). Respiratory exacerbations were also associated with small-cell lung cancer histology (OR 3.57, 95%CI, 1.47-10). **CONCLUSIONS:** The degree of COPD severity, including airflow obstruction, visual emphysema and respiratory exacerbations are independently predictive of lung cancer. These risk factors should be further studied as inclusion and exclusion criteria for the survival benefit of lung cancer screening. Studies are needed to determine if reduction in respiratory exacerbations among smokers can reduce lung cancer risk.

Underperformance of Mediastinal Lymph Node Evaluation in Resectable Non-Small Cell Lung Cancer. Tantraworasin A1, Taioli E2, Liu B3, Kaufman AJ4, Flores RM5. Ann Thorac Surg. 2018 Mar;105(3):943-949. doi: 10.1016/j.athoracsur.2017.10.007. Epub 2018 Feb 13.
BACKGROUND: Mediastinal lymph node evaluation (MLNE) is considered to be the standard of care in curative lung cancer surgery although it is not always performed. This study identifies factors

associated with patients not being evaluated (non-MLNE) in cases of resectable non-small cell lung cancer. **METHODS:** A retrospective observational study using the Surveillance, Epidemiology, and End Results Program database was conducted. Adult patients diagnosed with non-small cell lung cancer stage I to IIIA (2004 to 2013) were included. Multilevel logistic regression analysis was performed to identify factors that were associated with non-MLNE. **RESULTS:** There were 86,721 patients included in this study: 73,034 (84.2%) with MLNE and 13,687 (15.8%) without. The use of MLNE gradually increased from 82.7% in 2004 to 85.8% in 2013. In multivariable analysis, factors associated with non-MLNE included the following: age more than 75 years (adjusted odds ratio [ORadj] 1.20, 95% confidence interval [CI]: 1.13 to 1.27); black (ORadj 1.11, 95% CI: 1.32 to 1.20); Native American/Alaskan (ORadj 1.63, 95% CI: 1.15 to 2.31); uninsured (ORadj 1.28, 95% CI: 1.05 to 1.56); residing in a low-income county (ORadj 1.12, 95% CI: 1.04 to 1.21); lesion at the middle lobe (ORadj 1.42, 95% CI: 1.29 to 1.56); lower lobe (ORadj 1.06, 95% CI: 1.01 to 1.11) or main bronchus (ORadj 2.38, 95% CI: 1.93 to 2.94); stage IA (ORadj 1.24, 95% CI: 1.17 to 1.32); sublobar resection (ORadj 11.08, 95% CI: 11.30 to 12.33); and preoperative treatment (ORadj 1.21, 95% CI: 1.08 to 1.36). Non-MLNE was less likely to occur in patients with adenocarcinoma (ORadj 0.88, 95% CI: 0.83 to 0.92) and more likely in other cell types (ORadj 1.23, 95% CI: 1.15 to 1.32), compared with squamous cell carcinoma. **CONCLUSIONS:** Patient demographics and socioeconomic status are associated with the decision to perform MLNE. Thoracic surgeons should access these factors and perform MLNE to accurately determine tumor stage and improve survival.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

An overview of perioperative considerations in elderly patients for thoracic surgery: demographics, risk/benefit, and resource planning. Castillo M1. Curr Opin Anaesthesiol. 2018 Feb;31(1):1-5. doi: 10.1097/ACO.0000000000000535.
PURPOSE OF REVIEW: Increasing numbers of geriatric patients will present for thoracic surgery as the population ages. The changes in physiologic reserve as well as the increase in comorbid conditions among this population must be considered in order to optimize patient care in the perioperative period. **RECENT FINDINGS:** For elderly patients with cancer, the risk-benefit relationship for thoracic surgery remains favorable. Consideration of comorbidities, especially chronic obstructive pulmonary disease and congestive heart failure, is important in the setting of surgical treatment, as they have implications for perioperative care as well as postoperative morbidity and mortality. Overall survival, quality of life, and health status must be considered in decisions regarding cancer treatment. **SUMMARY:** Elderly patients with early-stage lung cancer derive benefit from surgical treatment, despite their increased prevalence of comorbidities, because survival associated with untreated lung cancer is so dismal. Some studies suggest that even late-stage lung cancer patients may benefit from surgery as part of a multimodal approach. Further studies could help target implementation of resources to optimize overall patient health and physiologic condition in order to decrease morbidity and mortality and to optimize quality of life.

Thoracic Skeletal Muscle is Associated with Adverse Outcomes After Lobectomy for Lung Cancer. Fintelmann FJ1, Troschel FM2, Mario J2, Chretien YR2, Knoll SJ2, Muniappan A2, Gaissert HA2. Ann Thorac Surg. 2018 Feb 2. pii: S0003-4975(18)30077-8. doi: 10.1016/j.athoracsur.2018.01.013. [Epub ahead of print]
BACKGROUND: Assessment of risk associated with lung cancer resection is primarily based on evaluation of cardiopulmonary function and remains imprecise. We investigated the relationship between

thoracic muscle and early outcomes after lobectomy. **METHODS:** Cross-sectional area of skeletal muscle was measured at the level of the fifth thoracic vertebra on computed tomography in 135 consecutive patients prior to lobectomy for lung cancer. Patients were stratified into low and high muscle groups using the gender-specific muscle median. Primary outcome was a composite of any postoperative complication as per Society of Thoracic Surgeons General Thoracic Surgical Database. Secondary outcomes included postoperative respiratory complications, postoperative intensive care unit (ICU) admission, hospital length of stay (LOS), and hospital readmission within 30 days of hospital discharge. Chi-square testing, adjusted multivariable regression and likelihood ratio test were performed. **RESULTS:** Patients with low muscle were significantly more likely to have any postoperative complication and respiratory postoperative complications. While postoperative ICU admission was similar for low and high muscle groups, low muscle patients experienced longer hospital LOS and a higher rate of hospital readmission. Adjusted multivariable regression revealed the independent association of thoracic muscle with all outcomes. The likelihood ratio test suggested that thoracic muscle adds predictive capability to information captured by preoperative pulmonary function testing. **CONCLUSIONS:** Low thoracic muscle is independently associated with increased postoperative complications and healthcare utilization among patients undergoing lobectomy for lung cancer. Evaluation of thoracic muscle may enhance risk prediction models.

Patients want more information after surgery: a prospective audit of satisfaction with perioperative information in lung cancer surgery. Oswald N1, Hardman J2, Kerr A2, Bishay E2, Steyn R2, Rajesh P2, Kalkat M2, Naidu B3. J Cardiothorac Surg. 2018 Feb 1;13(1):18. doi: 10.1186/s13019-018-0707-8. **BACKGROUND:** Receiving information about their disease and treatment is very important to patients with cancer. There is an association between feeling appropriately informed and better quality of life. This audit aimed to estimate patient satisfaction with perioperative information in those undergoing surgery for lung cancer and any change in satisfaction over time. **METHODS:** A questionnaire (EORTC-Info-25) was administered prospectively to patients preoperatively and up to six months postoperatively. The preoperative questionnaire was completed by 292 patients and 88 free text comments were completed. Intrapersonal responses were compared over time. **RESULTS:** Patients were highly satisfied with information prior to surgery. The overall helpfulness of information did not change over time but satisfaction with the amount of information decreased. Patients who received more information about 'the disease' and 'things you can do to help yourself get well' were less likely to report a drop in satisfaction (Odds Ratio 0.858, 95% Confidence interval 0.765 to 0.961, $p = 0.008$ and OR 0.102, 95% CI 0.018 to 0.590, $p = 0.011$ respectively). Free text responses revealed patients most frequently wanted more information on the disease, aftercare and self-care. Suffering complications from surgery was not associated with a change in satisfaction with information postoperatively. **CONCLUSIONS:** Patients want to know more about their diagnosis, but also how to recover and cope with issues once they have gone home after surgery. Postoperative satisfaction with information may improve if patients are given more information on these topics.

Outcomes of Pulmonary Resection and Mediastinal Node Dissection by Video-Assisted Thoracoscopic Surgery Following Neoadjuvant Chemoradiation Therapy for Stage IIIA N2 Non-Small Cell Lung Cancer. Jeon YJ1, Choi YS1, Lee KJ2, Lee SH3, Pyo H4, Choi JY5. Korean J Thorac Cardiovasc Surg. 2018 Feb;51(1):29-34. doi: 10.5090/kjtcs.2018.51.1.29. Epub 2018 Feb 5. **BACKGROUND:** We evaluated the feasibility and outcomes of pulmonary resection and mediastinal node dissection (MND) by video-assisted thoracoscopic surgery (VATS) following neoadjuvant therapy for stage IIIA N2 non-small cell lung cancer (NSCLC). **METHODS:** From November 2009 to December 2013, a total of 35 consecutive patients with pathologically or radiologically confirmed stage IIIA N2 lung cancer underwent pulmonary resection and MND, performed by a single surgeon, following

neoadjuvant chemoradiation. Preoperative patient characteristics, surgical outcomes, postoperative drainage, postoperative complications, and mortality were retrospectively analyzed. **RESULTS:** VATS was completed in 17 patients. Thoracotomy was performed in 18 patients, with 13 planned thoracotomies and 5 conversions from the VATS approach. The median age was 62.7±7.9 years in the VATS group and 60±8.7 years in the thoracotomy group. The patients in the VATS group tended to have a lower diffusing capacity for carbon monoxide (p=0.077). There were no differences between the 2 groups in the method of diagnosing the N stage, tumor response and size after induction, tumor location, or histologic type. Complete resection was achieved in all patients. More total and mediastinal nodes were dissected in the VATS group than in the thoracotomy group (p<0.05). The median chest tube duration was 5.3 days (range, 1 to 33 days) for the VATS group and 7.2 days (range, 2 to 28 days) for the thoracotomy group. The median follow-up duration was 36.3 months. The 5-year survival rates were 76% in the VATS group and 57.8% in the thoracotomy group (p=0.39). The 5-year disease-free survival rates were 40.3% and 38.9% in the VATS and thoracotomy groups, respectively (p=0.8). **CONCLUSION:** The VATS approach following neoadjuvant treatment was safe and feasible in selected patients for the treatment of stage IIIA N2 NSCLC, with no compromise of oncologic efficacy.

Oncologic considerations in the elderly. Kamel MK1, Port JL. Curr Opin Anaesthesiol. 2018 Feb;31(1):6-10. doi: 10.1097/ACO.0000000000000545.
PURPOSE OF REVIEW: Elderly patients presenting with thoracic malignancies tend to be largely undertreated because of a presumption that this group will incur a high treatment-associated morbidity and mortality. The current review highlights the current practice and recent updates in the surgical management of thoracic malignancies, mainly lung cancer, in the elderly population. **RECENT FINDINGS:** Lung resections appears to be relatively safe in the elderly patients presenting with lung cancer. Whenever possible, a lobectomy should be offered to patients with a good performance status who present with early stage disease. However, a limited resection may offer a valuable comparable alternative in patients with advanced comorbidities and borderline pulmonary functions. The use of minimally invasive approaches, namely video-assisted thoracoscopic surgery and robotic surgery are associated with lower morbidity and improved perioperative outcomes compared with the traditional thoracotomy approach and are ideal for the aged. In elderly patients presenting with advanced staged lung cancer, major lung resections following induction therapy, although feasible, should be discussed in a multispecialty tumor board committee. **SUMMARY:** There is growing evidence from the literature that surgical resection is relatively safe in the elderly population. Age by itself should not preclude patients from having curative resection. Resections can be tailored to performance status of the patient.

PD-L1 Testing in Guiding Patient Selection for PD-1/PD-L1 Inhibitor Therapy in Lung Cancer. Ancevski Hunter K1, Socinski MA2, Villaruz LC3. Mol Diagn Ther. 2018 Feb;22(1):1-10. doi: 10.1007/s40291-017-0308-6.
Immunotherapy with programmed death 1 (PD-1)- and programmed death-ligand 1 (PD-L1)-targeted monoclonal antibodies has dramatically changed the therapeutic and prognostic landscape for several types of malignancy. PD-1 and PD-L1 are immune checkpoint proteins whose binding ultimately result in T cell exhaustion and self-tolerance. Blocking this pathway 'releases the brakes' on the immune system and allows for attack of tumor cells that express PD-L1. The clinical trials that led to the US Food and Drug Administration (FDA) approval of these agents used different immunohistochemical (IHC) platforms with various PD-L1 antibodies to assess for PD-L1 expression on either tumor cells or tumor-infiltrating immune cells. There are four PD-L1 IHC assays registered with the FDA, using four different PD-L1 antibodies (22C3, 28-8, SP263, SP142), on two different IHC platforms (Dako and Ventana), each with their own scoring systems. Attempts at harmonization of PD-L1 IHC antibodies and staining platforms are underway. While PD-L1 IHC can be used to predict the likelihood of response to anti-PD-1

or anti-PD-L1 therapy, a proportion of patients that are negative can have a response and identification of alternative biomarkers is critical to further refine selection of patients most likely to respond to these therapies.

Outcomes for Thoracoscopy Versus Thoracotomy Not Just Technique Dependent: A Study of 9,787 Patients. Wolf A1, Liu B2, Leoncini E3, Nicastri D4, Lee DS4, Taioli E5, Flores R4. Ann Thorac Surg. 2018 Mar;105(3):886-891. doi: 10.1016/j.athoracsur.2017.09.059. Epub 2018 Feb 1.
BACKGROUND: Studies reporting the benefits of video-assisted thoracoscopic surgery (VATS) lung cancer resection over thoracotomy have been subject to selection bias. We evaluated patient and hospital characteristics associated with type of surgery and the independent effect of VATS on outcomes. **METHODS:** The Statewide Planning and Research Cooperative System of New York State database was queried to identify all lung cancer patients undergoing lobectomy or sublobar resection between 2007 and 2012. Multivariable logistic regression was performed to identify patient (age, sex, race, comorbidities, year, and insurance) and hospital (urban, teaching, and total lung surgery volume) cofactors associated with surgical technique and propensity scores were used to evaluate whether technique was independently associated with complications or in-hospital mortality. **RESULTS:** There were 5,505 lobectomy and 4,282 sublobar resection patients, with 2,318 (42%) and 2,416 (56%) undergoing VATS, respectively. For lobectomy, VATS was associated with being female, lower comorbidity index, private insurance, older age, surgery in recent year, nonteaching hospital, and higher annual lung surgery volume. For sublobar resection, VATS was associated with black race, lower comorbidity index, Medicaid or other insurance, surgery in recent year, rural hospital, and higher annual lung surgery volume. Complication rate was significantly lower for VATS lobectomy and not sublobar resection, whereas in-hospital mortality was lower for VATS in both resection groups. **CONCLUSIONS:** Numerous patient- and hospital-related variables that affect morbidity and mortality also affect whether a patient undergoes VATS or open lung resection. Studies evaluating VATS must account more accurately for selection bias and adjust for these confounders.

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

Phase IB Trial of the Anti-Cancer Stem Cell DLL4-Binding Agent Demcizumab with Pemetrexed and Carboplatin as First-Line Treatment of Metastatic Non-Squamous NSCLC. McKeage MJ1,2, Kotasek D3, Markman B4, et al. Target Oncol. 2018 Feb;13(1):89-98. doi: 10.1007/s11523-017-0543-0.
BACKGROUND: Delta-like ligand 4-Notch (DLL4-Notch) signaling contributes to the maintenance of chemotherapy-resistant cancer stem cells and tumor vasculature. **OBJECTIVE:** This phase IB trial of demcizumab, an IgG2 humanized monoclonal antibody directed against DLL4, was undertaken to determine its maximum tolerated dose, safety, immunogenicity, preliminary efficacy, pharmacokinetics, and pharmacodynamics, combined with standard chemotherapy. **PATIENTS AND METHODS:** Forty-six treatment-naive patients with metastatic non-squamous non-small cell lung cancer (NSCLC) were enrolled in this open-label, dose-escalation study using a standard 6 + 6 design. Demcizumab (2.5, 5.0, and 7.5 mg/kg) was given once every 3 weeks with standard doses of pemetrexed and carboplatin using a continuous (six cycles followed by demcizumab maintenance) or a truncated demcizumab regimen (four cycles followed by pemetrexed maintenance). **RESULTS:** Initially, continuous demcizumab was given until progression but two patients developed grade 3 pulmonary hypertension and congestive heart failure after eight or more infusions. Thereafter, 23 patients were treated with a truncated regimen of demcizumab, which was not associated with any grade 3 or greater cardiopulmonary toxicity. Common adverse events were hypertension, raised brain natriuretic peptide, and those expected from carboplatin and pemetrexed alone. Twenty of 40 evaluable patients (50%) had objective tumor responses. In peripheral blood, demcizumab treatment modulated the expression of genes regulating Notch signaling

and angiogenesis, and achieved concentrations exceeding those saturating DLL4 binding.
CONCLUSIONS: This study has identified a truncated dosing regimen and recommended phase II dose of demcizumab (5 mg/kg q3-weekly ×4) for subsequent clinical evaluation in combination with standard carboplatin and pemetrexed chemotherapy. NCT01189968.

Randomized phase 2 study of tivantinib plus erlotinib versus single-agent chemotherapy in previously treated KRAS mutant advanced non-small cell lung cancer. Gerber DE1, Socinski MA2, Neal JW3, et al. Lung Cancer. 2018 Mar;117:44-49. doi: 10.1016/j.lungcan.2018.01.010. Epub 2018 Feb 3.
BACKGROUND: KRAS mutations are identified in approximately 25% of non-small cell lung cancer (NSCLC) cases and are associated with resistance to currently available targeted therapies. The MET oncogene may be implicated in malignant progression of KRAS-mutant tumors. In a pre-specified subset analysis of KRAS mutant cancers in an earlier phase 2 study of erlotinib plus the oral MET inhibitor tivantinib, combination therapy was associated with substantial clinical benefit compared to erlotinib alone (progression-free survival [PFS] HR 0.18; $P < 0.01$). The current study was conducted to evaluate this combination further in KRAS mutant non-small cell lung cancer (NSCLC). **MATERIALS AND METHODS:** Previously treated patients with advanced KRAS mutant NSCLC were randomized to receive either oral tivantinib (360 mg twice daily) plus erlotinib (150 mg daily) (ET) or single-agent chemotherapy (investigator's choice of pemetrexed, docetaxel, or gemcitabine) (C). The primary endpoint was PFS. At progression, crossover from C to ET was permitted. **RESULTS:** Ninety-six patients were randomly assigned to ET ($n = 51$) or to C ($n = 45$). Median PFS was 1.7 months (mos) for ET and 4.3 mos for C (HR 1.19; 95% CI, 0.71-1.97; $P = 0.50$). There was no difference in overall survival (HR 1.20; 95% CI, 0.76-1.88; $P = 0.44$). There were 4 partial responses in the C arm, and none in the ET arm. Overall, adverse events occurred more frequently in the C arm, with more cytopenias, nausea, fatigue, and alopecia. Dermatologic toxicities were more common in the ET arm. **CONCLUSION:** In previously treated patients with advanced KRAS mutant NSCLC, the combination of the MET inhibitor tivantinib and erlotinib is not superior to conventional single-agent chemotherapy.

Immune Checkpoint Blockade: The New Frontier in Cancer Treatment. Clarke JM1, George DJ2, Lisi S3, Salama AKS4. Target Oncol. 2018 Feb;13(1):1-20. doi: 10.1007/s11523-017-0549-7.
Immune checkpoint blockers have revolutionized cancer treatment in recent years. These agents are now approved for the treatment of several malignancies, including melanoma, squamous and non-squamous non-small cell lung cancer, renal cell carcinoma, urothelial carcinoma, and head and neck squamous cell carcinoma. Studies have demonstrated the significant impact of immunotherapy versus standard of care on patient outcomes, including durable response and extended survival. The use of immunotherapy-based combination therapy has been shown to further extend duration of response and survival. Immunotherapies function through modulation of the immune system, which can lead to immune-mediated adverse events (imAEs). These include a range of dermatologic, gastrointestinal, endocrine, and hepatic toxicities, as well as other less common inflammatory events. ImAEs are typically low grade and manageable when identified early and treated with appropriate measures. Identifying the right patient for the right therapy will become more important as new immunotherapies and immunotherapy-based combinations are approved and costs of cancer care continue to rise.

Anlotinib as a third-line therapy in patients with refractory advanced non-small-cell lung cancer: a multicentre, randomised phase II trial (ALTER0302).
Han B1, Li K2, Zhao Y1, et al. Br J Cancer. 2018 Feb 13. doi: 10.1038/bjc.2017.478. [Epub ahead of print]

BACKGROUND: Anlotinib (AL3818) is a novel multitarget tyrosine kinase inhibitor, inhibiting tumour angiogenesis and proliferative signalling. The objective of this study was to assess the safety and efficacy of third-line anlotinib for patients with refractory advanced non-small-cell lung cancer (RA-NSCLC). **METHODS:** Eligible patients were randomised 1 : 1 to receive anlotinib (12 mg per day, per os; days 1-14; 21 days per cycle) or a placebo. The primary end point was progression-free survival (PFS). **RESULTS:** A total of 117 eligible patients enrolled from 13 clinical centres in China were analysed in the full analysis set. No patients received immune check-point inhibitors and epidermal growth factor receptor status was unknown in 60.7% of the population. PFS was better with anlotinib compared with the placebo (4.8 vs 1.2 months; hazard ratio (HR)=0.32; 95% confidence interval (CI), 0.20-0.51; P<0.0001), as well as overall response rate (ORR) (10.0%; 95% CI, 2.4-17.6% vs 0%; 95% CI, 0-6.27%; P=0.028). The median overall survival (OS) was 9.3 months (95% CI, 6.8-15.1) for the anlotinib group and 6.3 months (95% CI, 4.3-10.5) for the placebo group (HR=0.78; 95% CI, 0.51-1.18; P=0.2316). Adverse events were more frequent in the anlotinib than the placebo group. The percentage of grade 3-4 treatment-related adverse events was 21.67% in the anlotinib group. **CONCLUSIONS:** Anlotinib as a third-line treatment provided significant PFS benefits to patients with RA-NSCLC when compared with the placebo, and the toxicity profiles showed good tolerance.

FDA Approval Summary: Dabrafenib and Trametinib for the Treatment of Metastatic Non-Small Cell Lung Cancers Harboring BRAF V600E Mutations. Odogwu L1, Mathieu L2, Blumenthal G2, et al. Oncologist. 2018 Feb 7. pii: theoncologist.2017-0642. doi: 10.1634/theoncologist.2017-0642. [Epub ahead of print]

On June 22, 2017, the Food and Drug Administration expanded indications for dabrafenib and trametinib to include treatment of patients with metastatic non-small cell lung cancer (NSCLC) harboring BRAF V600E mutations. Approval was based on results from an international, multicenter, multicohort, noncomparative, open-label trial, study BRF113928, which sequentially enrolled 93 patients who had received previous systemic treatment for advanced NSCLC (Cohort B, n = 57) or were treatment-naïve (Cohort C, n = 36). All patients received dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily. In Cohort B, overall response rate (ORR) was 63% (95% confidence interval [CI] 49%-76%) with response durations ≥6 months in 64% of responders. In Cohort C, ORR was 61% (95% CI 44%-77%) with response durations ≥6 months in 59% of responders. Results were evaluated in the context of the Intergroupe Francophone de Cancérologie Thoracique registry and a chart review of U.S. electronic health records at two academic sites, characterizing treatment outcomes data for patients with metastatic NSCLC with or without BRAF V600E mutations. The treatment effect of dabrafenib 150 mg twice daily was evaluated in 78 patients with previously treated BRAF mutant NSCLC, yielding an ORR of 27% (95% CI 18%-38%), establishing that dabrafenib alone is active, but that the addition of trametinib is necessary to achieve an ORR of >40%. The most common adverse reactions (≥20%) were pyrexia, fatigue, nausea, vomiting, diarrhea, dry skin, decreased appetite, edema, rash, chills, hemorrhage, cough, and dyspnea. **IMPLICATIONS FOR PRACTICE:** The approvals of dabrafenib and trametinib, administered concurrently, provide a new regimen for the treatment of a rare subset of non-small cell lung cancer (NSCLC) and demonstrate how drugs active for treatment of BRAF-mutant tumors in one setting predict efficacy and can provide supportive evidence for approval in another setting. The FDA also approved the first next-generation sequencing oncology panel test for simultaneous assessment of multiple actionable mutations, which will facilitate selection of optimal, personalized therapy. The test was shown to accurately and reliably select patients with NSCLC with the BRAF V600E mutation for whom treatment with dabrafenib and trametinib is the optimal treatment.

The clinical features of squamous cell lung carcinoma with sensitive EGFR mutations. Taniguchi Y1, Matsumoto Y2, Furukawa R2, Ohara S2, Usui K2. Int J Clin Oncol. 2018 Feb 14. doi: 10.1007/s10147-017-1233-8. [Epub ahead of print]

BACKGROUND: The process of selecting patients on the basis of epidermal growth factor receptor (EGFR) mutations would likely result in a patient population with greater sensitivity to EGFR tyrosine kinase inhibitors (EGFR-TKIs). However, EGFR mutation status is not routinely examined in patients with squamous cell lung cancer (Sq) because of the low incidence of EGFR mutations and the poor clinical response to EGFR-TKIs. **METHODS:** We retrospectively reviewed the clinical features of patients at our hospital with Sq who carried EGFR-TKI-sensitive EGFR mutations and assessed their responses to EGFR-TKIs. **RESULTS:** EGFR mutation status was tested in 23 of 441 patients with Sq (5.2%) admitted to our hospital during the study period. An EGFR mutation (exon 19 deletion 3, L858R 2) was identified in five of the 23 patients (21.7%), all of whom were female never-smokers. Of these five patients, four (4/9; 44.4%) were in the normal lung group, one (1/12; 8.3%) was in the emphysematous lung group, and none (0/2; 0%) in the fibrotic lung group. Two of these five patients with the EGFR mutation received gefitinib and two received afatinib. Although the two patients who were treated with gefitinib did not respond well to treatment (stable disease, 1 patient; progressive disease, 1 patient), the two patients who were treated with afatinib showed a good response (partial response, 2 patients). **CONCLUSION:** The administration of afatinib to Sq patients after selecting patients using the EGFR mutation test based on their underlying pulmonary disease and smoking status would likely result in a population with a greater sensitivity to afatinib.

Safety profile of nivolumab administered as 30-min infusion: analysis of data from CheckMate 153. Waterhouse D1,2, Horn L3, Reynolds C4,5, et al. Cancer Chemother Pharmacol. 2018 Feb 13. doi: 10.1007/s00280-018-3527-6. [Epub ahead of print]

PURPOSE: Nivolumab has been administered using a 60-min infusion time. Reducing this time to 30 min would benefit both patients and infusion facilities. This analysis compared the safety of 30- and 60-min infusions of nivolumab in patients with previously treated advanced non-small cell lung cancer. **METHODS:** CheckMate 153 is an open-label, phase 3b/4, predominantly community-based study ongoing in the United States and Canada. Patients with stage IIIB/IV disease with progression/recurrence after at least one prior systemic therapy received nivolumab 3 mg/kg every 2 weeks over 30 or 60 min for 1 year or until disease progression. The primary outcome overall was to estimate the incidence of grade 3-5 treatment-related select adverse events; a retrospective objective was to estimate the incidence of hypersensitivity/infusion-related reactions (IRRs) with the 30-min infusion. Exploratory pharmacokinetic analyses were performed using a population pharmacokinetics model. **RESULTS:** Of 1420 patients enrolled, 369 received only 30-min infusions and 368 received only 60-min infusions. Similar frequencies of hypersensitivity/IRRs were noted in patients receiving 30-min [2% (n = 8)] and 60-min [2% (n = 7)] infusions. Grade 3-4 treatment-related hypersensitivity/IRRs led to treatment discontinuation in < 1% of patients in each group; < 1% of patients in each group received systemic corticosteroids. Hypersensitivity/IRRs were managed by dosing interruptions, with minimal impact on total dose received. Nivolumab pharmacokinetics were predicted to be similar in the two groups. **CONCLUSIONS:** Nivolumab infused over 30 min had a comparable safety profile to the 60-min infusion, including a low incidence of IRRs.

Randomized phase 2 trial of pemetrexed, pemetrexed/bevacizumab, and pemetrexed/ carboplatin/bevacizumab in patients with stage IIIB/IV non-small cell lung cancer and an Eastern Cooperative Oncology Group performance status of 2. Spigel DR1,2, Hainsworth JD1,2, et al. Cancer. 2018 Feb 16. doi: 10.1002/cncr.30986. [Epub ahead of print]

BACKGROUND: The best treatment for patients with advanced non-small cell lung cancer (NSCLC) and a poor performance status is not well defined. In this phase 2 trial, patients were randomized to receive treatment with either single-agent pemetrexed or 1 of 2 combination regimens. **METHODS:** Patients with newly diagnosed, histologically confirmed nonsquamous NSCLC and an Eastern Cooperative Oncology Group (ECOG) performance status of 2 were stratified by age and serum albumin level and were randomized (1:1:1) to 1 of 3 regimens: pemetrexed (arm 1), pemetrexed and bevacizumab (arm 2), or pemetrexed, carboplatin, and bevacizumab (arm 3). The response to treatment was assessed every 2 cycles; responding and stable patients continued treatment until progression or unacceptable toxicity. **RESULTS:** One hundred seventy-two patients were randomized, 162 patients began the study treatment, and 146 patients completed 2 cycles and were evaluated for their response. The median progression-free survival (PFS) was 2.8 months in arm 1, 4.0 months in arm 2, and 4.8 months in arm 3. The overall response rates were 15% in arm 1, 31% in arm 2, and 44% in arm 3. The overall survival was similar in the 3 treatment arms. All 3 regimens were relatively well tolerated. Patients receiving bevacizumab had an increased incidence of hypertension, proteinuria, and bleeding episodes, but most events were mild or moderate. **CONCLUSIONS:** All 3 regimens were feasible for patients with advanced NSCLC and an ECOG performance status of 2. The addition of bevacizumab to pemetrexed increased the overall response rate. The efficacy of pemetrexed/carboplatin/bevacizumab (median PFS, 4.8 months) approached the prespecified study PFS goal of 5 months. Larger studies will be necessary to define the role of bevacizumab in addition to standard pemetrexed and carboplatin in this population. Cancer 2018. © 2018 American Cancer Society.

A Randomized Phase II Study of Metformin plus Paclitaxel/Carboplatin/Bevacizumab in Patients with Chemotherapy-Naïve Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer.
Marrone KA1, Zhou X2, Forde PM1, et al. . Oncologist. 2018 Feb 27. pii: theoncologist.2017-0465. doi: 10.1634/theoncologist.2017-0465. [Epub ahead of print]
BACKGROUND: In the absence of a targeted oncogenic driver mutation or high programmed death-ligand 1 expression, systemic therapy with platinum-based doublet chemotherapy with or without bevacizumab has been the standard treatment in advanced or metastatic non-small cell lung cancer (NSCLC). Metformin has been shown to have antitumor effects via a variety of insulin-dependent and insulin-independent mechanisms and to be potentially synergistic with chemotherapy. **MATERIALS AND METHODS:** This open-label single-center phase II study (NCT01578551) enrolled patients with chemotherapy-naïve advanced or metastatic nonsquamous NSCLC and randomized them (3:1) to receive carboplatin, paclitaxel, and bevacizumab with (Arm A) or without (Arm B) concurrent metformin for four to six cycles followed by maintenance therapy with bevacizumab ± metformin continued until disease progression, intolerable toxicity, or study withdrawal. The primary outcome was 1-year progression free survival (PFS). Secondary outcomes included overall survival, response to therapy, and toxicity. **RESULTS:** A total of 25 patients were enrolled from August 2012 to April 2015, of whom 24 received at least one cycle of therapy administration. The study was stopped early due to slow accrual and changes in standard first-line therapy of advanced NSCLC. The 1-year PFS on Arm A (n = 18) was 47% (95% confidence interval [CI]: 25%-88%), which exceeded the historical control 1-year PFS of 15%. Median overall survival of patients treated on Arm A was 15.9 months (95% CI: 8.4-not available [NA]) and 13.9 months (95% CI: 12.7-NA) on Arm B. There were no significant differences in toxicity between the study arms. **CONCLUSION:** To the authors' knowledge, this is the first study to show a significant benefit in PFS with the use of metformin in this patient population and is a signal of efficacy for metformin in advanced NSCLC. **IMPLICATIONS FOR PRACTICE:** The anticancer effects of metformin continue to be elucidated. To the authors' knowledge, this is the first trial in nondiabetic advanced non-small cell lung cancer patients to show a significant change in outcome with the addition of metformin to standard

first-line chemotherapy. Well tolerated and widely available, metformin is a drug that should be considered for further study in the lung cancer treatment landscape.

Does EGFR Mutation Type Influence Patient-Reported Outcomes in Patients with Advanced EGFR Mutation-Positive Non-Small-Cell Lung Cancer? Analysis of Two Large, Phase III Studies Comparing Afatinib with Chemotherapy (LUX-Lung 3 and LUX-Lung 6). Wu YL1, Hirsh V2, Sequist LV3, et al. Patient. 2018 Feb;11(1):131-141. doi: 10.1007/s40271-017-0287-z.
INTRODUCTION: In LUX-Lung 3 and LUX-Lung 6, afatinib significantly improved progression-free survival (PFS) versus chemotherapy in patients with tumors harboring common epidermal growth factor receptor (EGFR) mutations (Del19/L858R) and significantly improved overall survival (OS) in patients with tumors harboring Del19 mutations. Patient-reported outcomes stratified by EGFR mutation type are reported. **PATIENTS AND METHODS:** Lung cancer symptoms and health-related quality of life (QoL) were assessed every 21 days until progression using the EORTC Quality of Life Core Questionnaire C30 and its lung cancer-specific module, LC13. Analyses of cough, dyspnea, and pain were prespecified and included analysis of percentage of patients who improved on therapy, time to deterioration of symptoms, and change over time. Global health status (GHS)/QoL was also assessed. Analyses were conducted for all patients with tumors harboring Del19 or L858R mutations and were exploratory. **RESULTS:** Compared with chemotherapy, afatinib more commonly improved symptoms of, delayed time to deterioration for, and was associated with better mean scores over time for cough and dyspnea in patients with Del19 or L858R mutations. All three prespecified analyses of pain showed a trend favoring afatinib over chemotherapy. In both Del19 and L858R mutations, afatinib was also associated with improvements in GHS/QoL. Longitudinal analyses demonstrated statistically significant improvements in GHS/QoL for afatinib over chemotherapy for patients with tumors harboring Del19 mutations or L858R mutations. **CONCLUSIONS:** These exploratory analyses suggest first-line afatinib improved lung cancer-related symptoms and GHS/QoL compared with chemotherapy in patients with non-small-cell lung cancer with tumors harboring common EGFR mutations, with benefits in both Del19 and L858R patients. When considered with OS (Del19 patients only) and PFS benefits, these findings substantiate the value of using afatinib over chemotherapy in these patient groups.

Nivolumab versus docetaxel in previously treated advanced non-small cell lung cancer (CheckMate 017 and CheckMate 057): 3-year update and outcomes in patients with liver metastases. Vokes EE1, Ready N2, Felip E3, et al. Ann Oncol. 2018 Feb 2. doi: 10.1093/annonc/mdy041. [Epub ahead of print]
BACKGROUND: Long-term data with immune checkpoint inhibitors in non-small cell lung cancer (NSCLC) are limited. Two phase III trials demonstrated improved overall survival (OS) and a favorable safety profile with the anti-programmed death-1 antibody nivolumab versus docetaxel in patients with previously treated advanced squamous (CheckMate 017) and non-squamous (CheckMate 057) NSCLC. We report results from ≥3 years' follow-up, including subgroup analyses of patients with liver metastases, who historically have poorer prognosis among patients with NSCLC. **PATIENTS AND METHODS:** Patients were randomized 1:1 to nivolumab (3 mg/kg every 2 weeks) or docetaxel (75 mg/m2 every 3 weeks) until progression or discontinuation. The primary endpoint of each study was OS. Patients with baseline liver metastases were pooled across studies by treatment for subgroup analyses. **RESULTS:** After 40.3 months' minimum follow-up in CheckMate 017 and 057, nivolumab continued to show an OS benefit versus docetaxel: estimated 3-year OS rates were 17% (95% confidence interval [CI], 14-21%) versus 8% (95% CI, 6-11%) in the pooled population with squamous or non-squamous NSCLC. Nivolumab was generally well tolerated, with no new safety concerns identified. Of 854 randomized patients across both studies, 193 had baseline liver metastases. Nivolumab resulted in improved OS compared with docetaxel in patients with liver metastases (hazard ratio, 0.68; 95% CI, 0.50-0.91), consistent with findings from the overall pooled study population (hazard ratio, 0.70; 95% CI, 0.61-0.81).

Rates of treatment-related hepatic adverse events (primarily grade 1-2 liver enzyme elevations) were slightly higher in nivolumab-treated patients with liver metastases (10%) than in the overall pooled population (6%). **CONCLUSIONS:** After 3 years' minimum follow-up, nivolumab continued to demonstrate an OS benefit versus docetaxel in patients with advanced NSCLC. Similarly, nivolumab demonstrated an OS benefit versus docetaxel in patients with liver metastases, and remained well tolerated.

NSCLC - RADIOTHERAPY

Enhanced efficacy of AZD3759 and radiation on brain metastasis from EGFR mutant non-small cell lung cancer. Li X1,2, Wang Y3, Wang J3, Zhang T3, Zheng L3, Yang Z3, Xing L2, Yu J2. Int J Cancer. 2018 Feb 12. doi: 10.1002/ijc.31303. [Epub ahead of print]
The prognosis of patients with brain metastasis (BM) is poor. In our study, we demonstrated that AZD3759, an EGFR tyrosine kinase inhibitors (TKIs) with excellent blood-brain barrier (BBB) penetration, combined with radiation enhanced the antitumor efficacy in BM model from EGFR mutant (EGFRm) NSCLC. Besides, the antitumor activity displayed no difference between radiation concurrently with AZD3759 and radiation sequentially with AZD3759. Mechanistically, we found that two factors determined the enhanced efficacy: cells with EGFRm which were sensitive to AZD3759, and a relative high concentration of AZD3759. We have validated mechanisms underlying the radiosensitizing effect of AZD3759, which were involved in decreased cell proliferation and survival, and suppressed repair of DNA damage. Moreover, our study found that AZD3759 inhibited both the non-homologous end joining (NHEJ) and homologous recombination (HR) DNA double-strand breaks (DSBs) repair pathway, and abrogated the G2/M checkpoint to suppress DNA damage repair. We also detected the BBB penetration of AZD3759 when combined with cranial radiation. The results showed the BBB penetration of AZD3759 was decreased within 24 hr after radiation, however, the free concentration of AZD3759 in brain kept at a high level in the context of radiation. In conclusion, our findings suggest that AZD3759 combined with radiation enhances the antitumor activity in BM from EGFRm NSCLC, this combination therapy may be an effective treatment option for BM from EGFRm NSCLC.

Impact of pemetrexed on intracranial disease control and radiation necrosis in patients with brain metastases from non-small cell lung cancer receiving stereotactic radiation. Cagney DN1, Martin AM2, Catalano PJ3, et al. Radiother Oncol. 2018 Feb 2. pii: S0167-8140(18)30022-7. doi: 10.1016/j.radonc.2018.01.005. [Epub ahead of print]
BACKGROUND: Pemetrexed is a folate antimetabolite used in the management of advanced adenocarcinoma of the lung. We sought to assess the impact of pemetrexed on intracranial disease control and radiation-related toxicity among patients with adenocarcinoma of the lung who received stereotactic radiation for brain metastases. **MATERIALS/METHODS:** We identified 149 patients with adenocarcinoma of the lung and newly diagnosed brain metastases without a targetable mutation receiving stereotactic radiation. Kaplan-Meier plots and Cox regression were employed to assess whether use of pemetrexed was associated with intracranial disease control and radiation necrosis. **RESULTS:** Among the entire cohort, 105 patients received pemetrexed while 44 did not. Among patients who were chemotherapy-naïve, use of pemetrexed (n = 43) versus alternative regimens after stereotactic radiation (n = 24) was associated with a reduced likelihood of developing new brain metastases (HR 0.42, 95% CI 0.22-0.79, p = 0.006) and a reduced need for salvage brain-directed radiation therapy (HR 0.36, 95% CI 0.18-0.73, p = 0.005). Pemetrexed use was associated with increased radiographic necrosis. (HR 2.70, 95% CI 1.09-6.70, p = 0.03). **CONCLUSIONS:** Patients receiving pemetrexed after brain-directed stereotactic radiation appear to benefit from improved intracranial disease control at the possible expense

of radiation-related radiographic necrosis. Whether symptomatic radiation injury occurs more frequently in patients receiving pemetrexed requires further study.

Response criteria in solid tumors (PERCIST/RECIST) and SUVmax in early-stage non-small cell lung cancer patients treated with stereotactic body radiotherapy. Pierson C1, Grinchak T1, Sokolovic C2, Holland B1, Parent T1, Bowling M3, Arastu H1, Walker P3, Ju A4. Radiat Oncol. 2018 Feb 27;13(1):34. doi: 10.1186/s13014-018-0980-7.

BACKGROUND: The purpose of this study was to evaluate the prognostic impact of Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) and Response Evaluation Criteria in Solid Tumors (RECIST) and of pre- and post-treatment maximum Standard Uptake Value (SUVmax) in regards to survival and tumor control for patients treated for early-stage non-small cell lung cancer (ES-NSCLC) with stereotactic body radiotherapy (SBRT). **METHODS:** This is a retrospective review of patients with ES-NSCLC treated at our institution using SBRT. Lobar, locoregional, and distant failures were evaluated based on PERCIST/RECIST and clinical course. Univariate analysis of the Kaplan-Meier curves for overall survival (OS), progression free survival (PFS), lobar control (LC), locoregional control (LRC), and distant control (DC) was conducted using the log-rank test. Pre- and post-treatment SUVmax were evaluated using cutoffs of < 5 and ≥ 5, < 4 and ≥ 4, and < 3 and ≥ 3. ΔSUVmax was also evaluated at various cutoffs. Cox regression analysis was conducted to evaluate survival outcomes based on age, gender, pre-treatment gross tumor volume (GTV), longest tumor dimension on imaging, and Charlson Comorbidity Index (CCI). **RESULTS:** This study included 95 patients (53 female, 42 male), median age 75. Lung SBRT was delivered in 3-5 fractions to a total of 48-60 Gy, with a BEDα/β = 10Gy of at least 100 Gy. Median OS and PFS from the end of SBRT was 15.4 and 11.9 months, respectively. On univariate analysis, PERCIST/RECIST response correlated with PFS ($p = 0.039$), LC ($p = 0.007$), and LRC ($p = 0.015$) but not OS ($p = 0.21$) or DC ($p = 0.94$). Pre-treatment SUVmax and post-treatment SUVmax with cutoff values of < 5 and ≥ 5, < 4 and ≥ 4, and < 3 and ≥ 3 did not predict for OS, PFS, LC, LRC, or DC. ΔSUVmax did not predict for OS, PFS, LC, LRC, or DC. On multivariate analysis, pre-treatment GTV ≥ 30 cm3 was significantly associated with worse survival outcomes when accounting for other confounding variables. **CONCLUSIONS:** PERCIST/RECIST response is associated with improved LC and PFS in patients treated for ES-NSCLC with SBRT. In contrast, pre- and post-treatment SUVmax is not predictive of disease control or survival.

SMALL CELL LUNG CANCER - SCLC

A Phase II Study of Irinotecan for Patients with Previously Treated Small-Cell Lung Cancer. Kondo R1, Watanabe S1, Shoji S1, et al. Oncology. 2018 Feb 14;94(4):223-232. doi: 10.1159/000486622. [Epub ahead of print]

OBJECTIVE: Chemotherapy with irinotecan plus cisplatin has shown promise in chemo-naïve small-cell lung cancer (SCLC) patients. However, irinotecan treatment for relapsed or refractory SCLC has not been adequately evaluated. This phase II study evaluated the appropriate treatment schedule of irinotecan as a single agent. This study was designed to determine the antitumor activity, toxicity, and survival in previously treated SCLC patients. **METHODS:** Previously treated SCLC patients with at least one platinum-based regimen received irinotecan (100 mg/m2) on days 1 and 8, every 3 weeks, until disease progression. The assessment of the response rate was the primary endpoint. **RESULTS:** Thirty patients were enrolled, with an objective response rate of 41.3% (95% confidence interval [CI] 25.5-59.3), and a disease control rate of 69%. Median progression-free and overall survival was 4.1 months (95% CI, 2.2-5.4) and 10.4 months (95% CI, 8.1-14), respectively. The grade 3/4 hematological toxicities were neutropenia (36.7%), thrombocytopenia (3.3%), anemia (13.3%), and febrile neutropenia (6.6%). There were no grade 4 nonhematological toxicities. Frequent grade 3 nonhematological toxicities included

diarrhea (10%), anorexia (6.6%), and hyponatremia (6.6%). **CONCLUSIONS:** This phase II study showed a high objective response rate and long survival. Irinotecan monotherapy schedule used was well tolerated, and could be an active treatment option for these patients.

Prognostic significance of pretreatment total lymphocyte count and neutrophil-to-lymphocyte ratio in extensive-stage small-cell lung cancer. Suzuki R1, Lin SH1, Wei X1, Allen PK1, Welsh JW1, Byers LA2, Komaki R3. Radiother Oncol. 2018 Feb 2. pii: S0167-8140(18)30015-X. doi: 10.1016/j.radonc.2017.12.030. [Epub ahead of print]
BACKGROUND: We evaluated pretreatment total lymphocyte count (TLC, marker of immunosuppression), neutrophil-to-lymphocyte ratio (NLR, marker of inflammation), and overall survival (OS) in patients with extensive-stage small-cell lung cancer (ES-SCLC). **METHODS:** Pretreatment blood characteristics, age, sex, performance status, race, stage (M1a vs. M1b), number and location of metastases, weight loss, smoking status, chemotherapy cycles (<4 vs. ≥4), thoracic radiotherapy dose (<45 vs. ≥45 Gy), and receipt of prophylactic cranial irradiation (PCI) were evaluated in 252 patients with ES-SCLC treated in 1998-2015. Factors significant in univariate analysis were selected as covariates for a multivariate Cox model. **RESULTS:** Pretreatment TLC was below normal (<1.0 × 103/μL) in 58 patients (23%). Median OS time was 11.0 months and was worse for those with TLC ≤ 1.5 × 103/μL (9.8 vs. 12.0 months) and pretreatment NLR > 4.0 (9.4 vs. 13.9 months). Multivariate analysis identified low TLC (hazard ratio [HR] 0.734, 95% confidence interval [CI] 0.565-0.955, P = 0.021) and high NLR (HR 1.521, 95% CI 1.172-1.976, P = 0.002) as predicting inferior survival. Age (>63 y), sex (male), performance status (≥2), chemotherapy cycles (<4), radiation dose (<45 Gy), and no PCI also predicted worse OS (P < 0.05). **CONCLUSIONS:** Pretreatment TLC and NLR may be useful for stratifying patients with ES-SCLC for treatment approaches.

WITHDRAWN: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group1. Cochrane Database Syst Rev. 2018 Feb 6;2:CD002805. doi: 10.1002/14651858.CD002805.pub2.
BACKGROUND: Prophylactic cranial irradiation halves the rate of brain metastases in patients with small cell lung cancer. Individual randomized trials conducted on patients in complete remission were unable to clarify whether this treatment improves survival. **OBJECTIVES:** This study aims to test whether prophylactic cranial irradiation prolongs survival of patients with small cell lung cancer in complete remission. **SEARCH METHODS:** Published and unpublished trials were eligible. Electronic databases (Medline, Cancerlit, Excerpta Medica, Biosis from 1965 to 1998), reference lists of trial publications, review articles and relevant books were used to identify potentially eligible trials. The search was also guided by discussions with investigators and experts, and the examination of meeting proceedings and of the Physician Data Query clinical trial registry. **SELECTION CRITERIA:** Randomized trials comparing prophylactic cranial irradiation with no prophylactic cranial irradiation in patients with small cell lung cancer in complete remission. **DATA COLLECTION AND ANALYSIS:** Meta-analysis based on updated individual data. The main endpoint was survival. **MAIN RESULTS:** Seven trials with a total of 987 participants were included. The relative risk of death in the treatment group compared to the control group was 0.84 (95% confidence interval=0.73 to 0.97, P=0.01), corresponding to a 5.4 percent increase in the 3-year survival rate (from 15.3 percent in the control group to 20.7 percent in the treatment group). Prophylactic cranial irradiation also increased disease-free survival (relative risk=0.75, 95% confidence interval=0.65 to 0.86, P<0.001) and decreased the risk of brain metastases (relative risk=0.46, 95% confidence interval=0.38 to 0.57, P<0.001). Increasing doses of irradiation decreased the risk of brain metastases when four groups (8 Gy, 24-25 Gy, 30 Gy, 36-40 Gy) were analyzed [trend test, P=0.02], but the effect on survival did not differ significantly according to the dose. We found a trend (P=0.01) for a decrease in the brain metastasis risk in favour of earlier

administration of cranial irradiation after the initiation of induction treatment. **AUTHORS' CONCLUSIONS:** Prophylactic cranial irradiation significantly improves survival and disease-free survival for patients with small cell lung cancer in complete remission. Further clinical trials are needed to confirm the potential greater benefit on brain metastasis rate suggested when cranial irradiation is given earlier or at higher doses.

Survival in Limited Disease Small Cell Lung Cancer According to N3 Lymph Node Involvement. Valan CD1,2, Slagsvold JE2, Halvorsen TO3,2, et al. Anticancer Res. 2018 Feb;38(2):871-876.
BACKGROUND/AIM: There are several definitions of limited disease (LD) in small cell lung cancer (SCLC), differing with respect to N3 disease accepted. We analyzed patients from a randomized trial comparing two schedules of thoracic radiotherapy (TRT) in LD SCLC to investigate whether there were survival differences between N3 subcategories (n=144). **PATIENTS AND METHODS:** Patients with a baseline CT scan available were analysed. Patients received four courses of cisplatin/etoposide and TRT of 45 Gy/30 fractions (twice daily) or 42 Gy/15 fractions (once daily). **RESULTS:** Median overall survival (OS) was 23.3 months in the whole cohort. N3-patients (n=37) had shorter survival than those with N0-2 (16.7 vs. 33.0 months; p<0.001). There were no significant OS-differences between the N3 subcategories, but patients with metastases to two or more N3 regions had shorter survival than other N3 patients (13.4 vs. 19.9 months; p=0.011). **CONCLUSION:** There were no survival differences between the N3 subcategories, suggesting that all N3 disease should be considered as LD.

Dynamic changes of phenotypically different circulating tumor cells sub-populations in patients with recurrent/refractory small cell lung cancer treated with pazopanib. Messaritakis I1, Politaki E1, Koinis F1, et al. Sci Rep. 2018 Feb 2;8(1):2238. doi: 10.1038/s41598-018-20502-1.
The aim of the study was to investigate the effect of 2nd-line pazopanib on the different CTCs subpopulations in SCLC patients and evaluate the clinical relevance of their changes. Different CTCs subpopulations were evaluated before pazopanib initiation (n = 56 patients), after one-cycle (n = 35) and on disease progression (n = 45) by CellSearch and double immunofluorescence using anti-CKs and anti-Ki67, anti-M30 or anti-Vimentin antibodies. Before treatment, CTCs were detected in 50% of patients by CellSearch whereas 53.4%, 15.5% and 74.1% patients had CK+/Ki67+, CK+/M30+ and CK+/Vim+ CTCs, respectively. One pazopanib cycle significantly decreased the number of CTCs as detected by CellSearch ($p = 0.043$) as well as the number of CK+/Ki67+ ($p < 0.001$), CK+/M30+ ($p = 0.015$) and CK+/Vim+ ($p < 0.001$) cells. On disease progression, both the incidence and CTC numbers were significantly increased (CellSearch, $p = 0.027$; CK+/Ki67+, $p < 0.001$; CK+/M30+, $p = 0.001$ and CK+/Vim+, $p < 0.001$). In multivariate analysis, the detection of CK+/Vim+ CTCs after one treatment cycle (HR: 7.9, 95% CI: 2.9-21.8; $p < 0.001$) and CTCs number on disease progression, as assessed by CellSearch, (HR: 2.0, 95% CI: 1.0-6.0; $p = 0.005$) were emerged as independent factors associated with decreased OS. In conclusion, pazopanib can eliminate different CTC subpopulations in patients with relapsed SCLC. The analysis of CTCs could be used as a dynamic biomarker of treatment efficacy.

PALLIATIVE AND SUPPORTIVE CARE

Exercise behavior and physical fitness in patients with advanced lung cancer. Titz C1,2,3, Hummler S2,4,5,6, Schmidt ME1, Thomas M2,5,6, Steins M2,5, Wiskemann J7,8. Support Care Cancer. 2018 Feb 26. doi: 10.1007/s00520-018-4105-5. [Epub ahead of print]
PURPOSE: The aim of this work was to evaluate exercise behavior and physical fitness of advanced lung cancer patients shortly after primary diagnosis.
METHODS:

Between November 2013 and December 2016, advanced lung cancer patients (n = 227, mean age 62.2 years) were enrolled shortly after diagnosis and 211 patients were tested for endurance capacity (six-minute walk test) and strength performance (maximum voluntary isometric contraction of upper and lower extremities). Current and previous exercise and walking behavior were assessed using a self-reported questionnaire regarding type, frequency, intensity, and duration. Paired Student's t tests were used to compare physical fitness to reference data. The relation of potential determinants with physical fitness was assessed using linear regression analysis. **RESULTS:** Exercise behavior was superior in the year before diagnosis compared to the time of study enrollment. Patients reduced frequency, intensity, and duration of sports/exercise after their lung cancer diagnosis. We observed significantly lower endurance capacity ($p < .01$) and strength performance in lower extremities ($p < .01$) in male and female patients compared to age and sex-matched reference data. We found significant correlations of previous exercise and walking behavior with physical fitness shortly after diagnosis in patients with advanced lung cancer. **CONCLUSION:** Patients with advanced lung cancer showed impaired physical fitness regarding endurance and strength capacity. The strong decline in participation of sports/exercise shortly after diagnosis supports early implementation of physical exercise during anti-cancer treatment.

Defining the Elements of Early Palliative Care That Are Associated With Patient-Reported Outcomes and the Delivery of End-of-Life Care.

Hoerger M1, Greer JA1, Jackson VA1, Park ER1, Pirl WF1, El-Jawahri A1, Gallagher ER1, Hagan T1, Jacobsen J1, Perry LM1, Temel JS1. J Clin Oncol. 2018 Feb 23:JCO2017756676. doi: 10.1200/JCO.2017.75.6676. [Epub ahead of print]

PURPOSE: We describe the key elements of early palliative care (PC) across the illness trajectory and examine whether visit content was associated with patient-reported outcomes and end-of-life care. **METHODS:** We performed a secondary analysis of patients with newly diagnosed advanced lung or noncolorectal GI cancer (N = 171) who were randomly assigned to receive early PC. Participants attended at least monthly visits with board-certified PC physicians and advanced practice nurses at Massachusetts General Hospital. PC clinicians completed surveys documenting visit content after each encounter. Patients reported quality of life (Functional Assessment of Cancer Therapy-General) and mood (Hospital Anxiety and Depression Scale and Patient Health Questionnaire-9) at baseline and 24 weeks. End-of-life care data were abstracted from the electronic health record. We summarized visit content over time and used linear and logistic regression to identify whether the proportion of visits addressing a content area was associated with patient-reported outcomes and end-of-life care. **RESULTS:** We analyzed data from 2,921 PC visits, most of which addressed coping (64.2%) and symptom management (74.5%). By 24 weeks, patients who had a higher proportion of visits that addressed coping experienced improved quality of life (P = .02) and depression symptoms (Depression subscale of the Hospital Anxiety and Depression Scale, P = .002; Patient Health Questionnaire-9, P = .004). Patients who had a higher proportion of visits address treatment decisions were less likely to initiate chemotherapy (P = .02) or be hospitalized (P = .005) in the 60 days before death. Patients who had a higher proportion of visits addressing advance care planning were more likely to use hospice (P = .03). **CONCLUSION:** PC clinicians' focus on coping, treatment decisions, and advance care planning is associated with improved patient outcomes. These data define the key elements of early PC to enable dissemination of the integrated care model.

COMPLEMENTARY & ALTERNATIVE THERAPY

Polygonum aviculare L. extract and quercetin attenuate contraction in airway smooth muscle.

Luo X1, Xue L1, Xu H1, et al. Sci Rep. 2018 Feb 15;8(1):3114. doi: 10.1038/s41598-018-20409-x.

Because of the serious side effects of the currently used bronchodilators, new compounds with similar functions must be developed. We screened several herbs and found that Polygonum aviculare L. contains

ingredients that inhibit the precontraction of mouse and human airway smooth muscle (ASM). High K+-induced precontraction in ASM was completely inhibited by nifedipine, a selective blocker of L-type voltage-dependent Ca2+ channels (LVDCCs). However, nifedipine only partially reduced the precontraction induced by acetylcholine chloride (ACH). Additionally, the ACH-induced precontraction was partly reduced by pyrazole-3 (Pyr3), a selective blocker of TRPC3 and stromal interaction molecule (STIM)/Orai channels. These channel-mediated currents were inhibited by the compounds present in P. aviculare extracts, suggesting that this inhibition was mediated by LVDCCs, TRPC3 and/or STIM/Orai channels. Moreover, these channel-mediated currents were inhibited by quercetin, which is present in P. aviculare extracts. Furthermore, quercetin inhibited ACH-induced precontraction in ASM. Overall, our data indicate that the ethyl acetate fraction of P. aviculare and quercetin can inhibit Ca2+-permeant LVDCCs, TRPC3 and STIM/Orai channels, which inhibits the precontraction of ASM. These findings suggest that P. aviculare could be used to develop new bronchodilators to treat obstructive lung diseases such as asthma and chronic obstructive pulmonary disease.

MISCELLANEOUS WORKS

Trends in Insurance Status Among Patients Diagnosed With Cancer Before and After Implementation of the Affordable Care Act. Moss HA1, Havrilesky LJ1, Zafar SY1, Suneja G1, Chino J1. J Oncol Pract. 2018 Feb;14(2):e92-e102. doi: 10.1200/JOP.2017.027102.
PURPOSE: The Affordable Care Act (ACA) aimed to increase insurance coverage through key provisions such as expansion of Medicaid eligibility and enforcement of an individual mandate. The objective of this study is to examine the impact of the ACA on insurance rates among patients newly diagnosed with colon, lung, or breast cancer. **METHODS:** Using the SEER database, patients younger than age 65 years diagnosed with colon, lung, or breast cancer between 2008 and 2014 were identified. Insurance rates were examined before versus after passage of the ACA (2011) and before (2011 to 2013) versus after (2014) Medicaid expansion in nine expansion states and five nonexpansion states. Difference-in-differences models were used to estimate the differential impact of ACA in expansion compared with nonexpansion states. **RESULTS:** A total of 414,085 patients with known insurance status were diagnosed with colon, lung, or breast cancer between 2008 and 2014. For all cancer types, there was a significant increase in patients enrolled in Medicaid after 2011 in expansion states. Between 2011 to 2013 and 2014, in patients living in states with Medicaid expansion, the uninsured rates decreased by ≥ 50% among patients with a new diagnosis of lung and colon cancer (6.5% in 2011 to 2013 to 3.1% in 2014 and 6.8% in 2011 to 2013 to 3.4% in 2014, respectively; $P < .001$); the uninsured rate decreased to a lesser degree for patients with breast cancer (2.7% in 2011 to 2013 to 1.6% in 2014; $P < .001$). This decrease in the rate of uninsured patients was absent in patients living in nonexpansion states. **CONCLUSION:** The ACA resulted in expanded insurance coverage for patients diagnosed with colon, lung, and breast cancer. However, the impact was only observed in states that increased their Medicaid eligibility.

Population impact of lung cancer screening in the United States: Projections from a microsimulation model. Criss SD1, Sheehan DF1, Palazzo L1, Kong CY1,2. PLoS Med. 2018 Feb 7;15(2):e1002506. doi: 10.1371/journal.pmed.1002506. eCollection 2018 Feb.
BACKGROUND: Previous simulation studies estimating the impacts of lung cancer screening have ignored the changes in smoking prevalence over time in the United States. Our primary rationale was to perform, to our knowledge, the first simulation study that estimates the health outcomes of lung cancer screening with explicit modeling of smoking trends for the whole US population.
METHODS/FINDINGS: Utilizing a well-validated microsimulation model, we estimated the benefits and harms of an annual low-dose computed tomography screening scenario with a realistic screening adherence rate versus a no-screening scenario for the US population from 2016-2030. The Centers for

Medicare and Medicaid Services (CMS) eligibility criteria were applied: age 55-77 years at time of screening, history of at least 30 pack-years of smoking, and current smoker or former smoker with fewer than 15 years since quitting. In the screened population, cumulative mortality reduction was projected to reach 16.98% (95% CI 16.90%-17.07%). Cumulative mortality reduction was estimated to be 3.52% (95% CI 3.50%-3.53%) for the overall study population, with annual mortality reduction peaking at 4.38% (95% CI 4.36%-4.41%) in 2021 and falling to 3.53% (95% CI 3.50%-3.56%) by 2030. Lung cancer screening would save a projected 148,484 life-years (95% CI 147,429-149,540) across the total population through 2030. There were estimated to be 9,054 (95% CI 9,011-9,098) overdiagnosed cases among the 252,429 (95% CI 251,208-253,649) screen-detected lung cancer diagnoses, yielding an overdiagnosis rate of 3.59%. The limitations of our study are that we do not explicitly model race or socioeconomic status and our model was calibrated to data from studies performed in academic centers, both of which may impact the generalizability of our results. We also exclusively model the effects of the CMS guidelines for lung cancer screening and not any other screening strategies. **CONCLUSIONS:** The mortality reduction and life-years gained estimated by this study are lower than those of single birth cohort studies. Single cohort studies neglect the changing dynamics of smoking behavior across generations, whereas this study reflects the trend of decreasing smoking prevalence since the 1960s. Maximum benefit could be derived from lung cancer screening through 2021; in later years, mortality reduction due to screening will decline. If a comprehensive screening program is not implemented in the near future, the opportunity to achieve these benefits will have passed.

Natural History of Ground Glass Lesions among Patients with Previous Lung Cancer.
Shewale JB1, Nelson DB2, Rice DC2, et al. Ann Thorac Surg. 2018 Feb 9. pii: S0003-4975(18)30146-2. doi: 10.1016/j.athoracsur.2018.01.031. [Epub ahead of print]
BACKGROUND: Among patients with previous lung cancer, the malignant potential of subsequent ground glass opacities (GGOs) on computed tomography (CT) remains unknown, with a lack of consensus regarding surveillance and intervention. We sought to describe the natural history of GGO in patients with a history of lung cancer. **METHODS:** A retrospective review was performed of 210 patients with a history of lung cancer and ensuing CT evidence of pure or mixed GGOs between 2007 and 2013. CT reports were reviewed to determine the fate of the GGOs, classifying all lesions as stable, resolved, or progressive over the course of the study. Multivariable analysis was performed to identify predictors of GGO progression and resolution. **RESULTS:** The mean follow-up time was 13 months. During this period, 55 (26%) patients' GGOs were stable, 131 (62%) resolved, and 24 (11%) progressed. Of the 24 GGOs that progressed, 3 were subsequently diagnosed as adenocarcinoma. Patients of Black race (odds ratio [OR] = 0.26) and other non-Caucasian race (OR 0.89) had smaller odds of GGO resolution ($p=0.033$) whereas patients with previous lung squamous cell carcinoma (OR= 5.16) or small cell carcinoma (OR= 5.36) were more likely to experience GGO resolution ($p<0.001$). On multivariable analysis, only history of adenocarcinoma was an independent predictor of GGO progression (OR= 6.9, $p=0.011$). **CONCLUSIONS:** Among patients with a history of lung cancer, prior adenocarcinoma emerged as a predictor of GGO progression, whereas history of squamous cell carcinoma or small cell carcinoma and Caucasian race were identified as predictors of GGO resolution.

Project transform: engaging patient advocates to share their perspectives on improving research, treatment, and policy. Bridges JFP1,2, Janssen EM1, Ferris A3, Dy SM1,4. Curr Med Res Opin. 2018 Feb 12:1-15. doi: 10.1080/03007995.2018.1440199. [Epub ahead of print]
OBJECTIVE: Incorporating the patient perspective into lung cancer research, policy and treatment is becoming increasingly recognized as important. This project sought to create an engagement partnership with lung cancer patient advocates and to explore their views on transforming lung cancer healthcare systems, treatment, and policy to be more patient centered. **METHODS:** A patient action committee

(PAC) of patient advocates living with lung cancer was engaged through group meetings, in-person and phone interviews, and email correspondence. Group meetings (two 1-hour meetings, one 3-hour meeting) served to discuss engagement strategies and project goals, while individual interviews (n = 19) (30-75 minutes) provided in-depth exploration of individuals' perspectives. Meetings and interviews were recorded to identify priorities for addressing issues within lung cancer research, treatment, and policy. PAC members corroborated the results through email and an in-person meetings. **RESULTS:** PAC members identified three general objectives: (i) for healthcare systems, increasing access to care through accessible, coordinated, and affordable care, (ii) for treatment, addressing patient needs in treatment and research through patient education, shared decisions, and clinical trials, and (iii) for policy, shining a light on lung cancer through screening policies, public awareness, and research funding. **CONCLUSION:** Patient advocates expressed their views that lung cancer is a neglected disease that is not highly prioritized in healthcare systems, treatment approaches, and public perceptions. This project represents an integral step in developing an ongoing partnership between researchers and these advocates.

Automated Information Extraction on Treatment and Prognosis for Non-Small Cell Lung Cancer Radiotherapy Patients: Clinical Study.

Zheng S1, Jabbour SK2, O'Reilly SE3, et al. JMIR Med Inform. 2018 Feb 1;6(1):e8. doi: 10.2196/medinform.8662.

BACKGROUND: In outcome studies of oncology patients undergoing radiation, researchers extract valuable information from medical records generated before, during, and after radiotherapy visits, such as survival data, toxicities, and complications. Clinical studies rely heavily on these data to correlate the treatment regimen with the prognosis to develop evidence-based radiation therapy paradigms. These data are available mainly in forms of narrative texts or table formats with heterogeneous vocabularies. Manual extraction of the related information from these data can be time consuming and labor intensive, which is not ideal for large studies. **OBJECTIVE:** The objective of this study was to adapt the interactive information extraction platform Information and Data Extraction using Adaptive Learning (IDEAL-X) to extract treatment and prognosis data for patients with locally advanced or inoperable non-small cell lung cancer (NSCLC). **METHODS:** We transformed patient treatment and prognosis documents into normalized structured forms using the IDEAL-X system for easy data navigation. The adaptive learning and user-customized controlled toxicity vocabularies were applied to extract categorized treatment and prognosis data, so as to generate structured output. **RESULTS:** In total, we extracted data from 261 treatment and prognosis documents relating to 50 patients, with overall precision and recall more than 93% and 83%, respectively. For toxicity information extractions, which are important to study patient posttreatment side effects and quality of life, the precision and recall achieved 95.7% and 94.5% respectively. **CONCLUSIONS:** The IDEAL-X system is capable of extracting study data regarding NSCLC chemoradiation patients with significant accuracy and effectiveness, and therefore can be used in large-scale radiotherapy clinical data studies.