Caring Ambassadors Lung Cancer Program
Literature Review, November 2018

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

A 5-MicroRNA Signature Identified from Serum MicroRNA Profiling Predicts Survival in Patients with Advanced Stage Non-Small Cell Lung Cancer. Zhang Y1,2, Roth JA3, Yu H1, et al. Carcinogenesis. 2018 Nov 14. doi: 10.1093/carcin/bgy132. [Epub ahead of print]
Circulating microRNAs (miRNAs) are potential biomarkers for cancer diagnosis, screening, and prognosis. This study aimed to identify serum miRNAs as predictors of survival in patients with advanced non-small cell lung cancer (NSCLC). We profiled serum miRNAs in a pilot set of 4 patients with good survival (>24 months) and 4 patients with poor survival (<6 months). We selected 140 stably detectable miRNAs and 42 miRNAs reported in literature for further analysis. Expression of these 182 miRNAs was measured using high-throughput polymerase chain reaction assay, and their association with 3-year survival in the discovery (n=345) and validation (n=177) cohorts was assessed. Five serum miRNAs (miR-191, miR-28-3p, miR-145, miR-328, and miR-18a) were significantly associated with 3-year overall survival in both cohorts. A combined 5-miRNA risk score was created to assess the cumulative impact of these miRNAs on risk of death. Quartile analysis of the risk score showed significant association with 3-year death risk, with a 4.6-month, 6.8-month, and 9.3-month reduction in median survival time for the second, third, and fourth quartile, respectively. Survival tree analysis also identified distinct risk groups with different 3-year survival durations. Data from The Cancer Genome Atlas revealed all 5 miRNAs were differentially expressed (P<0.0001) in paired tumor and normal tissues. Pathway analysis indicated that target genes of these 5 miRNAs were mainly enriched in inflammatory/immune response pathways and pathways implicated in resistance to chemoradiotherapy and/or targeted therapy. Our results suggested that the 5-miRNA signature could serve as a prognostic predictor in advanced NSCLC patients.

miR-181b/Notch2 overcome chemoresistance by regulating cancer stem cell-like properties in NSCLC. Wang X1, Meng Q1, Qiao W2, Ma R1, Ju W3, Hu J1, Lu H1, Cui J1, Jin Z1, Zhao Y4, Wang Y5. Stem Cell Res Ther. 2018 Nov 23;9(1):327. doi: 10.1186/s13287-018-1072-1.

BACKGROUND: Lung cancer stem cells have the ability to self-renew and are resistant to conventional chemotherapy. MicroRNAs (miRNAs) regulate and control the expression and function of many target genes; therefore, miRNA disorders are involved in the pathogenesis of human diseases, such as cancer. However, the effects of miRNA dysregulation on tumour stemness and drug resistance have not been fully elucidated. miR-181b has been reported to be a tumour suppressor miRNA and is associated with drug-resistant non-small cell lung cancer. **METHODS:** Cancer stem cell (CSC)-like properties were tested by a cell proliferation assay and flow cytometry; miR-181b expression was measured by real-time PCR; and Notch2 and related proteins were detected by Western blotting and immunohistochemistry. A mouse xenograft model was also established. **RESULTS:** In this study, we found that ectopic miR-181b expression suppressed cancer stem cell properties and enhanced sensitivity to cisplatin (DDP) treatment by directly targeting Notch2. miR-181b could inactivate the Notch2/Hes1 signalling pathway. In addition, tumours from nude mice treated with miR-181b were significantly smaller than tumours from mice treated with control agomir. Decreased miR-181b expression and increased Notch2 expression were observed to have a significant relationship with overall survival (OS) and CSC-like properties in non-small cell lung cancer (NSCLC) patients. **CONCLUSIONS:** This study elucidates an important role of miR-181b in the regulation of CSC-like properties, suggesting a potential therapeutic target for overcoming drug resistance in NSCLC.

H3K9 methyltransferases and demethylases control lung tumor-propagating cells and lung cancer progression. Rowbotham SP1,2, Li F3, Dost AFM1,2, et al. Nat Commun. 2018 Nov 19;9(1):4559. doi: 10.1038/s41467-018-07077-1.
Epigenetic regulators are attractive anticancer targets, but the promise of therapeutic strategies inhibiting some of these factors has not been proven in vivo or taken into account tumor cell heterogeneity. Here we show that the histone methyltransferase G9a, reported to be a therapeutic target in many cancers, is a suppressor of aggressive lung tumor-propagating cells (TPCs). Inhibition of G9a drives lung adenocarcinoma cells towards the TPC phenotype by de-repressing genes which regulate the extracellular matrix. Depletion of G9a during tumorigenesis enriches tumors in TPCs and accelerates disease progression metastasis. Depleting histone demethylases represses G9a-regulated genes and TPC phenotypes. Demethylase inhibition impairs lung adenocarcinoma progression in vivo. Therefore, inhibition of G9a is dangerous in certain cancer contexts, and targeting the histone demethylases is a more suitable approach for lung cancer treatment. Understanding cellular context and specific tumor populations is critical when targeting epigenetic regulators in cancer for future therapeutic development.

SCREENING, DIAGNOSIS AND STAGING

VCAM-1 targeted magnetic resonance imaging enables detection of brain micrometastases from different primary tumours. Cheng VWT1, Sarmiento Soto M2, Khrapitchev AA1, et al. Clin Cancer Res. 2018 Nov 2. pii: clincanres.1889.2018. doi: 10.1158/1078-0432.CCR-18-1889. [Epub ahead of print]
PURPOSE: A major issue for the effective treatment of brain metastasis is the late stage of diagnosis with existing clinical tools. The aim of this study was to evaluate the potential of vascular cell adhesion molecule-1 (VCAM-1) targeted magnetic resonance imaging (MRI) for early detection of brain micrometastases in mouse models across multiple primary tumour types. **EXPERIMENTAL DESIGN:** Xenograft models of brain micrometastasis for human breast carcinoma (MDA231Br-GFP), lung adenocarcinoma (SEBTA-001) and melanoma (H1_DL2) were established via intracardiac injection in mice. Animals (n=5-6/group) were injected intravenously with VCAM-1 targeted microparticles of iron oxide (VCAM-MPIO) and, subsequently, underwent T 2*-weighted MRI. Control groups of naïve mice injected with VCAM-MPIO and tumour-bearing mice injected with non-targeting IgG-MPIO were

included. **RESULTS:** All models showed disseminated micrometastases in the brain, together with endothelial VCAM-1 upregulation across the time-course. T 2*-weighted MRI of all tumour-bearing mice injected with VCAM-MPIO showed significantly more signal hypointensities ($p<0.001$; two-sided) than control cohorts, despite a lack of blood-brain barrier impairment. Specific MPIO binding to VCAM-1 positive tumour-associated vessels was confirmed histologically. VCAM-1 expression was demonstrated in human brain metastasis samples, across all three primary tumour types. **CONCLUSIONS:** VCAM-1-targeted MRI enables detection of brain micrometastases from the three primary tumour types known to cause the majority of clinical cases. These findings represent an important step forward in the development of a broadly applicable and clinically relevant imaging technique for early diagnosis of brain metastasis, with significant implications for improved patient survival. Copyright ©2018, American Association for Cancer Research.

Expert knowledge-infused deep learning for automatic lung nodule detection. Tan J1, Huo Y2, Liang Z3, Li L4. J Xray Sci Technol. 2018 Nov 15. doi: 10.3233/XST-180426. [Epub ahead of print]
BACKGROUND: Computer aided detection (CADe) of pulmonary nodules from computed tomography (CT) is crucial for early diagnosis of lung cancer. Self-learned features obtained by training datasets via deep learning have facilitated CADe of the nodules. However, the complexity of CT lung images renders a challenge of extracting effective features by self-learning only. This condition is exacerbated for limited size of datasets. On the other hand, the engineered features have been widely studied. **OBJECTIVE:** We proposed a novel nodule CADe which aims to relieve the challenge by the use of available engineered features to prevent convolution neural networks (CNN) from overfitting under dataset limitation and reduce the running-time complexity of self-learning. **METHODS:** The CADe methodology infuses adequately the engineered features, particularly texture features, into the deep learning process. **RESULTS:** The methodology was validated on 208 patients with at least one juxta-pleural nodule from the public LIDC-IDRI database. Results demonstrated that the methodology achieves a sensitivity of 88% with 1.9 false positives per scan and a sensitivity of 94.01% with 4.01 false positives per scan. **CONCLUSIONS:** The methodology shows high performance compared with the state-of-the-art results, in terms of accuracy and efficiency, from both existing CNN-based approaches and engineered feature-based classifications.

Machine learning to predict lung nodule biopsy method using CT image features: A pilot study. Sumathipala Y1, Shafiq M2, Bongen E3, Brinton C4, Paik D5. Comput Med Imaging Graph. 2018 Nov 3;71:1-8. doi: 10.1016/j.compmedimag.2018.10.006. [Epub ahead of print]
Computed tomography (CT)-based screening on lung cancer mortality is poised to make lung nodule management a growing public health problem. Biopsy and pathologic analysis of suspicious nodules is necessary to ensure accurate diagnosis and appropriate intervention. Biopsy techniques vary as do the specialists that perform them and the ways lung nodule patients are referred and triaged. The largest dichotomy is between minimally invasive biopsy (MIB) and surgical biopsy (SB). Cases of unsuccessful MIB preceding a SB can result in considerable delay in definitive care with potentially an adverse impact on prognosis besides potentially avoidable healthcare expenditures. An automated method that predicts the optimal biopsy method for a given lung nodule could save time and healthcare costs by facilitating referral and triage patterns. To our knowledge, no such method has been published. Here, we used CT image features and radiologist-annotated semantic features to predict successful MIB in a way that has not been described before. Using data from the Lung Image Database Consortium image collection (LIDC-IDRI), we trained a logistic regression model to determine whether a MIB or SB procedure was used to diagnose lung cancer in a patient presenting with lung nodules. We found that in successful MIB cases, the nodules were significantly larger and more spiculated. Our model illustrates that using robust machine learning tools on easily accessible semantic and image data can predict whether a patient's nodule is best

biopsied by MIB or SB. Pending further validation and optimization, clinicians could use our publicly accessible model to aid clinical decision-making.

Using a Smoking Cessation Quitline to Promote Lung Cancer Screening. Sharma A, Bansal-Travers M, Celestino P, Fine J, Reid ME, Hyland A, O'Connor R. Am J Health Behav. 2018 Nov 1;42(6):85-100. doi: 10.5993/AJHB.42.6.9.
OBJECTIVE: We assessed whether in-depth messaging delivered via a smoking cessation quitline results in participants: (1) speaking to their physician, or (2) insurance company regarding lung cancer screening (LCS). **METHODS:** Eligible participants lived in New York State and met the United States Preventive Services Task Force eligibility criteria for LCS (N = 1000). A randomized trial was conducted among New York State Smokers' Quitline participants to assess the impact of a brochure containing information on risks, benefits, and costs associated with LCS (control group) versus the brochure supplemented with phone-based in-depth messaging (treatment group). **RESULTS:** After a 4-month telephone survey (N = 431), associations between the study groups were examined for: (1) speaking with a physician regarding LCS, and (2) speaking with an insurance company about LCS coverage. Multivariate logistic regression models adjusted for demographics, insurance status, emphysema/COPD, and past 30-day cigarette use found no significant associations. However, sensitivity analyses among control participants found significant associations, including for speaking with a physician ($p < .05$) by receipt of the study brochure. Analyses repeated in the treatment group also had statistically significant findings emerge, including for speaking with insurance company ($p < .05$). **CONCLUSIONS:** The educational brochure may be an effective and low-cost way to deliver information about LCS.

Investigating unilateral pleural effusions: the role of cytology. Arnold DT1, De Fonseka D2, Perry S3, Morley A4, Harvey JE4, Medford A4, Brett M5, Maskell NA2. Eur Respir J. 2018 Nov 8;52(5). pii: 1801254. doi: 10.1183/13993003.01254-2018. Print 2018 Nov.
The vast majority of undiagnosed unilateral pleural effusions have fluid sent for cytological analysis. Despite widespread use, there is uncertainty about its sensitivity to diagnose malignant pleural effusions (MPEs). Our aim was to ascertain the utility of cytology using a large prospective cohort. Consecutive patients presenting with an undiagnosed unilateral pleural effusion were recruited to this UK-based study. All had pleural fluid sent for cytological analysis. Cytological sensitivity was based on the final diagnosis at 12 months, confirmed by two consultants. Over 8 years, 921 patients were recruited, of which 515 had a MPE. Overall sensitivity of fluid cytology to diagnose malignancy was 46% (95% CI 42-58%). There was variation in sensitivity depending on cancer primary, with mesothelioma (6%) and haematological malignancies (40%) being significantly lower than adenocarcinomas (79%). MPEs secondary to ovarian cancer had high pick-up rates (95%). In asbestos-exposed males with exudative effusions, the risk of MPE was 60%, but cytological sensitivity was 11%. This is the largest prospective study of pleural fluid cytology and informs discussions with patients about the likely requirement for investigations following thoracentesis. In patients presenting with a clinical suspicion of mesothelioma, cytological sensitivity is low, so more definitive investigations could be performed sooner.

The decision to biopsy in a lung cancer screening program: Potential impact of risk calculators. Gilbert CR1, Carlson AS2, Wilshire CL1, Aye RW1, Farivar AS1, Bograd AJ1, Gorden JA1. J Med Screen. 2018 Nov 12:969141318811362. doi: 10.1177/0969141318811362. [Epub ahead of print]
OBJECTIVE: The National Lung Screening Trial demonstrated the benefits of lung cancer screening, but the potential high incidence of unnecessary invasive testing for ultimately benign radiologic findings causes concern. We aimed to review current biopsy patterns and outcomes in our community-based program, and retrospectively apply malignancy prediction models in a lung cancer screening population, to identify the potential impact these calculators could have on biopsy decisions. **METHODS:**

Retrospective review of lung cancer-screening program participants from 2013 to 2016. Demographic, biopsy, and outcome data were collected. Malignancy risk calculators were retrospectively applied and results compared in patients with positive imaging findings. **RESULTS:** From 520 individuals enrolled in the screening program, pulmonary nodule(s) ≥6 mm were identified in 166, with biopsy in 30. Malignancy risk probabilities were significantly higher (Brock $p < 0.00001$; Mayo $p < 0.00001$) in those undergoing diagnostic sampling than those not undergoing sampling. However, there was no difference in the Brock ($p = 0.912$) or Mayo ($p = 0.435$) calculators when discriminating a final diagnosis of cancer from not cancer in those undergoing sampling. **CONCLUSIONS:** In our screening program, 5.7% of individuals undergo invasive testing, comparable with the National Lung Screening Trial (6.1%). Both Brock and Mayo calculators perform well in indicating who may be at risk of malignancy, based on clinical and radiologic factors. However, in our invasive testing group, the Brock and Mayo calculators and Lung Cancer Screening Program clinical assessment all lacked clarity in distinguishing individuals who have a cancer from those with a benign abnormality.

The Landscape of US Lung Cancer Screening Services. Kale MS1, Wisnivesky J2, Taioli E3, Liu B4. Chest. 2018 Nov 9. pii: S0012-3692(18)32720-X. doi: 10.1016/j.chest.2018.10.039. [Epub ahead of print]
BACKGROUND: Low adoption of lung cancer screening is potentially caused by inadequate access to a comprehensive lung cancer screening registry (LCSR), currently a requirement for reimbursement by the Centers for Medicare and Medicaid Services. However, variations in LCSR facilities have not been extensively studied. **METHODS:** We applied a hierarchical clustering method to a comprehensive database integrating state-level LCSR facility density, defined as the number of facilities per 100,000 at-risk persons, lung cancer outcomes including mortality and stage-specific incidence, and socioeconomic and behavioral factors. **RESULTS:** We found three distinct clusters of LCSR facilities roughly corresponding to the northern (cluster 1), southeastern (cluster 2), and southwestern (cluster 3) states. The southeastern states had the lowest total number of facilities (67 ± 44 in cluster $2 < 74 \pm 69$ in cluster $1 < 80 \pm 100$ in cluster 3), the slowest increase in facilities (23 ± 20 in cluster $2 < 26 \pm 28$ in cluster $1 < 27 \pm 32$ in cluster 3) between 2016 and 2018, and the highest lung cancer burden and current smokers. They ranked second in terms of facility density (2.9 ± 1.0 in cluster $3 < 3.8 \pm 1.3$ in cluster $2 < 6.3 \pm 2.8$ in cluster 1) and increase in facility density (1.1 ± 0.3 in cluster $3 < 1.3 \pm 0.7$ in cluster $2 < 2.5 \pm 2.5$ in cluster 1). **CONCLUSIONS:** We found substantial state-level variability in LCSR facilities tied to lung cancer burden, socioeconomic characteristics, and behavioral characteristics. Given the known risk factors of lung cancer, correcting a suboptimal distribution of screening programs will likely lead to improved lung cancer outcomes.

Financial analysis of free lung cancer screening program shows profitability using broader NCCN Guidelines. Chung JM1, Simmerman E1, Sadek R2, Wojtowicz S3, Dillard T4, Albo D5, Thomson N6, Schroeder C7. Ann Thorac Surg. 2018 Nov 9. pii: S0003-4975(18)31624-2. doi: 10.1016/j.athoracsur.2018.09.056. [Epub ahead of print]
BACKGROUND: Lung cancer screening with low-dose CT (LDCT) chest scans in high-risk populations has been established as an effective measure of preventive medicine by the National Lung Screening Trial (NLST). However, the sustainability of funding a program is still controversial. We present a 2.5 year profitability analysis of our screening program using the broader National Comprehensive Cancer Network (NCCN) criteria. **METHODS:** Retrospective chart review was performed on the initial 2.5 year data set of a free LDCT chest scan program targeting the underserved Southeastern United States. Patients were selected by the NCCN high-risk criteria, screening twice as many patients compared to CMS criteria. LDCT scans were performed during the off-service hours of our PET-CT scanner. Analysis of fiscal years 2015-2017 was done to evaluate indirect cost, direct cost, and adjusted net margin per case after factoring downstream revenue from positive scans and other findings. **RESULTS:** A total of 705

scans were performed with 418 patients referred for subsequent procedures or specialist evaluations. The mean overhead cost over total cost was 42.3%. The adjusted net margin per case was $-212 in the first year but turned positive to $177 in the third fiscal year. The total break-even point of adjusted net margin was between 6-7% of indirect cost as a function of charges. Of the 60 new patients introduced to the hospital system, a gross margin per case of $211 was found. **CONCLUSIONS:** Free lung cancer screening can demonstrate profitability from downstream revenue with a lag time of 2 years.

Role of FDG PET/CT in the Eighth Edition of TNM Staging of Non-Small Cell Lung Cancer.
Kandathil A1, Kay FU1, Butt YM1, Wachsmann JW1, Subramaniam RM1. Radiographics. 2018 Nov-Dec;38(7):2134-2149. doi: 10.1148/rg.2018180060.
Lung cancer is the leading cause of cancer-related mortality in the United States, and accurate staging plays a vital role in determining prognosis and treatment. The recently revised eighth edition of the TNM staging system for lung cancer defines new T and M descriptors and updates stage groupings on the basis of substantial differences in survival. There are new T descriptors that are based on the findings at histopathologic examination, and T descriptors are reassigned on the basis of tumor size and extent. No changes were made to the N descriptors in the eighth edition of the TNM staging of lung cancer, because the four N categories that are based on the location of the diseased nodes can be used to consistently predict prognosis. The eighth edition includes a new M1b descriptor for patients with a single extrathoracic metastatic lesion in a single organ (M1b), because they have better survival and different treatment options, compared with those with multiple extrathoracic lesions (M1c). Examination with fluorine 18 fluorodeoxyglucose (FDG) PET/CT is the standard of care and is an integral part of the clinical staging of patients with lung cancer. To provide the treating physicians with accurate staging information, radiologists and nuclear medicine physicians should be aware of the updated classification system and should be cognizant of the site-specific strengths and limitations of FDG PET/CT. In this article, the eighth edition of the TNM staging system is reviewed, as well as the role of FDG PET/CT in the staging of non-small cell lung carcinoma.

Lung cancer screening: Practice guidelines and insurance coverage are not enough. McDonnell KK1, Estrada RD1, Dievendorf AC1, Blew L1, Sercy E2, Khan S2, Hardin JW3, Warden D1, Eberth JM3. J Am Assoc Nurse Pract. 2018 Nov 9. doi: 10.1097/JXX.0000000000000096. [Epub ahead of print]
BACKGROUND AND PURPOSE: Low-dose computed tomography (LDCT) is expected to increase early detection of lung cancer and improve survival. The growth in the number of advanced nurse practitioners (NPs) in primary care settings increases the likelihood that an NP will serve as a patient's provider. This study's purpose was to examine knowledge, attitudes, and practices regarding LDCT among NPs who work in primary care settings. **METHODS:** An explanatory, sequential, mixed-method design used a 32-item questionnaire, followed by a semi-structured telephone interview. The development of the survey and interview questions were guided by a conceptual framework representing a temporal sequence for behavior change and potential barriers to guideline adherence. **CONCLUSIONS:** Nurse practitioners believe that shared decision making with their high-risk patients about LDCT is within their scope of their practice. Working in time-constrained primary care settings, NPs have limited abilities to improve the uptake of LDCT. Substantial patient barriers exist that deter follow through on providers' recommendation. Disseminating guidelines and authorizing health insurance reimbursement is insufficient. **IMPLICATIONS FOR PRACTICE:** Research is needed that investigates the screening process so that barriers can be closely studied. Culture change is needed where early detection has greater value for insurers, providers, and patients.

ACR Appropriateness Criteria® Lung Cancer Screening. Expert Panel on Thoracic Imaging:, Donnelly EF1, Kazerooni EA2, Lee E3, Henry TS4, Boiselle PM5, Crabtree TD6, Iannettoni MD7, Johnson GB8, Laroia AT9, Maldonado F10, Olsen KM11, Shim K12, Sirajuddin A13, Wu CC14, Kanne JP15. J Am Coll Radiol. 2018 Nov;15(11S):S341-S346. doi: 10.1016/j.jacr.2018.09.025.
Lung cancer remains the leading cause of cancer death in both men and women. Smoking is the single greatest risk factor for the development of lung cancer. For patients between the age of 55 and 80 with 30 or more pack years smoking history who currently smoke or who have quit within the last 15 years should undergo lung cancer screening with low-dose CT. In patients who do not meet these criteria but who have additional risk factors for lung cancer, lung cancer screening with low-dose CT is controversial but may be appropriate. Imaging is not recommended for lung cancer screening of patient younger than 50 years of age or patients older than 80 years of age or patients of any age with less than 20 packs per year history of smoking and no additional risk factor (ie, radon exposure, occupational exposure, cancer history, family history of lung cancer, history of COPD, or history of pulmonary fibrosis). The American College of Radiology Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed annually by a multidisciplinary expert panel. The guideline development and revision include an extensive analysis of current medical literature from peer reviewed journals and the application of well-established methodologies (RAND/UCLA Appropriateness Method and Grading of Recommendations Assessment, Development, and Evaluation or GRADE) to rate the appropriateness of imaging and treatment procedures for specific clinical scenarios. In those instances where evidence is lacking or equivocal, expert opinion may supplement the available evidence to recommend imaging or treatment.

The Case for Patient Navigation in Lung Cancer Screening in Vulnerable Populations: A Systematic Review. Shusted CS1, Barta JA2, Lake M2, et al. Popul Health Manag. 2018 Nov 8. doi: 10.1089/pop.2018.0128. [Epub ahead of print]
Patient navigation has been proposed to combat cancer disparities in vulnerable populations. Vulnerable populations often have poorer cancer outcomes and lower levels of screening, adherence, and treatment. Navigation has been studied in various cancers, but few studies have assessed navigation in lung cancer. Additionally, there is a lack of consistency in metrics to assess the quality of navigation programs. The authors conducted a systematic review of published cancer screening studies to identify quality metrics used in navigation programs, as well as to recommend standardized metrics to define excellence in lung cancer navigation. The authors included 26 studies evaluating navigation metrics in breast, cervical, colorectal, prostate, and lung cancer. After reviewing the literature, the authors propose the following navigation metrics for lung cancer screening programs: (1) screening rate, (2) compliance with follow-up, (3) time to treatment initiation, (4) patient satisfaction, (5) quality of life, (6) biopsy complications, and (7) cultural competency.

Early detection of lung cancer in a population at high risk due to occupation and smoking. Welch LS1, Dement JM2, Cranford K3, Shorter J3, Quinn PS1, Madtes DK4,5, Ringen K1. Occup Environ Med. 2018 Nov 10. pii: oemed-2018-105431. doi: 10.1136/oemed-2018-105431. [Epub ahead of print]
OBJECTIVE: The US National Comprehensive Cancer Network (NCCN) recommends two pathways for eligibility for Early Lung Cancer Detection (ELCD) programmes. Option 2 includes individuals with occupational exposures to lung carcinogens, in combination with a lesser requirement on smoking. Our objective was to determine if this algorithm resulted in a similar prevalence of lung cancer as has been found using smoking risk alone, and if so to present an approach for lung cancer screening in high-risk worker populations. **METHODS:** We enrolled 1260 former workers meeting NCCN criteria, with modifications to account for occupational exposures in an ELCD programme. **RESULTS:** At baseline, 1.6% had a lung cancer diagnosed, a rate similar to the National Lung Cancer Screening Trial (NLST).

Among NLST participants, 59% were current smokers at the time of baseline scan or had quit smoking fewer than 15 years prior to baseline; all had a minimum of 30 pack-years of smoking. Among our population, only 24.5% were current smokers and 40.1% of our participants had smoked fewer than 30 pack-years; only 43.5% would meet entry criteria for the NLST. The most likely explanation for the high prevalence of screen-detected lung cancers in the face of a reduced risk from smoking is the addition of occupational risk factors for lung cancer. **CONCLUSION:** Occupational exposures to lung carcinogens should be incorporated into criteria used for ELCD programmes, using the algorithm developed by NCCN or with an individualised risk assessment; current risk assessment tools can be modified to incorporate occupational risk.

Electromagnetic Navigation Bronchoscopy for Peripheral Pulmonary Lesions: One-Year Results of the Prospective, Multicenter NAVIGATE Study. Folch EE1, Pritchett MA2, Nead MA3, et al. J Thorac Oncol. 2018 Nov 23. pii: S1556-0864(18)33456-7. doi: 10.1016/j.jtho.2018.11.013. [Epub ahead of print]
INTRODUCTION: Electromagnetic navigation bronchoscopy (ENB) is a minimally invasive technology that guides endoscopic tools to pulmonary lesions. ENB has been evaluated primarily in small, single-center studies; thus, the diagnostic yield in a generalizable setting is unknown. **METHODS:** NAVIGATE is a prospective, multicenter, cohort study that evaluated ENB using the superDimension™ navigation system. In this United States cohort analysis, 1,215 consecutive subjects were enrolled at 29 academic and community sites from April 2015 to August 2016. **RESULTS:** The median lesion size was 20.0 mm. Fluoroscopy was used in 91% of cases (lesions visible in 60%) and radial endobronchial ultrasound in 57%. The median ENB planning time was 5 minutes; the ENB-specific procedure time was 25 minutes. Among 1,157 subjects undergoing ENB-guided biopsy, 94% (1,092/1,157) had navigation completed and tissue obtained. Follow-up was completed in 99% of subjects at 1 month and 80% at 12 months. The 12-month diagnostic yield was 73%. Pathology results of the ENB-aided tissue samples showed malignancy in 44% (484/1,092). Sensitivity, specificity, positive predictive value, and negative predictive value for malignancy were 69%, 100%, 100%, and 56%, respectively. ENB-related CTCAE Grade ≥2 pneumothoraces (requiring admission or chest tube placement) occurred in 2.9%. The ENB-related CTCAE Grade ≥2 bronchopulmonary hemorrhage and Grade ≥4 respiratory failure rates were 1.5% and 0.7%, respectively. **CONCLUSIONS:** NAVIGATE demonstrates that an ENB-aided diagnosis can be obtained in approximately three quarters of evaluable patients across a generalizable cohort based on prospective 12-month follow-up in a pragmatic setting, with a low procedural complication rate.

Patient-Physician Discussions on Lung Cancer Screening: A Missed Teachable Moment to Promote Smoking Cessation. Kathuria H1, Koppelman E2,3, Borrelli B4, Slatore CG5,6, Clark JA2,3, Lasser KE3,7, Wiener RS1,2. Nicotine Tob Res. 2018 Nov 23. doi: 10.1093/ntr/nty254. [Epub ahead of print]
INTRODUCTION: Little is known about whether patients and physicians perceive lung cancer screening as a teachable moment to promote smoking cessation or the degree to which physicians in 'real world' settings link lung cancer screening discussions with smoking cessation counseling. We sought to characterize patient and physician perspectives of discussions about smoking cessation during lung cancer screening. **METHODS:** We conducted a qualitative study (interviews and focus groups) with 21 physicians and 28 smokers screened in 4 diverse hospitals. Transcripts were analyzed for characteristics of communication about smoking cessation and lung cancer screening, the perceived effect on motivation to quit smoking, the degree to which physicians leverage lung cancer screening as a teachable moment to promote smoking cessation, and suggestions to improve patient-physician communication about smoking cessation in the context of lung cancer screening. **RESULTS:** Patients reported that lung cancer screening made them more cognizant of the health consequences of smoking, priming them for a teachable moment. While physicians and patients both acknowledged that smoking cessation counseling was frequent, they

described little connection between their discussions regarding lung cancer screening and smoking cessation counseling. Physicians identified several barriers to integrating discussions on smoking cessation and lung cancer screening. They volunteered communication strategies by which lung cancer screening could be leveraged to promote smoking cessation. **CONCLUSIONS:** Lung cancer screening highlights the harms of smoking to patients who are chronic, heavy smokers and thus may serve as a teachable moment for promoting smoking cessation. However, this opportunity is typically missed in clinical practice. **IMPLICATIONS:** Lung cancer screening highlights the harms of smoking to heavily addicted smokers. Yet both physicians and patients reported little connection between lung cancer screening and tobacco treatment discussions due to multiple barriers. On-site tobacco treatment programs and post-screening messaging tailored to the lung cancer screening results is needed to maximize the health outcomes of lung cancer screening, including smoking quit rates and longer-term smoking-related morbidity and mortality.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Surgical Management of Lung Cancer: History, Evolution, and Modern Advances. Abbas AE1. Curr Oncol Rep. 2018 Nov 13;20(12):98. doi: 10.1007/s11912-018-0741-7.
PURPOSE OF REVIEW: Although surgery for lung cancer was not common before the early twentieth century, it has enjoyed remarkable progress since then both in type of resection and technical approach. This has been coupled with significant technological advances. Here, we will review the history and evolution of this relatively new field of surgery. **RECENT FINDINGS:** The gold standard of the extent of resection for lung cancer evolved from pneumonectomy to lobectomy to even sublobar resection for select situations. In addition, major advances have occurred in the technical aspect of the surgical procedure. The incisional approach has evolved from rib spreading thoracotomy to thoracoscopic surgery with the latter showing significant improvement in short-term outcomes over open thoracotomy. However, standard video-assisted thoracoscopic surgery or VATS is associated with visual and mechanical limitations, including lack of depth perception and rigid straight instruments. This makes it appropriate only for early-stage peripheral and small tumors. Most of the limitations of VATS can be overcome with the more recently introduced robotic-assisted thoracic surgery (RATS). RATS utilizes wristed instruments that are introduced in the chest through 8-mm ports and can mimic the movements of the human hand. In addition, magnified, three-dimensional and high definition imaging gives the surgeon an image of the lung unlike any other modality. This has allowed surgeons to perform advanced resections such as pneumonectomy or sleeve resection in a minimally invasive fashion. In addition, RATS has become a platform for the addition of other technical enhancements such as incorporating a near infra-red light source into the camera allowing identification of autoflourescent agents, such as indocyanin green. This has allowed localization of small nodules for resection and identification of tissue planes for sublobar resection. However, new technologies also require investments in time and money. Thoracic surgery for lung cancer has evolved to include advanced minimally invasive techniques including video-assisted and robotic-assisted thoracoscopy. RATS in particular may enable surgeons to perform more advanced procedures in a minimally invasive fashion. It is hoped that the higher costs of new surgical technology may be offset by the potential for improved patient outcomes and resultant socioeconomic benefits.

Prognostic impact of underlying lung disease in pulmonary wedge resection for lung cancer.

Kawaguchi T1, Sawabata N2, Miura S3, Kawai N2, Yasukawa M2, Tojo T2, Taniguchi S2. Int J Clin Oncol. 2018 Nov 15. doi: 10.1007/s10147-018-1367-3. [Epub ahead of print]
BACKGROUND: Pulmonary wedge resection is an option for lung cancer patients with limited cardiopulmonary preservation. As the impact of underlying lung status on the prognosis of such patients remains unclear, we assessed this issue. **METHODS:** A total of 149 borderline surgical candidates with localized lung cancer who had undergone wedge resection were retrospectively investigated. Clinical variables related to perioperative morbidity, local control rate, and oncological outcomes based on underlying lung disease were analyzed. **RESULTS:** According to the risk analysis of postoperative complications, underlying lung disease did not influence the surgical morbidity. Postoperative recurrence occurred in 65 patients (locoregional recurrence in 36, distant metastasis in 12, and both simultaneously in 17). Multivariate analysis revealed that emphysema on computed tomography (CT) [hazard ratio (HR) 0.45; 95% confidence interval (CI) 0.21-0.99] was an independent indicator of locoregional recurrence. Forty-four patients died of lung cancer and 29 of other causes. Multivariate analysis demonstrated that interstitial lung disease on CT (HR 1.98; 95% CI 1.01-3.89) was a predictor of poor prognosis. **CONCLUSION:** Pulmonary wedge resection can be safely undergone by lung cancer patients regardless of pulmonary comorbidity, although underlying lung disease may influence the prognosis after wedge resection.

Right-sided vs Left-sided Pneumonectomy after Induction Therapy for Non-small-cell Lung Cancer. Yang CJ1, Shah S1, Lin BK1, et al. Ann Thorac Surg. 2018 Nov 15. pii: S0003-4975(18)31657-6. doi: 10.1016/j.athoracsur.2018.10.009. [Epub ahead of print]
BACKGROUND: A right-sided pneumonectomy after induction therapy for non-small-cell lung cancer (NSCLC) has been shown to be associated with significant perioperative risk. We examined the impact of laterality on long-term survival after induction therapy and pneumonectomy using the National Cancer Data Base (NCDB). **METHODS:** Perioperative and long-term outcomes of patients who underwent pneumonectomy following induction chemotherapy with or without radiation from 2004-2014 in the NCDB were evaluated using multivariable Cox proportional hazards modeling and propensity score-matched analysis. **RESULTS:** During the study period, 1465 patients (right n=693 [47.3%], left n=772 [52.7%]) met inclusion criteria. Right-sided pneumonectomy was associated with significantly higher 30-day (8.2% [57/693] vs 4.2% [32/772], p< 0.01) and 90-day mortality (13.6% [94/693] vs 7.9% [61/772], p<0.01), and right-sided pneumonectomy was a predictor of higher 90-day mortality (OR 2.23, p<0.01). However, overall survival between right and left pneumonectomy was not significantly different in univariate (5-year survival 37.6% [95% CI: 0.34-0.42] vs 35% [95% CI: 0.32-0.39], log-rank p=0.94) or multivariable analysis (hazard ratio, 1.07 [95% CI: 0.92-1.25], p=0.40). In a propensity score-matched analysis of 810 patients, there were no significant differences in 5-year survival between the right- vs left-sided groups (34.7% [95% CI: 0.30-0.40] vs 34.1%, [95% CI: 0.29-0.39], log-rank p =0.86).
CONCLUSIONS: In this national analysis, right-sided pneumonectomy after induction therapy was associated with a significantly higher perioperative but not worse long-term mortality compared to a left-sided procedure.

Comparison between Stereotactic Radiotherapy and Sublobar Resection for Non-Small Cell Lung Cancer. Tamura M1, Matsumoto I2, Tanaka Y2, et al. Ann Thorac Surg. 2018 Nov 17. pii: S0003-4975(18)31664-3. doi: 10.1016/j.athoracsur.2018.10.015. [Epub ahead of print]
BACKGROUND: The aim of this study was to compare outcomes of primary treatment with stereotactic body radiation therapy (SBRT) versus sublobar resection (SLR) for clinical stage I non-small cell lung cancer (NSCLC) in patients with medical comorbidities. **METHODS:** Consecutive patients who underwent SBRT (n=106) or SLR (wedge resection: n=100 and segmentectomy: n=41) because of medical comorbidities associated with stage I NSCLC were enrolled. Lesions located in the outer third of

the lung field on CT were defined as external, and others were defined as internal. A propensity matched analysis was also performed that compared SBRT and SLR results. Charts were reviewed to determine local tumor recurrence, disease-specific survival (DSS), and overall survival (OS). **RESULTS:** A propensity matched analysis, recurrence-free survival (RFS) became significant in favor of surgery (p=0.036). For large nodules of >2.0 cm in diameter, RFS was significantly better in the surgery group (p=0.042). No significant differences in OS, DSS, or RFS were observed with small nodules of <2.0 cm in diameter. In the external group, a higher recurrence rate was seen for SBRT group. For internal group, there was no statistical difference between each treatment. Local recurrence rate was higher in the SBRT group (p=0.0082) in the external group. **CONCLUSIONS:** In a matched comparison of stage I NSCLC in patients with medical comorbidities, RFS was in favor of surgery comparing SBRT, but there were no significant differences in OS or DSS. The tumor size, tumor location should be considered before deciding whether to perform SBRT or surgery.

Long-Term Prognostic Impact of Severe Postoperative Complications After Lung Cancer Surgery. Okada S1, Shimada J1, Kato D1, Tsunezuka H1, Teramukai S2, Inoue M3. Ann Surg Oncol. 2018 Nov 19. doi: 10.1245/s10434-018-7061-x. [Epub ahead of print]

BACKGROUND: Postoperative complications are reportedly related to poor prognosis following lung cancer surgery; however, the difference in the prognostic impact according to immune-nutritional status is unknown. **METHODS:** In 411 patients with completely resected non-small cell lung cancer, the relationship between severe postoperative complications (SPCs; Clavien-Dindo grade III or higher) and survival was retrospectively analyzed, with special reference to preoperative immune-nutritional status based on the prognostic nutritional index (PNI), which was calculated using serum albumin level and total lymphocyte count. **RESULTS:** A total of 52 (12.7%) patients had SPCs. The most common SPC was air leak (n = 39), atelectasis/sputum (n = 4), pneumonia (n = 2), pyothorax (n = 2), and bleeding (n = 2). The 5-year overall survival (OS) rates in patients with and without SPCs were 63.8% and 80.1%, respectively (p = 0.007). A multivariate Cox proportional hazard model revealed SPCs had a negative prognostic impact on patients with preserved immune-nutritional status (PNI ≥ 48.3; first to third quartile), but not on those with poor immune-nutritional status (PNI < 48.3; fourth quartile), with statistically significant interaction. Further analysis focused on 309 patients with preserved immune-nutritional status. The OS and relapse-free survival (RFS) rates were significantly worse in patients with SPCs than in those without (p < 0.001). After controlling for potential confounders, SPCs remained significantly associated with worse OS (adjusted hazard ratio [HR] 2.49, 95% confidence interval [CI] 1.21-4.83; p = 0.015) and RFS (adjusted HR 2.02, 95% CI 1.10-3.53; p = 0.025). **CONCLUSION:** Severe complications following lung cancer surgery could negatively impact prognosis, particularly in patients with preserved immune-nutritional status.

Clinical outcomes of hypofractionated image-guided multifocal irradiation using volumetric-modulated arc therapy for brain metastases. Furutani S1, Ikushima H2, Sasaki M3, et al. J Radiat Res. 2018 Nov 16. doi: 10.1093/jrr/rry091. [Epub ahead of print]

Volumetric-modulated arc therapy (VMAT) can be used to design hypofractionated radiotherapy treatment plans for multiple brain metastases. The purpose of this study was to evaluate treatment outcomes of hypofractionated image-guided multifocal irradiation using VMAT (HFIGMI-VMAT) for brain metastases. From July 2012 to December 2016, 67 consecutive patients with 601 brain metastases were treated with HFIGMI-VMAT at our institution. The prescribed dose was 50 Gy to a 95% volume of the planning target volume in 10 fractions. Fifty-five of the 67 patients had non-small-cell lung cancer, and the remaining 12 had other types of cancer. The median number of brain metastases was five, and the median maximum diameter was 1.2 cm. The median duration of follow-up was 12.0 months (range, 1.9-44.8 months), and the median survival time 18.7 months. Four patients with six lesions had local

recurrences. The local control rate in the 64 assessed patients was 98.4% and 95.3% at 6 and 12 months, respectively (three died before assessment). The local control rate for the 572 assessed lesions was 99.8% and 99.3% at 6 and 12 months, respectively. Thirty-nine patients developed distant brain metastases, the distant brain control rate being 59.7% and 40.5% at 6 and 12 months, respectively. Acute toxicities were generally mild (Grade 1-2). Three patients (4.5%) developed radiation necrosis requiring corticosteroid therapy. The HFIGMI-VMAT technique with flat dose delivery was well tolerated and achieved excellent local control. This technique is a promising treatment option for patients with multiple and large brain metastases.

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

Efficacy of Ceritinib After Alectinib for ALK-positive Non-small Cell Lung Cancer. Yoshida H1, Kim YH2, Ozasa H1, et al. In Vivo. 2018 Nov-Dec;32(6):1587-1590. doi: 10.21873/invivo.11418.
BACKGROUND: Alectinib is a new standard treatment for treatment-naïve anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC); however, resistance ultimately develops in almost all patients, and data regarding the efficiency of ceritinib for such patients are insufficient. **PATIENTS AND METHODS:** Patients with ALK-positive NSCLC treated at the Kyoto University Hospital from January 2012 to March 2017 were reviewed. Patients who were treated with ceritinib after alectinib were identified, and the efficacy of ceritinib after alectinib was retrospectively evaluated. **RESULTS:** There were 35 patients with ALK-positive NSCLC, nine of whom received ceritinib after alectinib. The overall response rate to ceritinib was 44%. It was 16% in patients who received ceritinib immediately after alectinib, and 100% in patients who received chemotherapy before ceritinib. The median progression-free survival for patients treated with ceritinib was 4.4 months (95% confidence interval(CI)=1.1-6.5 months). **CONCLUSION:** Ceritinib demonstrated a modest clinical benefit after failure of alectinib. Ceritinib may be a reasonable treatment option in this setting.

Peripheral blood biomarkers correlate with outcomes in advanced non-small cell lung Cancer patients treated with anti-PD-1 antibodies. Soyano AE1, Dholaria B1,2, Marin-Acevedo JA3, et al. J Immunother Cancer. 2018 Nov 23;6(1):129. doi: 10.1186/s40425-018-0447-2.
BACKGROUND: Anti-programmed cell death 1 (PD-1) antibodies have demonstrated improved overall survival (OS) and progression-free survival (PFS) in a subset of patients with metastatic or locally advanced non-small cell lung cancer (NSCLC). To date, no blood biomarkers have been identified in NSCLC to predict clinical outcomes of treatment with anti-PD-1 antibodies. **PATIENT AND METHODS:** We performed an analysis of retrospectively registered data of 157 patients with advanced NSCLC treated with anti-PD-1 antibodies at Mayo Clinic in Florida and Rochester. White blood cell count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), ANC to ALC (ANC: ALC) ratio, absolute eosinophil count, absolute monocyte count (AMC), platelet counts, and myeloid to lymphoid (M:L) ratio at baseline and throughout treatment were assessed. Kaplan-Meier method and Cox proportional hazards model were performed. **RESULTS:** We treated 146 patients with nivolumab and 11 with pembrolizumab between January 1, 2015 and April 15, 2017. At median follow-up of 20 months, median OS and PFS were 6.0 and 2.6 months, respectively. Higher baseline ANC, AMC, ANC: ALC ratio and M: L ratio correlated with worse clinical outcomes in patients who underwent anti-PD-1 treatment. A baseline ANC: ALC ratio of 5.9 or higher had a significantly increased risk of death (hazard ratio [HR] =1.94; 95% confidence interval [CI], 1.24-3.03; P = 0.004) and disease progression (HR, 1.65; 95% CI, 1.17-2.34; P = 0.005) compared with patients with lower ratio. Similarly, a baseline M: L ratio of 11.3 or higher had significantly increased risk of death (HR, 2.5; 95% CI, 1.54-4.05; P < 0.001), even after a multivariate analysis (HR, 2.31; P = 0.002), compared to those with lower ratio. **CONCLUSIONS:**

Increased baseline ANC: ALC ratio and M: L ratio before initiation of anti-PD1 antibodies were associated with poor PFS and OS in advanced NSCLC patients. The potential predictive value of these readily available biomarkers might help with risk stratification and treatment strategies. These findings warrant further investigation in a larger, prospective study.

Afatinib versus gemcitabine/cisplatin for first-line treatment of Chinese patients with advanced non-small-cell lung cancer harboring EGFR mutations: subgroup analysis of the LUX-Lung 6 trial. Wu YL1, Xu CR1, Hu CP2, et al. Onco Targets Ther. 2018 Nov 30;11:8575-8587. doi: 10.2147/OTT.S160358. eCollection 2018.
INTRODUCTION: Non-small-cell lung cancer (NSCLC) is the leading cause of cancer death in China. Four epidermal growth factor receptor (EGFR)-targeted tyrosine kinase inhibitors - afatinib, erlotinib, icotinib, and gefitinib - are available for first-line treatment of NSCLC in China; however, there are few data to guide treatment choice. The Phase III LUX-Lung 6 trial compared afatinib with platinum-based chemotherapy for first-line treatment of patients from Southeast Asia with EGFR mutation-positive advanced NSCLC. This post hoc analysis assessed the findings from LUX-Lung 6 in Chinese patients. **CLINICAL TRIAL REGISTRATION:** ClinicalTrials.gov: NCT01121393. **MATERIALS AND METHODS:** Previously untreated patients with EGFR mutation-positive stage IIIB/IV lung adenocarcinoma were randomized 2:1 to receive afatinib or ≤6 cycles of gemcitabine/ cisplatin. The key outcomes were progression-free survival (PFS; primary), objective response rate, disease control rate, overall survival (OS), duration of response and disease control, patient-reported outcomes, and safety. Three hundred and twenty-seven patients from mainland China were treated (89.8% of overall LUX-Lung 6 population; afatinib 217, gemcitabine/cisplatin 110). **RESULTS:** PFS was significantly longer with afatinib than gemcitabine/cisplatin (median 11.0 versus 5.6 months; hazard ratio [HR], 0.30 [95% CI, 0.21, 0.43]; P,0.0001). Overall, there was no significant difference in OS between treatment arms; however, in a subgroup analysis, afatinib significantly improved OS versus gemcitabine/cisplatin in patients with an EGFR Del19 mutation (median 31.6 versus 16.3 months; HR, 0.61 [95% CI, 0.41, 0.91]; P=0.0146). Afatinib was well tolerated, with most treatment-related adverse events (TRAEs) being of grade 1 or 2 severity. The most common grade 3/4 TRAEs with afatinib were rash/acne (15.9%/0.5%), stomatitis (6.1%/0%), and diarrhea (5.6%/0%). TRAEs leading to permanent discontinuation were reported in 12 patients (5.6%) receiving afatinib and 43 (41.7%) receiving gemcitabine/cisplatin. Afatinib significantly improved PFS compared with standard first-line chemotherapy in Chinese patients with EGFR mutation-positive NSCLC and demonstrated a manageable safety profile. **CONCLUSION:** The findings support the rationale for using afatinib as a first-line treatment option for this patient population.O

Real-world anaplastic lymphoma kinase (ALK) rearrangement testing patterns, treatment sequences, and survival of ALK inhibitor-treated patients. Davies J1, Martinec M2, Coudert M3, Delmar P2, Crane G1. Curr Med Res Opin. 2018 Nov 9:1-8. doi: 10.1080/03007995.2018.1533458. [Epub ahead of print]
BACKGROUND: The anaplastic lymphoma kinase (ALK) treatment landscape is crowded following recent ALK inhibitor approvals, and updated information on real-world treatment patterns in advanced non-small-cell lung cancer (aNSCLC) with ALK rearrangement (ALK+) is needed. **METHODS:** This retrospective US cohort study used Flatiron Health's longitudinal electronic health record (EHR)-derived database. Patients (≥ 18 years old) diagnosed with stage IIIB/IV aNSCLC, with documented ALK rearrangement and ≥2 visits after January 1, 2011 were followed until February 28, 2016. Patients enrolled on a clinical trial or exposed to ALK inhibitors other than crizotinib or ceritinib were excluded. Treatment patterns, time and type of biomarker testing, and overall survival (OS) were analyzed.

RESULTS: Median age (n = 300) was 62.5 years; 55% female; 48% non-smokers; 8.7% central nervous system (CNS) metastases at diagnosis. Overall, 73% and 86% received their first ALK biomarker test before/at diagnosis, or before/during first-line treatment, respectively. In total, 90.0%, 78.1%, and 74.7% received first-, second-, and third-line therapy, respectively. Most patients received ALK-targeted treatment; 62% received crizotinib, of which 21% reported a dose reduction. Progression was the most common reason for crizotinib (78%) and ceritinib (41%) discontinuation. Median OS was 29.4 months (95% CI =24.7-39.6) overall; 27.1 months (95% CI =22.0-35.0) in patients with CNS metastases, and 36.9 months (95% CI =25.1-not reached) without. **CONCLUSIONS:** Despite widespread crizotinib use in patients with ALK+ aNSCLC, a high proportion of patients progressed. Ongoing analyses of EHR-derived cohorts are valuable in assessing real-world testing rates and therapeutic use of ALK inhibitors.

Treatment patterns, duration and outcomes of pemetrexed maintenance therapy in patients with advanced NSCLC in a real-world setting. Winfree KB1, Torres AZ2, Zhu YE1, Muehlenbein C1, Aggarwal H1, Woods S1, Abernethy A2. Curr Med Res Opin. 2018 Nov 13:1-25. doi: 10.1080/03007995.2018.1547273. [Epub ahead of print]
OBJECTIVES: In patients with non-squamous non-small cell lung cancer (NSCLC), maintenance therapy regimens, including pemetrexed, have been shown to prolong overall survival (OS) and progression-free survival (PFS). The purpose of this study was to describe real-world maintenance use of pemetrexed and associated outcomes in patients with advanced NSCLC. **METHODS:** This was a retrospective, observational study that used longitudinal, demographically and geographically diverse electronic health record data in the United States. Eligible patients were adults with advanced non-squamous NSCLC who had received maintenance treatment with pemetrexed monotherapy or pemetrexed plus bevacizumab. Descriptive statistics were used to describe the patient population and multivariable logistic regression was used to identify the factors associated with duration of maintenance therapy. Kaplan-Meier curves and Cox regression models were used for time-to-event analysis. **RESULTS:** Patients receiving pemetrexed maintenance therapy were treated with either pemetrexed monotherapy (66.0%) or pemetrexed plus bevacizumab (34.0%). Carboplatin and pemetrexed (37.9%) or carboplatin, pemetrexed and bevacizumab (36.1%) were the most commonly used first-line therapies observed. The majority (84.9%) of these maintenance patients responded to first-line therapy. The median duration of maintenance therapy was 6.0 months for pemetrexed and bevacizumab and 4.1 months for pemetrexed monotherapy. The median OS from the start of first-line therapy of the total study cohort was 21.5 months (95% CI 20.0, 22.9). **CONCLUSION:** Real-world effectiveness of pemetrexed maintenance therapy is similar to that observed in published randomized controlled trials, confirming a role for pemetrexed maintenance in eligible patients in clinical practice.

Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Solomon BJ1, Besse B2, Bauer TM3, et al. .Lancet Oncol. 2018 Dec;19(12):1654-1667. doi: 10.1016/S1470-2045(18)30649-1. Epub 2018 Nov 6.
BACKGROUND: Lorlatinib is a potent, brain-penetrant, third-generation inhibitor of ALK and ROS1 tyrosine kinases with broad coverage of ALK mutations. In a phase 1 study, activity was seen in patients with ALK-positive non-small-cell lung cancer, most of whom had CNS metastases and progression after ALK-directed therapy. We aimed to analyse the overall and intracranial antitumour activity of lorlatinib in patients with ALK-positive, advanced non-small-cell lung cancer. **METHODS:** In this phase 2 study, patients with histologically or cytologically ALK-positive or ROS1-positive, advanced, non-small-cell lung cancer, with or without CNS metastases, with an Eastern Cooperative Oncology Group performance status of 0, 1, or 2, and adequate end-organ function were eligible. Patients were enrolled into six different expansion cohorts (EXP1-6) on the basis of ALK and ROS1 status and previous therapy, and were given lorlatinib 100 mg orally once daily continuously in 21-day cycles. The primary endpoint was overall and

intracranial tumour response by independent central review, assessed in pooled subgroups of ALK-positive patients. Analyses of activity and safety were based on the safety analysis set (ie, all patients who received at least one dose of lorlatinib) as assessed by independent central review. Patients with measurable CNS metastases at baseline by independent central review were included in the intracranial activity analyses. In this report, we present lorlatinib activity data for the ALK-positive patients (EXP1-5 only), and safety data for all treated patients (EXP1-6). This study is ongoing and is registered with ClinicalTrials.gov, number NCT01970865. **FINDINGS:** Between Sept 15, 2015, and Oct 3, 2016, 276 patients were enrolled: 30 who were ALK positive and treatment naive (EXP1); 59 who were ALK positive and received previous crizotinib without (n=27; EXP2) or with (n=32; EXP3A) previous chemotherapy; 28 who were ALK positive and received one previous non-crizotinib ALK tyrosine kinase inhibitor, with or without chemotherapy (EXP3B); 112 who were ALK positive with two (n=66; EXP4) or three (n=46; EXP5) previous ALK tyrosine kinase inhibitors with or without chemotherapy; and 47 who were ROS1 positive with any previous treatment (EXP6). One patient in EXP4 died before receiving lorlatinib and was excluded from the safety analysis set. In treatment-naive patients (EXP1), an objective response was achieved in 27 (90·0%; 95% CI 73·5-97·9) of 30 patients. Three patients in EXP1 had measurable baseline CNS lesions per independent central review, and objective intracranial responses were observed in two (66·7%; 95% CI 9·4-99·2). In ALK-positive patients with at least one previous ALK tyrosine kinase inhibitor (EXP2-5), objective responses were achieved in 93 (47·0%; 39·9-54·2) of 198 patients and objective intracranial response in those with measurable baseline CNS lesions in 51 (63·0%; 51·5-73·4) of 81 patients. Objective response was achieved in 41 (69·5%; 95% CI 56·1-80·8) of 59 patients who had only received previous crizotinib (EXP2-3A), nine (32·1%; 15·9-52·4) of 28 patients with one previous non-crizotinib ALK tyrosine kinase inhibitor (EXP3B), and 43 (38·7%; 29·6-48·5) of 111 patients with two or more previous ALK tyrosine kinase inhibitors (EXP4-5). Objective intracranial response was achieved in 20 (87·0%; 95% CI 66·4-97·2) of 23 patients with measurable baseline CNS lesions in EXP2-3A, five (55·6%; 21·2-86·3) of nine patients in EXP3B, and 26 (53·1%; 38·3-67·5) of 49 patients in EXP4-5. The most common treatment-related adverse events across all patients were hypercholesterolaemia (224 [81%] of 275 patients overall and 43 [16%] grade 3-4) and hypertriglyceridaemia (166 [60%] overall and 43 [16%] grade 3-4). Serious treatment-related adverse events occurred in 19 (7%) of 275 patients and seven patients (3%) permanently discontinued treatment because of treatment-related adverse events. No treatment-related deaths were reported. **INTERPRETATION:** Consistent with its broad ALK mutational coverage and CNS penetration, lorlatinib showed substantial overall and intracranial activity both in treatment-naive patients with ALK-positive non-small-cell lung cancer, and in those who had progressed on crizotinib, second-generation ALK tyrosine kinase inhibitors, or after up to three previous ALK tyrosine kinase inhibitors. Thus, lorlatinib could represent an effective treatment option for patients with ALK-positive non-small-cell lung cancer in first-line or subsequent therapy. **FUNDING:** Pfizer.

Effect of Anlotinib as a Third-Line or Further Treatment on Overall Survival of Patients With Advanced Non-Small Cell Lung Cancer: The ALTER 0303 Phase 3 Randomized Clinical Trial.
Han B1, Li K2, Wang Q3,4, et al. JAMA Oncol. 2018 Nov 1;4(11):1569-1575. doi: 10.1001/jamaoncol.2018.3039.
IMPORTANCE: Anlotinib is a novel multitarget tyrosine kinase inhibitor for tumor angiogenesis and proliferative signaling. A phase 2 trial showed anlotinib to improve progression-free survival with a potential benefit of overall survival, leading to the phase 3 trial to confirm the drug's efficacy in advanced non-small cell lung cancer (NSCLC). **OBJECTIVE:** To investigate the efficacy of anlotinib on overall survival of patients with advanced NSCLC progressing after second-line or further treatment. **DESIGN, SETTING, AND PARTICIPANTS:** The ALTER 0303 trial was a multicenter, double-blind, phase 3 randomized clinical trial designed to evaluate the efficacy and safety of anlotinib in patients with

advanced NSCLC. Patients from 31 grade-A tertiary hospitals in China were enrolled between March 1, 2015, and August 31, 2016. Those aged 18 to 75 years who had histologically or cytologically confirmed NSCLC were eligible (n = 606), and those who had centrally located squamous cell carcinoma with cavitary features or brain metastases that were uncontrolled or controlled for less than 2 months were excluded. Patients (n = 440) were randomly assigned in a 2-to-1 ratio to receive either 12 mg/d of anlotinib or a matched placebo. All cases were treated with study drugs at least once in accordance with the intention-to-treat principle. **MAIN OUTCOMES AND MEASURES:** The primary end point was overall survival. The secondary end points were progression-free survival, objective response rate, disease control rate, quality of life, and safety. **RESULTS:** In total, 439 patients were randomized, 296 to the anlotinib group (106 [36.1%] were female and 188 [64.0%] were male, with a mean [SD] age of 57.9 [9.1] years) and 143 to the placebo group (46 [32.2%] were female and 97 [67.8%] were male, with a mean [SD] age of 56.8 [9.1] years). Overall survival was significantly longer in the anlotinib group (median, 9.6 months; 95% CI, 8.2-10.6) than the placebo group (median, 6.3 months; 95% CI, 5.0-8.1), with a hazard ratio (HR) of 0.68 (95% CI, 0.54-0.87; P = .002). A substantial increase in progression-free survival was noted in the anlotinib group compared with the placebo group (median, 5.4 months [95% CI, 4.4-5.6] vs 1.4 months [95% CI, 1.1-1.5]; HR, 0.25 [95% CI, 0.19-0.31]; P < .001). Considerable improvement in objective response rate and disease control rate was observed in the anlotinib group over the placebo group. The most common grade 3 or higher adverse events in the anlotinib arm were hypertension and hyponatremia. **CONCLUSIONS AND RELEVANCE:** Among the Chinese patients in this trial, anlotinib appears to lead to prolonged overall survival and progression-free survival. This finding suggests that anlotinib is well tolerated and is a potential third-line or further therapy for patients with advanced NSCLC.

Effect of Platinum-Based Chemotherapy on PD-L1 Expression on Tumor Cells in Non-small Cell Lung Cancer. Shin J1, Chung JH2, Kim SH1, et al. Cancer Res Treat. 2018 Nov 5. doi: 10.4143/crt.2018.537. [Epub ahead of print]
PURPOSE: Programmed death-1 (PD-1)/PD-1 ligand (PD-L1) axis blockades have revolutionized the treatment of advanced non-small cell lung cancer (NSCLC). We assessed the effect of platinum-based chemotherapy on tumor PD-L1 expression and its clinical implications. **MATERIALS AND METHODS:** We used immunohistochemistry to retrospectively evaluate the percentage of tumor cells with membranous PD-L1 staining (tumor proportion score) in paired tumor specimens obtained before and after platinum-based neoadjuvant chemotherapy (NACT) in 86 patients with NSCLC. We analyzed the correlation between the change in PD-L1 tumor proportion score and clinicopathologic characteristics, response to NACT, and survival. **RESULTS:** The PD-L1 tumor proportion score increased in a significant proportion of patients with NSCLC after platinum-based NACT (Wilcoxon signed-rank test, p=0.002). That pattern was consistent across clinically defined subgroups except for patients with partial response to NACT. Tumors from 26 patients (30.2%) were PD-L1–negative before NACT but PD-L1-positive after NACT, whereas the reverse pattern occurred in six patients (7%) (McNemar's test, p<0.001). Increase in PD-L1 tumor proportion score was significantly associated with lack of response to NACT (Fisher exact test, p=0.015). There was a tendency, albeit not statistically significant, for patients with an increase in PD-L1 tumor proportion score to have shorter survival. **CONCLUSION:** Tumor PD-L1 expression increased after platinum-based NACT in a significant proportion of patients with NSCLC. Increase in tumor PD-L1 expression may predict poor clinical outcome.

Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. Gadgeel S1, Peters S2, Mok T3, Shaw AT4, et al. Ann Oncol. 2018 Nov 1;29(11):2214-2222. doi: 10.1093/annonc/mdy405.

BACKGROUND: The phase III ALEX study in patients with treatment-naive advanced anaplastic lymphoma kinase mutation-positive (ALK+) non-small-cell lung cancer (NSCLC) met its primary end point of improved progression-free survival (PFS) with alectinib versus crizotinib. Here, we present detailed central nervous system (CNS) efficacy data from ALEX. **PATIENTS AND METHODS:** Overall, 303 patients aged ≥18 years underwent 1:1 randomization to receive twice-daily doses of alectinib 600 mg or crizotinib 250 mg. Brain imaging was conducted in all patients at baseline and every subsequent 8 weeks. End points (analyzed by subgroup: patients with/without baseline CNS metastases; patients with/without prior radiotherapy) included PFS, CNS objective response rate (ORR), and time to CNS progression. **RESULTS:** In total, 122 patients had Independent Review Committee-assessed baseline CNS metastases (alectinib, n = 64; crizotinib, n = 58), 43 had measurable lesions (alectinib, n = 21; crizotinib, n = 22), and 46 had received prior radiotherapy (alectinib, n = 25; crizotinib, n = 21). Investigator-assessed PFS with alectinib was consistent between patients with baseline CNS metastases [hazard ratio (HR) 0.40, 95% confidence interval (CI): 0.25-0.64] and those without (HR 0.51, 95% CI: 0.33-0.80, P interaction = 0.36). Similar results were seen in patients regardless of prior radiotherapy. Time to CNS progression was significantly longer with alectinib versus crizotinib and comparable between patients with and without baseline CNS metastases (P < 0.0001). CNS ORR was 85.7% with alectinib versus 71.4% with crizotinib in patients who received prior radiotherapy and 78.6% versus 40.0%, respectively, in those who had not. **CONCLUSION:** Alectinib demonstrated superior CNS activity and significantly delayed CNS progression versus crizotinib in patients with previously untreated, advanced ALK+ NSCLC, irrespective of prior CNS disease or radiotherapy.

SELECT: A Phase II Trial of Adjuvant Erlotinib in Patients With Resected Epidermal Growth Factor Receptor-Mutant Non-Small-Cell Lung Cancer. Pennell NA1, Neal JW1, Chaft JE1, et al. J Clin Oncol. 2018 Nov 16:JCO1800131. doi: 10.1200/JCO.18.00131. [Epub ahead of print]
PURPOSE: Given the pivotal role of epidermal growth factor receptor (EGFR) inhibitors in advanced EGFR-mutant non-small-cell lung cancer (NSCLC), we tested adjuvant erlotinib in patients with EGFR-mutant early-stage NSCLC. **MATERIALS AND METHODS:** In this open-label phase II trial, patients with resected stage IA to IIIA (7th edition of the American Joint Committee on Cancer staging system) EGFR-mutant NSCLC were treated with erlotinib 150 mg per day for 2 years after standard adjuvant chemotherapy with or without radiotherapy. The study was designed for 100 patients and powered to demonstrate a primary end point of 2-year disease-free survival (DFS) greater than 85%, improving on historic data of 76%. **RESULTS:** Patients (N = 100) were enrolled at seven sites from January 2008 to May 2012; 13% had stage IA disease, 32% had stage IB disease, 11% had stage IIA disease, 16% had stage IIB disease, and 28% had stage IIIA disease. Toxicities were typical of erlotinib; there were no grade 4 or 5 adverse events. Forty percent of patients required erlotinib dose reduction to 100 mg per day and 16% to 50 mg per day. The intended 2-year course was achieved in 69% of patients. The median follow-up was 5.2 years, and 2-year DFS was 88% (96% stage I, 78% stage II, 91% stage III). Median DFS and overall survival have not been reached; 5-year DFS was 56% (95% CI, 45% to 66%), 5-year overall survival was 86% (95% CI, 77% to 92%). Disease recurred in 40 patients, with only four recurrences during erlotinib treatment. The median time to recurrence was 25 months after stopping erlotinib. Of patients with recurrence who underwent rebiopsy (n = 24; 60%), only one had T790M mutation detected. The majority of patients with recurrence were retreated with erlotinib (n = 26; 65%) for a median duration of 13 months. **CONCLUSION:** Patients with EGFR-mutant NSCLC treated with adjuvant erlotinib had an improved 2-year DFS compared with historic genotype-matched controls. Recurrences were rare for patients receiving adjuvant erlotinib, and patients rechallenged with erlotinib after recurrence experienced durable benefit.

Crizotinib in advanced non-small-cell lung cancer with concomitant ALK rearrangement and c-Met overexpression. Chen RL1, Zhao J2, Zhang XC1, et al. BMC Cancer. 2018 Nov 26;18(1):1171. doi: 10.1186/s12885-018-5078-y.

OBJECTIVE: Crizotinib can target against mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK), which has been considered as a multi-targeted tyrosine kinase inhibitor (TKI). The objective of this study was to explore the efficacy of crizotinib in advanced non-small-cell lung cancer (NSCLC) with concomitant ALK rearrangement and c-Met overexpression. **METHODS:** Totally, 4622 advanced NSCLC patients from two institutes (3762 patients at the Guangdong Lung Cancer Institute from January 2011 to December 2016 and 860 cases at the Perking Cancer Hospital from January 2015 to December 2016) were screened for ALK rearrangement with any method of IHC, RACE-coupled PCR or FISH. C-Met expression was performed by IHC in ALK-rearranged patients, and more than 50% of cells with high staining were defined as c-Met overexpression. The efficacy of crizotinib was explored in the ALK-rearranged patients with or without c-Met overexpression. **RESULTS:** Sixteen patients were identified with c-Met overexpression in 160 ALK-rearranged cases, with the incidence of 10.0% (16/160). A total of 116 ALK-rearranged patients received the treatment of crizotinib. Objective response rate (ORR) was 86.7% (13/15) in ALK-rearranged patients with c-Met overexpression and 59.4% (60/101)in those without c-Met overexpression, P = 0.041. Median PFS showed a trend of superiority in c-Met overexpression group (15.2 versus 11.0 months, P = 0.263). Median overall survival (OS) showed a significant difference for ALK-rearranged patients with c-Met overexpression group of 33.5 months with the hazard ratio (HR) of 3.2. **CONCLUSIONS:** C-Met overexpression co-exists with ALK rearrangement in a small population of advanced NSCLC. There may be a trend of favorable efficacy of crizotinib in such co-altered patients.

Impact of Age on Outcomes with Immunotherapy in Patients with Non-Small Cell Lung Cancer (NSCLC). Lichtenstein M1, Nipp RD1, Muzikansky A1, Goodwin K1, Anderson D1, Newcomb RA1, Gainor JF2. J Thorac Oncol. 2018 Nov 23. pii: S1556-0864(18)33454-3. doi: 10.1016/j.jtho.2018.11.011. [Epub ahead of print]

INTRODUCTION: Immunotherapy has revolutionized the treatment of non-small cell lung cancer (NSCLC), but little is known about the activity of PD-(L)1 blockade across age groups. **METHODS:** We retrospectively evaluated patients with NSCLC initiated on PD-(L)1 inhibitors from 1/2013-7/2017. Medical records and radiographic imaging were reviewed to determine progression-free survival (PFS) and overall survival (OS). We also compared immunotherapy-related toxicities, steroid use, and hospitalizations by age. **RESULTS:** Of 245 patients, 26.1% were age<60 years, 31.4% were age 60-69, 31.0% were age 70-79, and 11.4% were ≥80 years. Median PFS by age group was: age<60, 1.81 months; 60-69, 2.53 months; 70-79, 3.75 months; ≥80, 1.64 months (log-rank p-value=0.055). Median OS by age group was: age<60, 13.01 months; 60-69, 14.56 months; 70-79, 12.92 months; ≥80, 3.62 months (log-rank p-value=0.011). Rates of immunotherapy-related toxicities, steroid use, and hospitalizations did not differ by age. **CONCLUSIONS:** Although the OS and PFS benefits of immunotherapy differ by age, rates of toxicity are similar regardless of age.

The impact of prophylactic cranial irradiation for post-operative patients with limited stage small cell lung cancer. Chen MY1,2, Hu X1, Xu YJ1, Chen M1. Medicine (Baltimore). 2018 Nov;97(44):e13029. doi: 10.1097/MD.0000000000013029.
To evaluate the impact of prophylactic cranial irradiation (PCI) on the prognosis of patients who received definitive surgery for surgically resected small cell lung cancer (SCLC).A retrospective analysis was performed on post-operative SCLC patients treated in Zhejiang Cancer Hospital from January 2003 to December 2015. According to the treatment modality, patients were allocated to PCI group and non-PCI group. Univariate survival analysis was performed by the Kaplan-Meier method. Multivariate survival analysis was performed by a Cox proportional hazards model.A total of 52 patients were included for analysis, among which, 19 patients were in PCI group and 33 were in non-PCI group. Multivariate analysis revealed that PCI (HR=.330; P=.041) was an independently favorable prognostic factor for the overall survival. The median overall survival (OS) time was 32.9 months in PCI group, and 20.4 months in non-PCI group. The 2-year OS rates were 78.0% and 38.0% in PCI and non-PCI group respectively (P=.023). The brain metastasis-free survival (BMFS) rate at 2-year in PCI group was significantly higher than those of non-PCI group (89.0% vs 53.0%, respectively, P=.026). In conclusion, PCI might be suggested for limited SCLC patients who received definitive surgery.

Clinical outcomes of stereotactic body radiotherapy for de novo pulmonary tumors in patients with completely resected early stage non-small cell lung cancer. Zhao Q1, Chen G1, Ye L1, Zeng Z1, Shi S1, He J1. Cancer Manag Res. 2018 Nov 28;10:6391-6398. doi: 10.2147/CMAR.S180345. eCollection 2018.
PURPOSE: Following surgery for early stage non-small-cell lung cancer (NSCLC), de novo pulmonary tumors are common. This study aimed to assess the efficacy, patterns of failure, and toxicity of stereotactic body radiotherapy (SBRT) in the treatment of de novo pulmonary tumors following curative resection of early stage NSCLC. **PATIENTS AND METHODS:** We reviewed the medical data of patients who had received definitive intent SBRT for small lung cancer at Zhongshan Hospital, Fudan University, between June 2011 and December 2017. Patients who had experienced complete resection for prior early stage NSCLC before SBRT were identified for further analysis. Incidences of locoregional recurrence (LR) and distant metastasis (DM) were evaluated using the alternative cumulative incidence competing risk method. The probability of survival was estimated using the Kaplan-Meier method. **RESULTS:** A total of 33 patients with 36 lesions were eligible and included in this study. The median follow-up time was 32 months. Estimated incidences of LR and DM were 37.62% and 15.92%, respectively, at 1 year and 48.02% and 21.23%, respectively, at 2 years. The progression-free survival and overall survival of all patients were 62.40% and 90.30%, respectively, at 1 year and 52.00% and 69.90%, respectively, at 2 years. In all, 26 patients experienced grade 1 SBRT-related toxicity, 11 patients experienced grade 2 SBRT-related toxicity, and three patients experienced grade 3 toxicity. There were no grade 4/5 toxicities or SBRT-related deaths during the follow-up period. **CONCLUSION:** SBRT appears to be a safe and potentially effective alternative therapeutic option for de novo pulmonary tumors following early stage NSCLC radical resection, despite impaired pulmonary reserve.

The use of texture-based radiomics CT analysis to predict outcomes in early-stage non-small cell lung cancer treated with stereotactic ablative radiotherapy. Starkov P1, Aguilera TA2, Golden DI3, et al. Br J Radiol. 2018 Nov 20:20180228. doi: 10.1259/bjr.20180228. [Epub ahead of print]
OBJECTIVE: Stereotactic ablative radiotherapy (SABR) is being increasingly used as a non-invasive treatment for early-stage non-small cell lung cancer (NSCLC). A non-invasive method to estimate

treatment outcomes in these patients would be valuable, especially since access to tissue specimens is often difficult in these cases. **METHODS:** We developed a method to predict survival following SABR in NSCLC patients using analysis of quantitative image features on pre-treatment CT images. We developed a Cox Lasso model based on two-dimensional Riesz wavelet quantitative texture features on CT scans with the goal of separating patients based on survival. **RESULTS:** The median log-rank p-value for 1000 cross-validations was 0.030. Our model was able to separate patients based upon predicted survival. When we added tumor size into the model, the p-value lost its significance, demonstrating that tumor size is not a key feature in the model but rather decreases significance likely due to the relatively small number of events in the dataset. Furthermore, running the model using Riesz features extracted either from the solid component of the tumor or from the ground glass opacity (GGO) component of the tumor maintained statistical significance. However, the p-value improved when combining features from the solid and the GGO components, demonstrating that there are important data that can be extracted from the entire tumor. **CONCLUSIONS:** The model predicting patient survival following SABR in NSCLC may be useful in future studies by enabling prediction of survival-based outcomes using radiomics features in CT images. **ADVANCES IN KNOWLEDGE:** Quantitative image features from NSCLC nodules on CT images have been found to significantly separate patient populations based on overall survival ($p = 0.04$). In the long term, a non-invasive method to estimate treatment outcomes in patients undergoing SABR would be valuable, especially since access to tissue specimens is often difficult in these cases.

Design and validation of a MV/kV imaging-based markerless tracking system for assessing real-time lung tumor motion. Zhang P1, Hunt M1, Telles AB2, et al. Med Phys. 2018 Dec;45(12):5555-5563. doi: 10.1002/mp.13259. Epub 2018 Nov 13.

PURPOSE: Localizing lung tumors during treatment delivery is critical for managing respiratory motion, ensuring tumor coverage, and reducing toxicities. The purpose of this project is to develop a real-time system that performs markerless tracking of lung tumors using simultaneously acquired MV and kV images during radiotherapy of lung cancer with volumetric modulated arc therapy. **METHOD:** Continuous MV/kV images were simultaneously acquired during dose delivery. In the subsequent analysis, a gantry angle-specific region of interest was defined according to the treatment aperture. After removing imaging artifacts, processed MV/kV images were directly registered to the corresponding daily setup cone-beam CT (CBCT) projections that served as reference images. The registration objective function consisted of a sum of normalized cross-correlation, weighted by the contrast-to-noise ratio of each MV and kV image. The calculated 3D shifts of the tumor were corrected by the displacements between the CBCT projections and the planning respiratory correlated CT (RCCT) to generate motion traces referred to a specific respiratory phase. The accuracy of the algorithm was evaluated on both anthropomorphic phantom and patient studies. The phantom consisted of localizing a 3D printed tumor, embedded in a thorax phantom, in an arc delivery. In an IRB-approved study, data were obtained from VMAT treatments of two lung cancer patients with three electromagnetic (Calypso) beacon transponders implanted in airways near the lung tumor. **RESULT:** In the phantom study, the root mean square error (RMSE) between the registered and actual (programmed couch movement) target position was 1.2 mm measured by the MV/kV imaging system, which was smaller compared to the MV or kV alone, of 4.1 and 1.3 mm, respectively. In the patient study, the mean and standard deviation discrepancy between electromagnetic-based tumor position and the MV/KV-markerless approach was -0.2 ± 0.6 mm, 0.2 ± 1.0 mm, and -1.2 ± 1.5 mm along the superior-inferior, anterior-posterior, and left-right directions, respectively; resulting in a 3D displacement discrepancy of 2.0 ± 1.1 mm. Poor contrast around the tumor was the main contribution to registration uncertainties. **CONCLUSION:** The combined MV/kV imaging system can provide real-time 3D localization of lung tumor, with comparable accuracy to the electromagnetic-based system when features of tumors are detectable. Careful design of a registration

algorithm and a VMAT plan that maximizes the tumor visibility are key elements for a successful MV/KV localization strategy.

Doses of radiation to the pericardium, instead of heart, are significant for survival in patients with non-small cell lung cancer. Xue J1, Han C2, Jackson A3, et al. Radiother Oncol. 2018 Nov 8. pii: S0167-8140(18)33553-9. doi: 10.1016/j.radonc.2018.10.029. [Epub ahead of print]
BACKGROUND AND PURPOSE: Higher cardiac dose was associated with worse overall survival in the RTOG0617 study. Pericardial effusion (PCE) is a common cardiac complication of thoracic radiation therapy (RT). We investigated whether doses of radiation to the heart and pericardium are associated with PCE and overall survival in patients treated with thoracic radiation for non-small cell lung cancer (NSCLC). **MATERIALS AND METHODS:** A total of 94 patients with medically inoperable/unresectable NSCLC treated with definitive RT in prospective studies were reviewed for this secondary analysis. Heart and pericardium were contoured consistently according to the RTOG1106 Atlas, with the great vessels and thymus of the upper mediastinal structures included in the upper part of pericardium, only heart chambers included in the heart structure. Clinical factors and dose-volume parameters associated with PCE or survival were identified via Cox proportional hazards modeling. The risk of PCE and death were mapped using DVH atlases. **RESULTS:** Median follow-up for surviving patients was 58 months. The overall rate of PCE was 40.4%. On multivariable analysis, dosimetric factors of heart and pericardium were significantly associated with the risk of PCE. Pericardial V30 and V55 were significantly correlated with overall survival, but presence of PCE and heart dosimetric factors were not. **CONCLUSION:** PCE was associated with both heart and pericardial doses. The significance of pericardial dosimetric parameters, but not heart chamber parameters, on survival suggests the potential significance of radiation damage to the cranial region of pericardium.

Radiation and the heart: systematic review of dosimetry and cardiac endpoints. Niska JR1, Thorpe CS1, Allen SM2, Daniels TB1, Rule WG1, Schild SE1, Vargas CE1, Mookadam F2. Expert Rev Cardiovasc Ther. 2018 Dec;16(12):931-950. doi: 10.1080/14779072.2018.1538785. Epub 2018 Nov 1.
Recent trials in radiotherapy have associated heart dose and survival, inadequately explained by the existing literature for radiation-related late cardiac effects. Authors aimed to review the recent literature on cardiac dosimetry and survival/cardiac endpoints. Areas covered: Systematic review of the literature in the past 10 years (2008-2017) was performed to identify manuscripts reporting both cardiac dosimetry and survival/cardiac endpoints. Authors identified 64 manuscripts for inclusion, covering pediatrics, breast cancer, lung cancer, gastrointestinal diseases (primarily esophageal cancer), and adult lymphoma. Expert commentary: In the first years after radiotherapy, high doses (>40 Gy) to small volumes of the heart are associated with decreased survival from an unknown cause. In the long-term, mean heart dose is associated with a small increased absolute risk of cardiac death. For coronary disease, relative risk increases roughly 10% per Gy mean heart dose, augmented by age and cardiac risk factors. For valvular disease and heart failure, doses >15 Gy substantially increase risk, augmented by anthracyclines. Arrhythmias after radiotherapy are poorly described but may account for the association between upper heart dose and survival. Symptomatic pericardial effusion typically occurs with doses >40 Gy. Close follow-up and mitigation of cardiovascular risk factors are necessary after thoracic radiotherapy.

Treatment completion, treatment compliance and outcomes of old and very old patients treated by dose adapted stereotactic ablative radiotherapy (SABR) for T1-T3N0M0 non-small cell lung cancer. Mihai A1, Milano MT2, Santos A3, Kennedy AM4, Thirion P4, Rock L4, Westrup J3, McDermott R3, Armstrong JG4. Geriatr Oncol. 2018 Nov 10. pii: S1879-4068(18)30288-1. doi: 10.1016/j.jgo.2018.10.011. [Epub ahead of print]

AIM: This is a retrospective single-institution review of the treatment completion and clinical outcomes of patients aged 75 and older, treated with stereotactic ablative body radiotherapy (SABR) for T1-T3 N0 M0 non-small cell lung cancer (NSCLC). **MATERIAL AND METHODS:** From April 2008 to September 2015, 200 patients, aged 75-93, received respiratory-managed, intensity-modulated-based SABR. Dose fractionation was risk-adapted and delivered in 2-3 weekly treatments. Treatment completion, local control, overall survival and treatment-related toxicities were evaluated. **RESULTS:** All patients completed the prescribed SABR course. However, 29 patients required interruption of at least one fraction of SABR and optimization of pain control before continuation of the fraction. Median follow-up was 20.9 months. The median OS was 31.6 months with 1-,3-year survival rates of 80.7%, and 44.4% respectively. Local control at 1- and 3- years were 97.6%, 83.5% respectively. Treatment was well-tolerated. However, there were two (1%) G5 (fatal) toxicities: one acute sudden dyspnoea of unknown cause and one late SABR-related haemoptysis. No statistically significant differences in outcomes/toxicities were observed between old (75-84 years old) and very old patients (>85 years old). **CONCLUSIONS:** Old and very old patients can successfully complete SABR for NSCLC, with good local control, survival and acceptable toxicity. Old patients might require increased supportive care for successful treatment delivery.

Clinical outcomes following advanced respiratory motion management (respiratory gating or dynamic tumor tracking) with stereotactic body radiation therapy for stage I non-small-cell lung cancer. Aridgides P1, Nsouli T1, Chaudhari R1, et al. Lung Cancer (Auckl). 2018 Nov 5;9:103-110. doi: 10.2147/LCTT.S175168. eCollection 2018.
PURPOSE: To report the outcomes of stereotactic body radiation therapy (SBRT) for stage I non-small-cell lung cancer (NSCLC) according to respiratory motion management method. **METHODS:** Patients with stage I NSCLC who received SBRT from 2007 to 2015 were reviewed. Computed tomography (CT) simulation with four-dimensional CT was performed for respiratory motion assessment. Tumor motion >1 cm in the craniocaudal direction was selectively treated with advanced respiratory management: either respiratory gating to a pre-specified portion of the respiratory cycle or dynamic tracking of an implanted fiducial marker. Comparisons were made with internal target volume approach, which treated all phases of respiratory motion. **RESULTS:** Of 297 patients treated with SBRT at our institution, 51 underwent advanced respiratory management (48 with respiratory gating and three with tumor tracking) and 246 underwent all-phase treatment. Groups were similarly balanced with regard to mean age (P=0.242), tumor size (P=0.315), and histology (P=0.715). Tumor location in the lower lung lobes, as compared to middle or upper lobes, was more common in those treated with advanced respiratory management (78.4%) compared to all-phase treatment (25.6%, P<.0001). There were 17 local recurrences in the treated lesions. Kaplan-Meier analyses showed that there were no differences with regard to mean time to local failure (91.5 vs 98.8 months, P=0.56), mean time to any failure (73.2 vs 78.7 months, P=0.73), or median overall survival (43.3 vs 45.5 months, P=0.56) between patients who underwent advanced respiratory motion management and all-phase treatment. **CONCLUSION:** SBRT with advanced respiratory management (the majority with respiratory gating) showed similar efficacy to all-phase treatment approach for stage I NSCLC.

SMALL CELL LUNG CANCER - SCLC

Phase II Study of Weekly Amrubicin for Refractory or Relapsed Small Cell Lung Cancer. Yoshioka H1,2,3, Kogure Y4,5, Ando M6, Kitagawa C4, Iwasaku M7,8, Niwa T7,9, Saka H4. In Vivo. 2018 Nov-Dec;32(6):1581-1586. doi: 10.21873/invivo.11417.

BACKGROUND: Amrubicin hydrochloride is administered as second- or third-line therapy for small cell lung cancer, and is known to cause severe myelotoxicity. This study evaluated the efficacy and safety of weekly amrubicin for refractory/relapsed small cell lung cancer. **PATIENTS AND METHODS:** A single-arm, open-label, multicenter, phase II study of weekly amrubicin was performed in 21 patients at seven centers in Japan from 2012 through 2015. **RESULTS:** A partial response (PR) was noted in one out of the first 18 patients. The study was terminated early according to the termination criteria in the protocol. In total, the response rate was 19% (no complete responses and four PRs) and the disease control rate was 81% (17/21). Median overall survival was 288 days (95% confidence interval(CI)=208-424 days), while median progression-free survival was 113 days (95% CI=45-202 days). **CONCLUSION:** This study failed to demonstrate any efficacy of weekly amrubicin for refractory/ relapsed small cell lung cancer.

Impact of prophylactic cranial irradiation on pattern of brain metastases as a first recurrence site for limited-disease small-cell lung cancer. Nakamura M1, Onozawa M1, Motegi A1, et al. J Radiat Res. 2018 Nov 1;59(6):767-773. doi: 10.1093/jrr/rry066.
This study sought to evaluate the impact of prophylactic cranial irradiation (PCI) on the pattern of brain recurrence after radical treatment in patients with limited-disease small-cell lung cancer (LD-SCLC). Patients treated with radiotherapy and chemotherapy between January 2006 and December 2014 at a single institution were retrospectively examined. Radiotherapy was performed using accelerated hyperfractionated radiotherapy (twice daily, 45 Gy in 30 fractions) or conventional fractionated radiotherapy (once daily, 50 Gy in 25 fractions). The chemotherapy regimen consisted of intravenous platinum-etoposide. A total of 162 patients were included and the median follow-up duration was 38 months. Ninety-three patients underwent PCI, and the 3-year overall survival (OS) rates were 14% among patients without PCI and 41% among those with PCI ($P < 0.001$). The frequency of brain metastases as a first recurrence site (BMFR) was significantly lower among patients who underwent PCI, compared with those who did not ($P = 0.002$). The median time to the l of BMFR was significantly shorter among patients without PCI than among those with PCI ($P = 0.012$). In addition, 68% of the BMFR patients who did not undergo PCI exhibited five or more lesions, while only 12% of BMFR patients who did undergo PCI exhibited five or more lesions ($P < 0.001$). PCI had a significant positive impact on patient prognosis after radical treatment for LD-SCLC, and the difference in the number of, and time to the appearance of, BMFR between patients treated with PCI and those treated without PCI might affect the clinical outcomes.

Paraneoplastic syndrome as the presentation of limited stage small cell carcinoma. Nikoomanesh K1, Choi J2, Arabian S2. BMC Pulm Med. 2018 Nov 14;18(1):169. doi: 10.1186/s12890-018-0729-y.
BACKGROUND: Small cell lung carcinoma (SCLC) is one of the deadliest forms of lung cancer due to its poor prognosis upon diagnosis, rapid doubling time, and affinity for metastasis. As 60-70% of patients with SCLC have disseminated disease upon presentation, it is imperative to determine the extent of disease burden for treatment. As a neuroendocrine carcinoma, clinicians must pay close attention to abnormal findings in a smoker that could lead to earlier diagnosis and better prognostication. **CASE PRESENTATION:** A 64 year-old 20-pack year smoker presented to the emergency department with nausea and vomiting for 3 days. No inciting events were elicited. History and review of symptoms were negative including symptoms most-commonly associated with malignancy such as fevers and weight loss. He also denied any pulmonary symptoms. Physical examination was benign except for right lung end-expiratory wheezing. Our patient was clinically euvolemic. Initial blood laboratories showed a sodium 110, serum osmolarity 227, and urine osmolarity of 579. Fluid restriction led to normalization of his sodium and resolution of nausea & vomiting. Chest radiography was obtained to follow-up on the wheezing, which was read as no acute cardiopulmonary disease by radiology. Due to high suspicion of

SIADH from malignancy, a CT of the chest was performed which showed a conglomerate of nodules and opacities in the right upper lobe. Biopsy revealed SCLC. At outpatient follow-up, patient had a PET-CT showing one active mediastinal lymph node as the only site of metastasis. He received three round of chemotherapy, chest and prophylactic cranial radiation, and deemed in remission by oncology.
DISCUSSION AND CONCLUSIONS: Due to its affinity for metastases, 70% of patients with SCLC present with symptoms related to the spread of cancer to affected organ systems. Given the aggressive nature of this disease, screening measures have been implemented to help diagnose limited stage SCLC. Unfortunately, in our patient and many others, screening guidelines may fail to identify appropriate patients to scan. It is therefore imperative to use our clinical index of suspicion and identify any early presentations (including paraneoplastic syndromes) which may tip off the beginning stages of SCLC. This could improve survival rates by up to 45%.

PALLIATIVE AND SUPPORTIVE CARE

Palliative Care in Lung Cancer: When to Start. Bhattacharya P1, Dessain SK2, Evans TL3,4. Author information: Curr Oncol Rep. 2018 Nov 9;20(11):90. doi: 10.1007/s11912-018-0731-9.
PURPOSE OF REVIEW: Despite recent advances in the care of patients with advanced non-small cell lung cancer (NSCLC), significant morbidity and mortality remains. Symptoms caused by the cancer and its treatments can be profoundly debilitating. Palliative care aims to reduce this burden. In this review, we discuss the definition, purpose, benefits, and optimal timing of palliative care in advanced NSCLC.
RECENT FINDINGS: Several studies evaluating the value of early palliative care for patients with advanced NSCLC and other advanced malignancies have identified benefits for patients, caregivers, and health systems. For patients with advanced NSCLC, introduction of palliative care early in the disease course improves quality of life and even overall survival. Early institution of palliative care should become standard of care for patients with advanced NSCLC.

Clinical utility of portable electrophysiology to measure fatigue in treatment-naïve non-small cell lung cancer. O'Connor B1,2, Markicevic M3,4, Newman L3,4, Poduval RK3,4, Tiernan E5, Hanrahan E6, Cuffe S7, Reilly RB3,4,8, Walsh D9,8,10. Support Care Cancer. 2018 Nov 22. doi: 10.1007/s00520-018-4542-1. [Epub ahead of print]
PURPOSE: Cancer-related fatigue (CRF) biology remains poorly understood. Responsible mechanisms may be central or peripheral and originate anywhere from the brain to muscle fiber. Objective measurement is complex and previously limited to specialized laboratories. Portable electroencephalography (EEG) and electromyography (EMG) may enhance objective measurement. This study evaluated the feasibility and acceptability of portable EMG-EEG in CRF assessment. **METHODS:** A prospective observational feasibility study compared ten outpatients with inoperable, treatment-naïve non-small cell lung cancer and CRF to ten healthy volunteers. All completed a sustained isometric hand-grip contraction at 30% maximal level until self-perceived exhaustion. 128-channel EEG and 2-channel EMG signals of forearm muscles were recorded. Device acceptability was evaluated by questionnaire. **RESULTS:** The task was evaluated in two stages; first and last 20 s. CRF cohort perceived exhaustion earlier than volunteers (mean 137 ± 76 s vs 208 ± 51 s). As fatigue progressed, EMG amplitude increased significantly (CRF $p = 0.02$; volunteers: $p = 0.04$) in both groups as did EMG beta band power (CRF $p = 0.008$; volunteers: $p = 0.006$). The increase was significantly less in CRF (amplitude $p = 0.032$; beta power: $p = 0.014$). EEG beta band power in the contralateral motor cortex increased significantly (CRF $p = 0.03$; volunteers: $p = 0.019$) in both cohorts but to greater extent ($p = 0.024$) in CRF. One hundred percent device acceptability was reported. **CONCLUSIONS:** A laboratory-based evaluation was successfully adapted to the outpatient setting during routine visits. High acceptability supports clinical

utility. In CRF, a higher degree of cortical activation was required to drive a much lower level of muscle performance. This suggests impairment of both central and peripheral mechanisms in CRF.

Early Skeletal Muscle Loss in Non-Small Cell Lung Cancer Patients Receiving Chemoradiation and Relationship to Survival. Kiss N1,2,3, Beraldo J4, Everitt S4,5,6. Support Care Cancer. 2018 Nov 26. doi: 10.1007/s00520-018-4563-9. [Epub ahead of print]
PURPOSE: Sarcopenia is associated with reduced survival in cancer. Currently, data on sarcopenia at presentation and muscle loss throughout treatment are unknown in patients receiving chemoradiation therapy (CRT) for non-small cell lung cancer (NSCLC). This study evaluated skeletal muscle changes in NSCLC patients receiving CRT and relationship with survival. **METHODS:** Secondary analysis of 41 patients with NSCLC treated with CRT assessed for skeletal muscle area and muscle density by computed tomography pre-treatment and 3 months post-treatment. Images at week 4 of treatment were available for 32 (78%) patients. Linear mixed models were applied to determine changes in skeletal muscle over time and related to overall survival using Kaplan-Meier plots. **RESULTS:** Muscle area and muscle density decreased significantly by week 4 of CRT (- 6.6 cm2, 95% CI - 9.7 to - 3.1, $p < 0.001$; - 1.3 HU, 95% CI - 1.9 to - 0.64, $p < 0.001$, respectively), with minimal change between week 4 of CRT and 3 months post-CRT follow-up (- 0.2 cm2, 95% CI - 3.6-3.1, $p = 0.91$; - 0.27, 95% CI - 0.91-0.36, $p = 0.36$, respectively). Sarcopenia was present in 25 (61%) and sarcopenic obesity in 6 (14%) of patients prior to CRT, but not associated with poorer survival. Median survival was shorter in patients with low muscle density prior to treatment although not statistically significant (25 months + 8.3 vs 53 months + 13.0, log-rank $p = 0.17$). **CONCLUSION:** Significant loss of muscle area and muscle density occurs in NSCLC patients early during CRT. A high proportion of patients are sarcopenic prior to CRT; however, this was not significantly associated with poorer survival.

NSAIDs may prevent EGFR-TKI-related skin rash in non-small cell lung cancer patients
Iimura Y, Shimomura H, Yasu T, Imanaka K, Ogawa R, Ito A, Suzuki K, Yamaguchi G, Kawasaki N, Konaka C. Int J Clin Pharmacol Ther. 2018 Nov;56(11):551-554. doi: 10.5414/CP203323.
OBJECTIVES: Skin rash is a common adverse event induced by epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI). Here, we aimed to predict factors that reduce EGFR-TKI-related skin rash. **MATERIALS AND METHODS:** We conducted a single-center, retrospective study to predict factors that reduce skin rash in patients undergoing treatment for non-small cell lung cancer (NSCLC) with EGFR-TKIs using Cox proportional hazards model. **RESULTS:** Cox proportional hazard analysis revealed that coadministration of non-steroidal anti-inflammatory drug (NSAID) had protective effects against rash. Steroid coadministration showed a trend to being effective in reducing rash. **ONCLUSION:** NSAIDs may be useful in preventing EGFR-TKI-related skin rash.

Prognostic Value of Patient Knowledge of Cancer on Quality of Life in Advanced Lung Cancer During Chemotherapy. Adamowicz K1, Janiszewska J2, Lichodziejewska-Niemierko M2,3. J Cancer Educ. 2018 Nov 12. doi: 10.1007/s13187-018-1444-3. [Epub ahead of print]
The purpose of the study was to assess the impact of cancer knowledge and patient's lifestyle on QOL and the relationship between QOL and various environmental factors in patients with non-small-cell lung cancer treated with chemotherapy. The study group consisted of 129 patients with metastatic lung cancer patients treated between May 2010 and December 2015 in two centres. The knowledge of cancer and their lifestyle was rated by method of diagnostic survey, using the Behavioral Health Inventory IZZ by Prof. Juczyński. We sought factors affecting to response to treatment, overall survival and quality of life. The general level of knowledge of cancer and the level of health behaviours was low. Ninety percent of lung cancer patients were smokers. The average age of the study group was 64 years. Eighty-nine patients received chemotherapy with cisplatin, 28 schemes containing carboplatin, 6 inhibitors of EGFR tyrosine

kinase, and 6 vinorelbine or gemcitabine monotherapy. Complete regression was observed in 2 patients, partial response in 33 patients (26%), stable disease in 51 (40%) and 54 (42%) patients had progression. In multivariate analysis, significant effects on survival were performance status, schemes of treatment and response to treatment. Quality of life before and after treatment did not differ from each other. We found impact on quality of life: performance status, response to treatment and knowledge of cancer and lifestyle. The level of knowledge of oncological patients and their lifestyle observed in clinical practice are associated with QOL.

COMPLEMENTARY & ALTERNATIVE THERAPY

Study of the anti-allergic and anti-inflammatory activity of Brachychiton rupestris and Brachychiton discolor leaves (Malvaceae) using in vitro models. Thabet AA1, Youssef FS1, Korinek M2,3,4,5, et al. BMC Complement Altern Med. 2018 Nov 9;18(1):299. doi: 10.1186/s12906-018-2359-6.
BACKGROUND: Brachychiton rupestris and Brachychiton discolor (Malvaceae) are ornamental trees native to Australia. Some members of Brachychiton and its highly related genus, Sterculia, are employed in traditional medicine for itching, dermatitis and other skin diseases. However, scientific studies on these two genera are scarce. Aiming to reveal the scientific basis of the folk medicinal use of these plants, the cytotoxicity, anti-inflammatory and anti-allergic activities of Brachychiton rupestris and Brachychiton discolor leaves extracts and fractions were evaluated. Also, phytochemical investigation of B. rupestris was performed to identify the compounds exerting the biological effect. **METHODS:** Extracts as well as fractions of Brachychiton rupestris and Brachychiton discolor were tested for their cytotoxicity versus hepatoma HepG2, lung A549, and breast MDA-MB-231 cancer cell lines. Assessment of the anti-allergic activity was done using degranulation assay in RBL-2H3 mast cells. Anti-inflammatory effect was tested by measuring the suppression of superoxide anion production as well as elastase release in fMLF/CB-induced human neutrophils. Phytochemical investigation of the n-hexane, dichloromethane and ethyl acetate fractions of B. rupestris was done using different chromatographic and spectroscopic techniques. **RESULTS:** The tested samples showed no cytotoxicity towards the tested cell lines. The nonpolar fractions of both B. rupestris and B. discolor showed potent anti-allergic potency by inhibiting the release of β-hexosaminidase. The dichloromethane fraction of both species exhibited the highest anti-inflammatory activity by suppressing superoxide anion generation and elastase release with IC50 values of 2.99 and 1.98 μg/mL, respectively for B. rupestris, and 0.78 and 1.57 μg/mL, respectively for B. discolor. Phytochemical investigation of various fractions of B. rupestris resulted in the isolation of β-amyrin acetate (1), β-sitosterol (2) and stigmasterol (3) from the n-hexane fraction. Scopoletin (4) and β-sitosterol-3-O-β-D-glucoside (5) were obtained from the dichloromethane fraction. Dihydrodehydrodiconiferyl alcohol 4-O-β-D-glucoside (6) and dihydrodehydrodiconiferyl alcohol 9-O-β-D-glucoside (7) were separated from the ethyl acetate fraction. Scopoletin (4) showed anti-allergic and anti-inflammatory activity. **CONCLUSIONS:** It was concluded that the nonpolar fractions of both Brachychiton species exhibited anti-allergic and anti-inflammatory activities.

Maintenance Chemotherapy With Chinese Herb Medicine Formulas vs. With Placebo in Patients With Advanced Non-small Cell Lung Cancer After First-Line Chemotherapy: A Multicenter, Randomized, Double-Blind Trial. Wang Q1, Jiao L1,2, Wang S3, et al. Front Pharmacol. 2018 Nov 6;9:1233. doi: 10.3389/fphar.2018.01233. eCollection 2018.
BACKGROUND: Chinese Herb Medicine Formulas (CHMF) was reported to improve the quality of life (QoL) in advanced NSCLC patients. The present study was designed to investigate whether maintenance chemotherapy plus CHMF in patients would improve QoL and progression-free survival (PFS).
METHODS: Seventy-one patients were enrolled from 8 medical centers in China, and were randomly

assigned to a maintenance chemotherapy plus CHMF group (n = 35) or a maintenance chemotherapy plus placebo group (n = 36). The outcome measures included PFS, Karnofsky performance status (KPS) scores, QoL (assessed with the lung cancer symptom scale (LCSS) questionnaire), and adverse events (AEs). **RESULTS:** Patients in the CHMF group showed significant improvements in median PFS (HR = 0.55, 95% CI 0.28-0.88, P = 0.019), KPS scores (P = 0.047), fatigue (cycle [C] 3: P = 0.03), interference with daily activities (C3: P = 0.04) and dyspnea (C2: P = 0.03) compared with patients in the placebo group. Compared with the placebo group, the incidence of AEs decreased in the CHMF group, including loss of appetite (C2: P = 0.011, C4: P = 0.004) and dry mouth (C4: P = 0.011). **CONCLUSION:** The essential finding of our study is that maintenance chemotherapy combined with CHMF may prolong PFS, relieve symptoms, improve QoL and alleviate the side effects.

Investigate the mechanisms of Chinese medicine Fuzhengkangai towards EGFR mutation-positive lung adenocarcinomas by network pharmacology. Bing Z1,2,3, Cheng Z1,2, Shi D4, et al. BMC Complement Altern Med. 2018 Nov 6;18(1):293. doi: 10.1186/s12906-018-2347-x.
BACKGROUND: Chinese traditional herbal medicine Fuzhengkangai (FZKA) formulation combination with gefitinib can overcome drug resistance and improve the prognosis of lung adenocarcinoma patients. However, the pharmacological and molecular mechanisms underlying the active ingredients, potential targets, and overcome drug resistance of the drug are still unclear. Therefore, it is necessary to explore the molecular mechanism of FZKA. **METHODS:** A systems pharmacology and bioinformatics-based approach was employed to investigate the molecular pathogenesis of EGFR-TKI resistance with clinically effective herb formula. The differential gene expressions between EGFR-TKI sensitive and resistance cell lines were calculated and used to find overlap from targets as core targets. The prognosis of core targets was validated from the cancer genome atlas (TCGA) database by Cox regression. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment is applied to analysis core targets for revealing mechanism in biology. **RESULTS:** The results showed that 35 active compounds of FZKA can interact with eight core targets proteins (ADRB2, BCL2, CDKN1A, HTR2C, KCNMA1, PLA2G4A, PRKCA and LYZ). The risk score of them were associated with overall survival and relapse free time (HR = 6.604, 95% CI: 2.314-18.850; HR = 5.132, 95% CI: 1.531-17.220). The pathway enrichment suggested that they involved in EGFR-TKI resistance and non-small cell lung cancer pathways, which directly affect EGFR-TKI resistance. The molecular docking showed that licochalcone a and beta-sitosterol can closely bind two targets (BCL2 and PRKCA) that involved in EGFR-TKI resistance pathway. **CONCLUSIONS:** This study provided a workflow for understanding mechanism of CHM for against drug resistance.

MISCELLANEOUS WORKS

Surveillance for Cancers Associated with Tobacco Use - United States, 2010-2014. Gallaway MS1,2, Henley SJ1, Steele CB1, et al. MMWR Surveill Summ. 2018 Nov 2;67(12):1-42. doi: 10.15585/mmwr.ss6712a1.
PROBLEM/CONDITION: Tobacco use is the leading preventable cause of cancer, contributing to at least 12 types of cancer, including acute myeloid leukemia (AML) and cancers of the oral cavity and pharynx; esophagus; stomach; colon and rectum; liver; pancreas; larynx; lung, bronchus, and trachea; kidney and renal pelvis; urinary bladder; and cervix. This report provides a comprehensive assessment of recent tobacco-associated cancer incidence for each cancer type by sex, age, race/ethnicity, metropolitan county classification, tumor characteristics, U.S. census region, and state. These data are important for initiation, monitoring, and evaluation of tobacco prevention and control measures. **PERIOD COVERED:** 2010-2014. **DESCRIPTION OF SYSTEM:** Cancer incidence data from CDC's National Program of Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology, and End

Results program were used to calculate average annual age-adjusted incidence rates for 2010-2014 and trends in annual age-adjusted incidence rates for 2010-2014. These cancer incidence data cover approximately 99% of the U.S. **POPULATION:** This report provides age-adjusted cancer incidence rates for each of the 12 cancer types known to be causally associated with tobacco use, including liver and colorectal cancer, which were deemed to be causally associated with tobacco use by the U.S. Surgeon General in 2014. Findings are reported by demographic and geographic characteristics, percentage distributions for tumor characteristics, and trends in cancer incidence by sex. **RESULTS:** During 2010-2014, approximately 3.3 million new tobacco-associated cancer cases were reported in the United States, approximately 667,000 per year. Age-adjusted incidence rates ranged from 4.2 AML cases per 100,000 persons to 61.3 lung cancer cases per 100,000 persons. By cancer type, incidence rates were higher among men than women (excluding cervical cancer), higher among non-Hispanics than Hispanics (for all cancers except stomach, liver, kidney, and cervical), higher among persons in nonmetropolitan counties than those in metropolitan counties (for all cancers except stomach, liver, pancreatic, and AML), and lower in the West than in other U.S. census regions (all except stomach, liver, bladder, and AML). Compared with other racial/ethnic groups, certain cancer rates were highest among whites (oral cavity and pharyngeal, esophageal, bladder, and AML), blacks (colon and rectal, pancreatic, laryngeal, lung and bronchial, cervical, and kidney), and Asians/Pacific Islanders (stomach and liver). During 2010-2014, the rate of all tobacco-associated cancers combined decreased 1.2% per year, influenced largely by decreases in cancers of the larynx (3.0%), lung (2.2%), colon and rectum (2.1%), and bladder (1.3%). **INTERPRETATION:** Although tobacco-associated cancer incidence decreased overall during 2010-2014, the incidence remains high in several states and subgroups, including among men, whites, blacks, non-Hispanics, and persons in nonmetropolitan counties. These disproportionately high rates of tobacco-related cancer incidence reflect overall demographic patterns of cancer incidence in the United States and also reflect patterns of tobacco use. **PUBLIC HEALTH ACTION:** Tobacco-associated cancer incidence can be reduced through prevention and control of tobacco use and comprehensive cancer-control efforts focused on reducing cancer risk, detecting cancer early, and better assisting communities disproportionately affected by cancer. Ongoing surveillance to monitor cancer incidence can identify populations with a high incidence of tobacco-associated cancers and evaluate the effectiveness of tobacco control programs and policies. Implementation research can be conducted to achieve wider adoption of existing evidence-based cancer prevention and screening programs and tobacco control measures, especially to reach groups with the largest disparities in cancer rates.

Impact of Perceived Stigma in People Newly Diagnosed With Lung Cancer: A Cross-Sectional Analysis. Rose S1, Kelly B1, Boyes A1, Cox M1, Palazzi K2, Paul C1. Oncol Nurs Forum. 2018 Nov 1;45(6):737-747. doi: 10.1188/18.ONF.737-747.

OBJECTIVES: To investigate perceived stigma and its possible associations with treatment expectations and preferences in newly diagnosed patients with lung cancer. **SAMPLE & SETTING:** 274 patients with lung cancer diagnosed in the previous four months at oncology and respiratory outpatient clinics in Australia. **METHODS & VARIABLES:** Participants completed a self-report survey about perceived lung cancer stigma and treatment expectations and preferences. **RESULTS:** A mean perceived stigma score of 52 of a possible 124 was reported, which is lower than scores reported in other studies using the same measure; the current study determined that perceived lung cancer stigma was observed less frequently. Significantly higher scores were observed in participants who were younger or who had a history of smoking. Perceived lung cancer stigma was significantly related to treatment expectations. No relationship was found between perceived lung cancer stigma and treatment preferences. **IMPLICATIONS FOR NURSING:** Healthcare providers are in a key position to provide support and communicate empathetically with patients to minimize potential stigma experiences.

Primary care providers' views on a future lung cancer screening program. **(Canada)** O'Brien MA1, Llovet D2,3, Sullivan F1,4,5,6, Paszat L4,7,8. Fam Pract. 2018 Nov 5. doi: 10.1093/fampra/cmy099. [Epub ahead of print]

BACKGROUND: The National Lung Screening Trial demonstrated that screening with low-dose computed tomography significantly reduces mortality from lung cancer in high-risk individuals. **OBJECTIVE:** To describe the role preferences and information needs of primary care providers (PCPs) in a future organized lung cancer screening program. **METHODS:** We purposively sampled PCPs from diverse health regions of Ontario and from different practice models including family health teams and community health centres. We also recruited family physicians with a leadership role in cancer screening. We used focus groups and a nominal group process to identify informational priorities. Two analysts systematically applied a coding scheme to interview transcripts. **RESULTS:** Four groups were held with 34 providers and administrative staff [28 (82%) female, 21 (62%) physicians, 7 (20%) other health professionals and 6 (18%) administrative staff]. PCPs and staff were generally positive about a potential lung cancer screening program but had variable views on their involvement. Informational needs included evidence of potential benefits and harms of screening. Most providers preferred that a new program be modelled on positive features of an existing breast cancer screening program. Lung cancer screening was viewed as a new opportunity to counsel patients about smoking cessation. **CONCLUSIONS:** The development of a future lung cancer screening program should consider the wide variability in the roles that PCPs preferred. An explicit link to existing smoking cessation programs was seen as essential. As providers had significant information needs, learning materials and opportunities should be developed with them.

Disparities in the Diagnosis and Treatment of Lung Cancer among People with Disabilities. Shin DW1, Cho JH2, Noh JM3, Han H4, Han K5, Park SH5, Kim SY6, Park JH7, Park JH8, Kawachi I9. .J Thorac Oncol. 2018 Nov 16. pii: S1556-0864(18)33407-5. doi: 10.1016/j.jtho.2018.10.158. [Epub ahead of print]

INTRODUCTION: Potential disparities in the diagnosis, treatment, and survival of patients with lung cancer with and without disabilities have rarely been investigated. **METHODS:** We conducted a retrospective cohort study with a data set linking the Korean National Health Service database, disability registration data, and Korean Central Cancer Registry data. A total of 13,591 people with disabilities in whom lung cancer had been diagnosed and 43,809 age- and sex-matched control subjects in whom lung cancer had been diagnosed were included. **RESULTS:** Unknown stage was more common in people with severe disabilities (13.1% versus 10.3%), especially those with a communication (14.2%) or mental/cognitive disability (15.7%). People with disabilities were less likely to undergo a surgical procedure (adjusted OR [aOR] = 0.82, 95% confidence interval [CI]: 0.77-0.86), chemotherapy (aOR = 0.80, 95% CI: 0.77-0.84), or radiotherapy (aOR = 0.92, 95% CI: 0.88-0.96). This higher likelihood was more evident for people with severe communication impairment (aORs of 0.46 for surgery and 0.64 for chemotherapy) and severe brain/mental impairment (aORs 0.39 for surgery, 0.47 for chemotherapy, and 0.49 for radiotherapy). Patients with disabilities had a slightly higher overall mortality than did people with no disability (adjusted hazard ratio = 1.08, 95% CI: 1.06-1.11), especially in the group with a severe disability (a hazard ratio = 1.20, 95% CI: 1.16-1.24). **CONCLUSIONS:** Patients with lung cancer and disabilities, especially severe ones, underwent less staging work-up and treatment even though their treatment outcomes were only slightly worse than those of people without a disability. Although some degree of disparity might be attributed to reasonable clinical judgement, unequal clinical care for people with communication and brain/mental disabilities suggests unjustifiable disability-related barriers that need to be addressed.

Alcohol consumption and lung cancer risk: A pooled analysis from the International Lung Cancer Consortium and the SYNERGY study. Brenner DR1, Fehringer G2, Zhang ZF3, et al. Cancer Epidemiol. 2018 Nov 13;58:25-32. doi: 10.1016/j.canep.2018.10.006. [Epub ahead of print]
BACKGROUND: There is inadequate evidence to determine whether there is an effect of alcohol consumption on lung cancer risk. We conducted a pooled analysis of data from the International Lung Cancer Consortium and the SYNERGY study to investigate this possible association by type of beverage with adjustment for other potential confounders. **METHODS:** Twenty-one case-control studies and one cohort study with alcohol-intake data obtained from questionnaires were included in this pooled analysis (19,149 cases and 362,340 controls). Adjusted odds ratios (OR) or hazard ratios (HR) with corresponding 95% confidence intervals (CI) were estimated for each measure of alcohol consumption. Effect estimates were combined using random or fixed-effects models where appropriate. Associations were examined for overall lung cancer and by histological type. **RESULTS:** We observed an inverse association between overall risk of lung cancer and consumption of alcoholic beverages compared to non-drinkers, but the association was not monotonic. The lowest risk was observed for persons who consumed 10-19.9 g/day ethanol (OR vs. non-drinkers = 0.78; 95% CI: 0.67, 0.91), where 1 drink is approximately 12-15 g. This J-shaped association was most prominent for squamous cell carcinoma (SCC). The association with all lung cancer varied little by type of alcoholic beverage, but there were notable differences for SCC. We observed an association with beer intake (OR for ≥20 g/day vs nondrinker = 1.42; 95% CI: 1.06, 1.90). **CONCLUSIONS:** Whether the non-monotonic associations we observed or the positive association between beer drinking and squamous cell carcinoma reflect real effects await future analyses and insights about possible biological mechanisms.

A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors. Verma V1, Sprave T2, Haque W3, Simone CB 2nd4, Chang JY5, Welsh JW5, Thomas CR Jr6. J Immunother Cancer. 2018 Nov 23;6(1):128. doi: 10.1186/s40425-018-0442-7.
BACKGROUND: Escalating healthcare costs are necessitating the practice of value-based oncology. It is crucial to critically evaluate the economic impact of influential but expensive therapies such as immune checkpoint inhibitors (ICIs). To date, no systematic assessment of the cost-effectiveness (CE) of ICIs has been performed. **METHODS:** PRISMA-guided systematic searches of the PubMed database were conducted. Studies of head/neck (n = 3), lung (n = 5), genitourinary (n = 4), and melanoma (n = 8) malignancies treated with ICIs were evaluated. The reference willingness-to-pay (WTP) threshold was $100,000/QALY. **RESULTS:** Nivolumab was not cost-effective over chemotherapy for recurrent/metastatic head/neck cancers (HNCs). For non-small cell lung cancer (NSCLC), nivolumab was not cost-effective for a general cohort, but increased PD-L1 cutoffs resulted in CE. Pembrolizumab was cost-effective for both previously treated and newly-diagnosed metastatic NSCLC. For genitourinary cancers (GUCs, renal cell and bladder cancers), nivolumab and pembrolizumab were not cost-effective options. Regarding metastatic/unresected melanoma, ipilimumab monotherapy is less cost-effective than nivolumab, nivolumab/ipilimumab, and pembrolizumab. The addition of ipilimumab to nivolumab monotherapy was not adequately cost-effective. Pembrolizumab or nivolumab monotherapy offered comparable CE profiles. **CONCLUSIONS:** With limited data and from the reference WTP, nivolumab was not cost-effective for HNCs. Pembrolizumab was cost-effective for NSCLC; although not the case for nivolumab, applying PD-L1 cutoffs resulted in adequate CE. Most data for nivolumab and pembrolizumab in GUCs did not point towards adequate CE. Contrary to ipilimumab, either nivolumab or pembrolizumab is cost-effective for melanoma. Despite these conclusions, it cannot be overstated that careful patient selection is critical for CE. Future publication of CE investigations and clinical trials (along with longer follow-up of existing data) could substantially alter conclusions from this analysis.