Caring Ambassadors Lung Cancer Program
Literature Review, July 2018

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Curcumin inhibits proliferation and enhances apoptosis in A549 cells by downregulating lncRNA UCA1. Wang WH, Chen J, Zhang BR, Lu SJ, Wang F, Peng L, Dai JH, Sun YZ. Pharmazie. 2018 Jul 1;73(7):402-407. doi: 10.1691/ph.2018.8402.

OBJECTIVE: Curcumin has been reported to possess anti-tumor effects on multiple cancers, including lung cancer. However, the mechanisms of its anti-tumor effect on lung cancer have not been fully elucidated. Our study attempted to identify the effect of curcumin on A549 cells and further explore the potential mechanism. **METHODS:** Different concentrations of curcumin were exposed to A549 cells for 24 h and cell viability was measured by CCK-8 assay. The expression of UCA1 was overexpressed in A549 cells by transfection with pEX-UCA1. Cell proliferation was determined by BrdU staining and assessing the expression of CyclinD1 using western blot and RT-PCR assay. Apoptotic cells were measured by flow cytometry assay. Western blot was performed to assess the expression of apoptosis-related, Wnt and mTOR pathways-related factors. **RESULTS:** Curcumin incubation dramatically reduced viability of A549 cells in a dosage-dependent manner. Curcumin (0.6 μM) significantly reduced BrdU+-positive cells, declined the expression of CyclinD1, and enhanced cell apoptosis. Interestingly, we found that curcumin inhibited the expression of UCA1 and UCA1 overexpression abolished the effect of curcumin on cell apoptosis. In addition, we also found that curcumin inhibited Wnt and mTOR pathways through down-regulation of UCA1. **CONCLUSION:** We demonstrated that curcumin inhibited the growth of A549 cells through downregulation of UCA1, which might provide new insight for the treatment of lung cancer.

Study of EGCG induced apoptosis in lung cancer cells by inhibiting PI3K/Akt signaling pathway. Gu JJ1, Qiao KS, Sun P, Chen P, Li Q. Eur Rev Med Pharmacol Sci. 2018 Jul;22(14):4557-4563. doi: 10.26355/eurrev_201807_15511.

OBJECTIVE: To investigate the role of phosphatidylinositol-3-kinase protein kinase B (PI3K/Akt) signaling pathway in the apoptosis of H1299 lung cancer cells induced by epigallocatechin gallate (EGCG). **MATERIALS AND METHODS:** H1299 lung cancer cells were treated with EGCG at a dose of 10 μM, 20 μM, and 40 μM, respectively. Cell culture was performed for 72 h and then: 1, cell

proliferation was detected by MTT assay; 2, cell apoptosis rate was detected by flow cytometry; 3, expression of Caspase-3, Bax, and Bcl-2 was detected by Western blot; 4, expression of PI3K, p-PI3K, Akt, and p-Akt was detected by Western blot. **RESULTS:** The proliferation of H1299 cells was significantly inhibited 72 h after treatment with different doses of EGCG, and cell apoptosis rate was significantly increased ($p<0.05$). Compared with those in the control group, expression of PI3K and Akt in the lung cancer cells H1299 after EGCG treatment showed no significant differences ($p>0.05$), while expression levels of p-PI3K and p-Akt were significantly reduced ($p<0.05$). **CONCLUSIONS:** EGCG can inhibit the proliferation and induce apoptosis of H1299 lung cancer cells, and the effect is related to the inhibition of the activation of PI3K/Akt signaling pathway.

Overexpressed CDR1as functions as an oncogene to promote the tumor progression via miR-7 in non-small-cell lung cancer. Zhang X#1, Yang D#2, Wei Y1. Onco Targets Ther. 2018 Jul 10;11:3979-3987. doi: 10.2147/OTT.S158316. eCollection 2018.
BACKGROUND: Circular RNA (circRNA) is a novel member of the noncoding RNA and function as efficient microRNA sponges with gene-regulatory potential, especially the circular RNA ciRS-7 (CDR1as)/tumor suppressor miRNA-7 (miR-7) signals. However, the function of CDR1as/miR-7 in non-small cell lung cancer (NSCLC) is unknown. **METHODS:** Normal lung tissues (n=20), adjacent non-tumor tissues (n=60), and NSCLC tissues (n=60) were collected to determine the expression and significance of CDR1as/miR-7. Lung cancer cell lines A549 and H460 were overexpressed or knocked down of CDR1as, miR-7 to determine the tumor growth etc. The CDR1as/miR-7-related pathway were analyzed. **RESULTS:** CDR1as levels was robustly increased with the development of NSCLC ($P<0.001$) and the NSCLC tissues harbored highest expression of CDR1as, which negatively correlated to the expression of miR-7. Patients with high expression of CDR1as had high TNM stage ($P=0.004$), more lymph nodes metastasis (LNM) ($P=0.021$) and shorted overall survival time (OS) ($P=0.0135$). The CDR1as level was an independent prognostic factor for the patients with NSCLC. Overexpression of CDR1as induced increased cell vitalities and growth, which could be abrogated by knockdown of CDR1as or overexpressed miR-7 to induce apoptosis and G1/S arrest. Mechanistically, CDR1as functioned as miR-7 sponges to up-regulate the key target genes of miR-7 including EGFR, CCNE1 and PIK3CD. The results in vivo further confirmed that CDR1as functioned as oncogene to inhibit the anti-tumor effects of tumor suppressor miR-7 by up-regulation of proliferation index Ki-67, EGFR, CCNE1 and PIK3CD levels. **CONCLUSION:** Overexpressed CDR1as in NSCLC functions promotes the tumor progression via miR-7 signals.

Altered cell-cycle control, inflammation and adhesion in high-risk persistent bronchial dysplasia. Merrick DT1, Edwards MG2, Franklin WA3, et al. Cancer Res. 2018 Jul 11. pii: canres.3822.2017. doi: 10.1158/0008-5472.CAN-17-3822. [Epub ahead of print]
Persistent bronchial dysplasia (BD) is associated with increased risk of developing invasive squamous cell carcinoma (SCC) of the lung. In this study, we hypothesized that differences in gene expression profiles between persistent and regressive BD would identify cellular processes that underlie progression to SCC. RNA expression arrays comparing baseline biopsies from 32 bronchial sites that persisted/progressed to 31 regressive sites showed 395 differentially expressed genes (ANOVA, FDR ≤ 0.05). 31 pathways showed significantly altered activity between the two groups, many of which were associated with cell cycle control and proliferation, inflammation, or epithelial differentiation/cell-cell adhesion. Cultured persistent BD cells exhibited increased expression of polo-like kinase 1 (PLK1), which was associated with multiple cell cycle pathways. Treatment with PLK1 inhibitor induced apoptosis and G2/M arrest and decreased proliferation compared to untreated cells; these effects were not seen in normal or regressive BD cultures. Inflammatory pathway activity was decreased in persistent BD, and the presence of an inflammatory infiltrate was more common in regressive BD. Regressive BD were also associated with

trends toward overall increases in macrophages and T lymphocytes and altered polarization of these inflammatory cell subsets. Increased desmoglein 3 and plakoglobin expression was associated with higher grade and persistence of BD. These results identify alterations in the persistent subset of BD that are associated with high risk for progression to invasive SCC. These alterations may serve as strong markers of risk and as effective targets for lung cancer prevention.

Telomerase-Mediated Strategy for Overcoming Non-Small Cell Lung Cancer Targeted Therapy and Chemotherapy Resistance. Mender I1, LaRanger R1, Luitel K1, et al. Neoplasia. 2018 Aug;20(8):826-837. doi: 10.1016/j.neo.2018.06.002. Epub 2018 Jul 6.
Standard and targeted cancer therapies for late-stage cancer patients almost universally fail due to tumor heterogeneity/plasticity and intrinsic or acquired drug resistance. We used the telomerase substrate nucleoside precursor, 6-thio-2'-deoxyguanosine (6-thio-dG), to target telomerase-expressing non-small cell lung cancer cells resistant to EGFR-inhibitors and commonly used chemotherapy combinations. Colony formation assays, human xenografts as well as syngeneic and genetically engineered immune competent mouse models of lung cancer were used to test the effect of 6-thio-dG on targeted therapy- and chemotherapy-resistant lung cancer human cells and mouse models. We observed that erlotinib-, paclitaxel/carboplatin-, and gemcitabine/cisplatin-resistant cells were highly sensitive to 6-thio-dG in cell culture and in mouse models. 6-thio-dG, with a known mechanism of action, is a potential novel therapeutic approach to prolong disease control of therapy-resistant lung cancer patients with minimal toxicities.

SCREENING, DIAGNOSIS AND STAGING

New Subsolid Pulmonary Nodules in Lung Cancer Screening: The NELSON Trial.
Walter JE1, Heuvelmans MA2, Yousaf-Khan U3, et al. J Thorac Oncol. 2018 Jul 11. pii: S1556-0864(18)30605-1. doi: 10.1016/j.jtho.2018.05.006. [Epub ahead of print]
INTRODUCTION: Low-dose computed tomography (LDCT) lung cancer screening is recommended in the United States. While new solid nodules after baseline screening have a high lung cancer probability at small size and require lower size cutoff values than baseline nodules, there only is limited evidence on management of new subsolid nodules. **METHODS:** Within the Dutch-Belgian randomized controlled LDCT lung cancer screening trial (NELSON), 7557 participants underwent baseline screening between April 2004 and December 2006. Participants with new subsolid nodules detected after the baseline screening round were included. **RESULTS:** In the three incidence screening rounds, 60 new subsolid nodules (43 [72%] part-solid, 17 [28%] nonsolid) not visible in retrospect were detected in 51 participants, representing 0.7% (51 of 7295) of participants with at least one incidence screening. Eventually, 6% (3 of 51) of participants with a new subsolid nodule were diagnosed with (pre-)malignancy in such a nodule. All (pre-)malignancies were adenocarcinoma (in situ) and diagnostic workup (referral 950, 364, and 366 days after first detection, respectively) showed favorable staging (stage I). Overall, 67% (33 of 49) of subsolid nodules with an additional follow-up screening were resolving. **CONCLUSIONS:** Less than 1% of participants in LDCT lung cancer screening presents with a new subsolid nodule after baseline. Contrary to new solid nodules, data suggest that new subsolid nodules may not require a more aggressive follow-up.

Concordance of PD-L1 Expression Detection in Non-Small Cell Lung Cancer (NSCLC) Tissue Biopsy Specimens Between OncoTect iO Lung Assay and Immunohistochemistry (IHC). Young S1, Griego-Fullbright C1, Wagner A1, Chargin A2, Patterson BK2, Chabot-Richards D1. Am J Clin Pathol. 2018 Jul 24. doi: 10.1093/ajcp/aqy063. [Epub ahead of print]

OBJECTIVES: We report on the validity of a fully quantitative technology to determine tumor cells' PD-L1 expression compared with a standard immunohistochemical (IHC) assay in non-small cell lung cancer. **METHODS:** Nineteen fresh tissue specimens were processed into single-cell suspensions using the IncellPREP Kit. Cells were treated with the OncoTect iO Lung Assay, which quantitatively assessed tumor-infiltrating lymphocytes (TILs), DNA content, and PD-L1 expression on diploid and aneuploid tumor populations. **RESULTS:** Comparison of the OncoTect iO Lung Assay with IHC revealed a concordance of 95% overall (negative percent agreement, 97%; positive percent agreement, 89%). PD-L1 expression varied depending on the DNA content. The number of TILs and antigen-presenting cells (APCs) was significantly decreased in tumor compared with normal lung tissue. **CONCLUSIONS:** The nonsubjective OncoTect iO Lung Assay has been shown to be at least as accurate and sensitive as IHC for the detection of PD-L1 expression while providing additional information to guide treatment.

Surgical Disparities among Patients with Stage I Lung Cancer in the National Lung Screening Trial. Balekian AA1, Wisnivesky JP2, Gould MK3. Chest. 2018 Jul 26. pii: S0012-3692(18)31078-X. doi: 10.1016/j.chest.2018.07.011. [Epub ahead of print]

BACKGROUND: Low-dose computed tomography (LDCT) reduces lung cancer mortality in high-risk patients fit to undergo surgical resection. Racial disparities in resection of lung cancer in non-screening populations are well described. We describe surgical resection patterns of early-stage non-small cell lung cancer (NSCLC) patients in the National Lung Screening Trial (NLST) and examine whether racial disparities exist among Black patients. **METHODS:** We identified all NLST participants with clinical Stage I NSCLC. Covariates included demographics, smoking history, co-morbidities, tumor characteristics, and timing of cancer detection. Using logistic regression, we assessed resection rates of Black vs. white patients. **RESULTS:** Among 752 patients with clinical Stage I disease, 692 patients (92%) underwent resection. Unadjusted surgical resection rates for white men, white women, Black men, and Black women were 92%, 91%, 61%, and 90%, respectively. In adjusted analyses, compared to white men, Black men had a 28% lower risk [relative risk (RR): 0.72, 95% CI 0.50 - 0.99)] of undergoing surgery; although white women and Black women underwent surgery at comparable rates as white men, the odds of undergoing limited resection instead of full resection were 70% greater in white women than white men (OR 1.69, 95% CI 1.08 - 2.65). **CONCLUSIONS:** Our study shows that disparities in the surgical treatment of lung cancer persist, even among NLST participants who were considered fit to undergo thoracic surgery. As lung cancer screening disseminates into clinical practice, efforts targeting Black men should be prioritized.

The Present and Future of Liquid Biopsies in Non-Small Cell Lung Cancer: Combining Four Biosources for Diagnosis, Prognosis, Prediction, and Disease Monitoring. Bracht JWP1, Mayo-de-Las-Casas C1, Berenguer J1, Karachaliou N2,3, Rosell R4,5,6,7. Curr Oncol Rep. 2018 Jul 20;20(9):70. doi: 10.1007/s11912-018-0720-z.

PURPOSE OF REVIEW: Liquid biopsies have potential as tools for diagnosis, prognosis, and prediction of response to therapy. Herein, we will extensively review four liquid biosources, tumor-educated platelets (TEPs), cell-free DNA (cfDNA), circulating tumor cells (CTCs), and extracellular vesicles (EVs) and we will clarify their optimal application in non-small cell lung cancer (NSCLC) diagnosis and therapy. **RECENT FINDINGS:**

Liquid biopsies are a minimally invasive alternative to tissue biopsies-especially important in NSCLC patients-since tumor tissue is often unavailable or insufficient for complete genetic analysis. The main advantages of liquid biopsies include the possibility for repeated sampling, the lower cost, and the fact that they can reflect the complete molecular status of the patient better than a single-site biopsy. This is specifically important for lung adenocarcinoma patients since the detection of specific genetic alterations can predict response to targeted therapies. Molecular analysis is currently cardinal for therapy decision-

making and disease monitoring in lung cancer patients. Liquid biopsies can make easier our daily clinical practice and if prospectively tested and validated may serve as a means for lung cancer early detection.

Evaluation of ground glass nodules. Mironova V1, Blasberg JD1,2. Curr Opin Pulm Med. 2018 Jul;24(4):350-354. doi: 10.1097/MCP.0000000000000492.
PURPOSE OF REVIEW: Ground glass nodules (GGNs) represent an indolent subset of lung nodules including preinvasive nonsmall-cell lung cancer associated with a favorable prognosis and low risk for progression. Increased performance of screening cat-scan (CT) for high-risk patients has identified an increasing number of GGNs. The management of these nodules is founded mostly on single institution data and currently no universally accepted recommendations help guide clinicians managing these patients. **RECENT FINDINGS:** The solid component within a GGN is the key determinant of prognosis and is best defined by evaluating nodule density on mediastinal windows of a chest CT. When a GGN is small (<3 cm), associated with minimal change in size (<25% growth per year), and there is no demonstration of a significant solid component on mediastinal windows (<2 mm in diameter), patients can be safely observed with serially imaging. These imaging features also help distinguish patients that may harbor early-stage lung cancers that benefit from local treatment options. **SUMMARY:** The majority of GGNs do not undergo significant progression during surveillance. Evidence of nodule progression on interval imaging may be a trigger for consideration of a local treatment option such as surgical resection. Large prospective studies are needed in the United States to validate the more robust data derived from Asian studies to help formulate formal recommendations for surveillance and treatment. Future improvements in imaging and the molecular characterization of these GGNs may further refine which patients are at risk for progression.

PET and Neck Ultrasound for the Detection of Cervical Lymphadenopathy in Patients with Lung Cancer and Mediastinal Lymphadenopathy. Ahmed M1, Flannery A1, Daneshvar C2, Breen D1. Respiration. 2018 Jul 4:1-6. doi: 10.1159/000487957. [Epub ahead of print]
BACKGROUND: Cervical lymph nodes are frequently involved in patients with lung cancer and indicate inoperability. Some guidelines recommend neck ultrasound (NUS) in patients with bulky mediastinal lymphadenopathy. Positron emission tomography (PET) is indicated for patients with potentially curable disease. **OBJECTIVES:** We aimed to assess the diagnostic yield of NUS and the diagnostic accuracy of PET for cervical lymphadenopathy in this group with a high pre-test probability of N3 disease. **METHODS:** Records of all patients with lung cancer who underwent an NUS over a consecutive 5-year period were reviewed. Only patients with mediastinal lymphadenopathy on computerised tomography (CT) were included. The diagnostic accuracy of PET was assessed with NUS-guided fine needle aspiration cytology used as the reference test. **RESULTS:** During the study period, 123 patients met the inclusion criteria. Malignant cervical lymphadenopathy was confirmed in 49/123 (39.8% [95% CI 31.1-49.1]). PET-CT had a specificity of 81.1%, sensitivity of 87.5%, negative predictive value of 96.8% and positive predictive value of 50% for the detection of cervical lymphadenopathy, and it contributed no additional staging information in the neck area. Overall, PET led to a change in management in only 2.2% of cases. **CONCLUSION:** A significant proportion of patients with lung cancer and mediastinal lymphadenopathy have cervical lymphadenopathy detected by NUS. In this group of patients, PET offers minimal additional value in staging and management.

New recommendation and coverage of low-dose computed tomography for lung cancer screening: uptake has increased but is still low. Li J1, Chung S2, Wei EK3, Luft HS2. BMC Health Serv Res. 2018 Jul 5;18(1):525. doi: 10.1186/s12913-018-3338-9.
BACKGROUND: In 2013, the US Preventive Services Task Force (USPSTF) issued recommendations for low-dose computed tomography for lung cancer screening (LDCT-LCS), but there continues to be a

dearth of information on the adoption of LDCT-LCS in healthcare systems. Using a multilevel perspective, our study aims to assess referrals for LDCT-LCS and identify facilitators and barriers to adoption following recent policy changes. **METHODS:** A retrospective analysis of electronic medical record data from patients aged 55-80 years with no history of lung cancer who visited a primary care provider in a large healthcare system in California during 2010-2016 (1,572,538 patient years). Trends in documentation of smoking history, number of eligible patients, and lung cancer screening orders were assessed. Using Hierarchical Generalized Linear Models, we also evaluated provider-level and patient-level factors associated with lung cancer screening orders among 970 primary care providers and 12,801 eligible patients according to USPSTF guidelines between January 1st, 2014 and December 31st, 2016. **RESULTS:** Documentation of smoking history to determine eligibility (59.2% in 2010 to 77.8% in 2016) and LDCT-LCS orders (0% in 2010 to 7.3% in 2016) have increased since USPSTF guidelines. Patient factors associated with increased likelihood of lung cancer screening orders include: younger patient age (78-80 vs. 55-64 years old: OR, 0.4; 95% CI, 0.3-0.7), Asian race (vs. Non-Hispanic White: OR, 1.6; 95% CI, 1.1-2.4), reported current smoking (vs. former smoker: OR, 1.7; 95% CI, 1.4-2.0), no severe comorbidity (severe vs. no major comorbidity: OR = 0.2, 95% CI = 0.1-0.3; moderate vs. no major comorbidity: OR = 0.5; 95% CI = 0.4-0.7), and making a visit to own primary care provider (vs. other primary care providers: OR, 2.4; 95% CI, 1.7-3.4). Appropriate referral for lung cancer screening varies considerably across primary care providers. Provider factors include being a female physician (vs. male: OR, 1.6; 95% CI, 1.1-2.3) and receiving medical training in the US (foreign vs. US medical school graduates: OR = 0.4, 95% CI = 0.3-0.7). **CONCLUSIONS:** Future interventions to improve lung cancer screening may be more effective if they focus on accurate documentation of smoking history and target former smokers who do not regularly see their own primary care providers.

Lung cancer screening with MRI: Evaluation of MRI for lung cancer screening by comparison of LDCT- and MRI-derived Lung-RADS categories in the first two screening rounds. Meier-Schroers M1, Homsi R1, Gieseke J2, Schild HH1, Thomas D3. Eur Radiol. 2018 Jul 10. doi: 10.1007/s00330-018-5607-8. [Epub ahead of print]

PURPOSE: To evaluate MRI for lung cancer screening comparing LDCT- and MRI-derived Lung-RADS categories in the first two screening rounds. **MATERIALS AND METHODS:** 224 participants in a lung cancer screening study were examined with MRI and low-dose CT (LDCT). Acquired MRI sequences were T2, balanced, T1 and DWI. MRI was prospectively analysed regarding nodules. Minimum nodule size was 4 mm. Nodules were assigned a Lung-RADS score based on appearance and size at baseline and after 3, 6 and 12 months. MRI findings were correlated with LDCT. **RESULTS:** The early recall rate dropped from 13.8% at baseline to 1.9% in the second screening round with biopsy rates of 3.6% in the first round and 0.5% in the second round. Histology revealed lung cancer in 8/9 participants undergoing biopsy/surgery. All eight cancers were accurately depicted by MRI. The following categories were assigned on MRI (results of LDCT in parentheses): 4B/4X in 10 (10) cases, 4A in 16 (15) cases, 3 in 13 (12) cases, 2 in 77 (92) cases and 1 in 140 (126) cases. Lung-RADS scoring correlated significantly between MRI and CT. The score was overestimated by MRI in one case for category 4A, in two cases for category 3 and in five cases for category 2. MRI-based Lung-RADS score was underestimated for category 1 in 20 cases. **CONCLUSION:** Lung-RADS might be applied for lung cancer screening with MRI, since findings correlated with LDCT. Relevant findings with a Lung-RADS score of 3 and higher were never missed or underestimated by MRI KEY POINTS: • MRI performed comparably to low-dose CT in a lung cancer-screening programme. • Lung-RADS might be applied for lung cancer screening with MRI. • Lung-RADS findings score of 3 and higher were never missed by MRI.

Importance of Long-term Low-Dose CT Follow-up after Negative Findings at Previous Lung Cancer Screening. Kavanagh J1, Liu G1, Menezes R1, O'Kane GM1, McGregor M1, Tsao M1, Shepherd FA1, Schmidt H1. Radiology. 2018 Jul 10:180053. doi: 10.1148/radiol.2018180053. [Epub ahead of print]

PURPOSE: To assess the incidence of lung cancer in a cohort of patients with negative findings at previous lung cancer screening. **MATERIALS AND METHODS:** In this prospective cohort study, the authors first identified 4782 individuals who had negative screening results as part of the International Early Lung Cancer Action Program (1993-2005). Subjects were assigned a lung cancer risk score by using a validated risk model. Starting with those at highest risk, subjects were interviewed by phone and invited to undergo low-dose CT between March 2013 and October 2016. Subjects with a diagnosis of lung cancer and those who had died of lung cancer were determined. Descriptive statistics were used to summarize data. The independent samples t test and Fisher exact test were used to compare age, sex, and risk scores. **RESULTS:** A total of 327 study participants were contacted, and 200 subjects participated in this study. The average age was 74 years (range, 57-88 years), and the median time since previous CT was 7 years. The incidence rate of developing lung cancer during the next 6 years was estimated at 5.6%. The period prevalence of lung cancer was 20.8% (new and preexisting lung cancer, 68 of total cohort of 327). The detection rate of low-dose CT was 7% (14 of 200 subjects). Of the 14 screening-detected cancers, 12 were stage I or II. **CONCLUSION:** High-risk individuals have a high incidence of lung cancer after previous negative lung cancer screening. Early-stage lung cancer can be successfully detected in older high-risk individuals.

A qualitative study exploring patient motivations for screening for lung cancer. Roth JA1,2, Carter-Harris L3, Brandzel S4, Buist DSM5, Wernli KJ5. PLoS One. 2018 Jul 5;13(7):e0196758. doi: 10.1371/journal.pone.0196758. eCollection 2018.

BACKGROUND: Low-dose computed tomography (LDCT) of the chest for lung cancer screening of heavy smokers was given a 'B' rating by the U.S. Preventive Services Task Force (USPSTF) in 2013, and gained widespread insurance coverage in the U.S. in 2015. Lung cancer screening has since had low uptake. However, for those that do choose to screen, little is known about patient motivations for completing screening in real-world practice. **OBJECTIVE:** To explore the motivations for screening-eligible patients to screen for lung cancer. **METHODS:** Semi-structured qualitative interviews were conducted with 20 LDCT screen-completed men and women who were members of an integrated mixed-model healthcare system in Washington State. From June to September 2015, participants were recruited and individual interviews performed about motivations to screen for lung cancer. Audio-recorded interviews were transcribed and analyzed using inductive content analysis by three investigators. **RESULTS:** Four primary themes emerged as motivations for completing LDCT lung cancer screening: 1) trust in the referring clinician; 2) early-detection benefit; 3) low or limited harm perception; and 4) friends or family with advanced cancer. **CONCLUSION:** Participants in our study were primarily motivated to screen for lung cancer based on perceived benefit of early-detection, absence of safety concerns, and personal relationships. Our findings provide new insights about patient motivations to screen, and can potentially be used to improve lung cancer screening uptake and shared decision-making processes.

5-Hydroxymethylome in Circulating Cell-free DNA as A Potential Biomarker for Non-small-cell Lung Cancer. Zhang J1, Han X2, Gao C2, et al. Genomics Proteomics Bioinformatics. 2018 Jun;16(3):187-199. doi: 10.1016/j.gpb.2018.06.002. Epub 2018 Jul 18.

Non-small-cell lung cancer (NSCLC), the most common type of lung cancer accounting for 85% of the cases, is often diagnosed at advanced stages owing to the lack of efficient early diagnostic tools. 5-Hydroxymethylcytosine (5hmC) signatures in circulating cell-free DNA (cfDNA) that carries the cancer-

specific epigenetic patterns may represent the valuable biomarkers for discriminating tumor and healthy individuals, and thus could be potentially useful for NSCLC diagnosis. Here, we employed a sensitive and reliable method to map genome-wide 5hmC in the cfDNA of Chinese NSCLC patients and detected a significant 5hmC gain in both the gene bodies and promoter regions in the blood samples from tumor patients compared with healthy controls. Specifically, we identified six potential biomarkers from 66 patients and 67 healthy controls (mean decrease accuracy >3.2, P < 3.68E-19) using machine-learning-based tumor classifiers with high accuracy. Thus, the unique signature of 5hmC in tumor patient's cfDNA identified in our study may provide valuable information in facilitating the development of new diagnostic and therapeutic modalities for NSCLC.

Randomized trial of a patient-centered decision aid for promoting informed decisions about lung cancer screening: Implementation of a PCORI study protocol and lessons learned. Lowenstein LM1, Escoto KH2, Leal VB1, et al. Contemp Clin Trials. 2018 Jul 20;72:26-34. doi: 10.1016/j.cct.2018.07.007. [Epub ahead of print]
PURPOSE: We describe the methods, stakeholder engagement, and lessons learned from a study comparing a video decision aid to standard educational materials on lung cancer screening decisions. **METHODS:** The study followed rigorous methodology standards from the Patient-Centered Outcomes Research Institute. The importance of patient-centeredness and patient/stakeholder engagement are reflected across the study's conceptualization, execution, interpretation, and dissemination efforts. Advisory groups of current and former smokers, quitline service providers, clinicians, and patient advocates were formed for the project. The study used both retrospective and prospective recruitment strategies. Randomization of patients occurred within state-based quitlines, with aggressive tracking of participants. We collected data at baseline and 1-week, 3-month and 6-months after receiving the intervention. The patient-centered outcomes included whether patients' receiving the decision aid a) felt better prepared to make a decision, b) felt more informed about the screening decision, c) had more clarity on their values regarding the benefits and harms of lung cancer screening, and d) were more knowledgeable about lung cancer screening than patients receiving the standard education materials. Exploratory outcomes included making an appointment with a health care provider to discuss screening, scheduling and completing lung cancer screening. **RESULTS:** We have enrolled and randomized 516 quitline patients and learned many lessons about executing the trial based on significant patient and stakeholder engagement. **CONCLUSIONS:** Conducting patient-centered outcomes research requires new ways of thinking and continuously checking-in with patients/stakeholders. The engagement of quitline service providers and patient advisors has been key to successful recruitment and dissemination planning. PCORI- CER-1306-03385 ClinicalTrials.gov NCT ID: NCT02286713.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Preoperative Watchful-Waiting Time and Surgical Outcome of Patients with Non-small Cell Lung Cancer Found by Chest Low-Dose CT Screening. Hanaoka T1, Kurai M2, Okada M3, Ishizone S4, Karasawa F4, Iizuka A4. World J Surg. 2018 Jul;42(7):2164-2172. doi: 10.1007/s00268-017-4439-z.
BACKGROUNDS: Chest low-dose CT screening (LDCTS) has been finding unprecedented numbers of peripheral non-small cell lung cancers (NSCLC) at an early stage and increased the number of patients with surgical indication. It is important to explore the influence of preoperative watchful-waiting time (WWT) on surgical outcomes. Objective is to clarify relationship between WWT and surgical outcomes of LDCTS-finding NSCLC from the view point of treatment delay. **METHODS:** Total 283 cases of NSCLC, found by LDCTS and consecutively resected, were surveyed for preoperative WWT and surgical

outcomes. Validity of the present guideline for management of pulmonary nodules detected by LDCTS was verified whether WWT before surgery was suitable for eradication of NSCLC. **RESULTS:** The median value of WWT was 4.0 months in total, and the distribution of WWT exhibited long-tail-type pattern. That was 5.0 months in the group of pure ground-glass nodule (pGGN), 4.0 months in the group of part-solid nodule (PSN), and 1.7 months in the group of solid nodule (SON). During long-term postoperative observation time (median 79 months), 10-year progression-free survival rates were 100% in pGGN, 96% in PSN, and 72% in SON ($P < .0001$). They decreased significantly depending on enlargement of size: 91% or higher in size of 2 cm or smaller, and 71% or lower in size of larger than 2 cm ($P < .0001$). **CONCLUSIONS:** Limited to LDCTS-finding nodules, surgical outcome will depend mainly on some malignant potential of NSCLC per se, rather than on duration of WWT or treatment delay.

Delayed discharge does not decrease the cost of readmission after pulmonary lobectomy. Jean RA1, Chiu AS2, Boffa DJ3, Detterbeck FC3, Kim AW4, Blasberg JD5. Surgery. 2018 Jul 28. pii: S0039-6060(18)30302-7. doi: 10.1016/j.surg.2018.05.049. [Epub ahead of print]
BACKGROUND: Readmission after pulmonary lobectomy has become a potentially avoidable source of excess health care costs. Initiatives that focus on expedited discharge after lobectomy may decrease costs, but a criticism of this approach is that expedited discharge may be associated with more frequent and more expensive readmissions. We explored whether patients are at greater risk for costly readmission after expedited discharge. **METHODS:** The Nationwide Readmission Database was queried for cases of lobectomy for lung cancer between 2010 and 2014. Patients 65 years of age and older were categorized into three groups: patients discharged between hospital day 1 and 3 (expedited), between hospital days 4 and 7 (routine), or discharge after day 8 (late). Risk-adjusted 90-day readmission rates and hospital costs for readmission were compared among groups. **RESULTS:** A total of 104,905 patients underwent lobectomy for lung cancer during the study period. There were 18,652 (17.8%) expedited discharges, 54,551 (52.0%) routine discharges, and 31,702 (30.2%) late discharges. Compared with the expedited group, patients in the routine discharge group had a 3.2% greater risk-adjusted readmission rate ($P < .0001$), and patients in the late discharge group had 12.7% greater risk-adjusted readmission rate ($P < .0001$). After adjustment, expedited discharge was associated with a $4,066 decrease in index hospital costs compared with routine discharge, and a $19,233 decrease compared with late discharges (both $P < .0001$) but was not associated with costlier readmission (routine mean -$24 ± standard error $153, $P = .87$; late mean +$2,528 ± standard error $178; $P < .0001$). **CONCLUSION:** Expedited discharge after lobectomy is associated with a greater risk-adjusted readmission rate and greater index hospital costs over routine and late discharge, with no increased costs for readmission. These data demonstrate that prolonged hospital duration of stay does not decrease the risk of 90-day readmission after lobectomy, providing support for protocols that expedite patient discharge and decrease overall health care utilization.

Inflammation-Based Prognostic Score Predicts Postoperative Survival of Patients with Interstitial Pneumonia After Undergoing Lung Cancer Resection. Kobayashi S1, Matsumura Y2, Karube Y1, Nishihira M1, Inoue T1, Araki O1, Maeda S1, Chida M1. World J Surg. 2018 Jul;42(7):2143-2152. doi: 10.1007/s00268-017-4426-4.
OBJECTIVES: Idiopathic interstitial pneumonias (IIPs) are associated with an increased risk of lung cancer. Glasgow prognostic score (GPS), which uses serum C-reactive protein (CRP) and albumin levels to indicate systemic inflammatory response and nutrition level, has been reported to be a predictor of overall survival in patients with various types of cancer. We evaluated the usefulness of GPS for prediction of survival of patients with both lung cancer and IIPs following a lung resection procedure. **METHODS:** Patients with IIPs who underwent lung cancer resection from January 2006 through December 2015 were investigated. Routine laboratory measurements, including serum CRP and albumin

for determining GPS, were performed before the operation. Univariate and multivariate analyses with a COX proportional hazards regression model were used to identify independent risk factors for overall survival (OS), relapse-free survival (RFS), cancer-specific survival (CSS), and other disease-specific survival (ODSS). **RESULTS:** A total of 135 patients underwent lung resection during the study period. Multivariate analysis selected sublobar resection ($p = 0.035$), UIP pattern ($p = 0.025$), and GPS of 1-2 ($p = 0.042$) as predictive factors associated with OS, while GPS of 1-2 ($p = 0.039$) was shown to be a predictive factor associated with RFS. Multivariate analysis also revealed pTNM ($p < 0.001$), usual interstitial pneumonia pattern ($p = 0.006$), and GPS of 2 ($p = 0.003$) as predictive factors associated with CSS, while univariate analysis indicated pTNM ($p = 0.042$), GPS of 1 ($p = 0.044$), and %DLCO ($p = 0.038$) as predictive factors associated with ODSS. **CONCLUSION:** GPS is an independent prognostic factor of OS and RFS in lung cancer patients with IIPs undergoing a lung resection procedure. Furthermore, a GPS of 2 was found to be associated with CSS following lung cancer resection, while a score of 1 was associated with ODSS.

Percutaneous Computed Tomography-Guided Radiotracer-Assisted Localization of Difficult Pulmonary Nodules in Uniportal Video-Assisted Thoracic Surgery. Dailey WA1, Frey GT2, McKinney JM2, Paz-Fumagalli R2, Sella DM2, Toskich BB2, Thomas M3. J Laparoendosc Adv Surg Tech A. 2018 Jul 6. doi: 10.1089/lap.2018.0248. [Epub ahead of print]

OBJECTIVE: To report our institutional experience with radiotracer-assisted localization of lung nodules (RALN) in combination with uniportal video-assisted thoracoscopic surgery (UVATS). **METHODS:** We retrospectively reviewed electronic medical records and radiology images of 27 consecutive adult patients who underwent planned UVATS lung resections combined with RALN from January 2014 to May 2017. Based on preoperative imaging, 29 nondescript nodules were marked with technetium 99 m macroaggregated albumin under computed tomography guidance before resection. Perioperative outcomes were analyzed. **RESULTS:** All 29 nodules were successfully marked and resected with negative margins by UVATS; 12 (41.5%) were pure ground-glass opacities. Three patients had prior ipsilateral lung resections. There were no conversions to multiport VATS or thoracotomy. The majority (86.5%) of the nodules were malignant. The median nodule size was 8 mm (range: 3-20 mm) and depth, 56 mm (range: 22-150 mm). The majority (21/27; 77.8%) of patients underwent wedge resections alone, while 6 patients had anatomical resections. Median times were as follows: radiotracer injection to surgery, 219 minutes (range: 139-487 minutes); operative time, 85.5 minutes (32-236 minutes); chest tube removal, 1 day (range: 1-2 days); and length of stay, 2 days (range: 1-4 days). Four patients (14.8%) had a pigtail catheter placed for pneumothorax after radiotracer injection. One patient was readmitted 1 week after discharge for a spontaneous pneumothorax. There were no other morbidities or any 90-day mortality. **CONCLUSION:** RALN can be combined with UVATS to effectively resect small, deep, or low-density lung lesions that are difficult to visualize or palpate by thoracoscopy.

The cost and quality of life outcomes in developing a robotic lobectomy program. Worrell SG1,2, Dedhia P2, Gilbert C3, James C3, Chang AC1,2,3, Lin J1,2,3, Reddy RM4,5,6. J Robot Surg. 2018 Jul 11. doi: 10.1007/s11701-018-0844-z. [Epub ahead of print]

The use of the robotic platform is increasingly being utilized for lung resections. Our aim was to compare outcomes of thoracoscopic (VATS) versus robotic-assisted thoracoscopic (RATS) lobectomy early in a program's adoption of robotic surgery, including perioperative outcomes, cost, and long-term quality of life. A prospective database was retrospectively reviewed for all patients undergoing minimally invasive lobectomy by either VATS or RATS techniques from 2010 to 2012. Patients' operative, post-operative complications, cost (operating room and hospital) and quality of life were compared between the two resection techniques. Long-term follow-up including assessment using the European Organization for Research and Treatment of Cancer quality of life questionnaire was documented. During the first 25

RATS lobectomies, there were 73 VATS lobectomies performed, for a total of 98 cases. There was no significant difference in cancer stage, operative time, estimated blood loss, lymph node count, or hospital length of stay. The RATS resections had significantly higher operative and total hospital cost ($p < 0.0001$ and $p < 0.05$). At a median of 65-month follow-up, 29 patients (9 robotic; 20 VATS) completed the EORTC questionnaire. The global health status and symptom scale median scores were similar to the general population and did not significantly differ between groups. While transitioning from thoracoscopic to robotic lobectomy incurs increased operative and total hospital cost, equivalent operative outcomes, length of hospitalization, and long-term quality of life can be maintained during this transition. With increasing patient and surgeon interest in robotic resection, it appears both safe and feasible to adopt this approach while maintaining outcomes.

A Review of Quality of Life Measures used in Surgical Outcomes for Stage I Lung Cancers.
Yip R1, Taioli E2, Schwartz R2,3, Li K1,4, Becker BJ5, Tam K1, Htwe YM6, Yankelevitz DF1, Henschke CI1. Cancer Invest. 2018 Jul 24:1-13. doi: 10.1080/07357907.2018.1474892. [Epub ahead of print]
This review summarizes the literature on QoL in early stage lung cancer patients who underwent surgery. PubMed and PsycINFO were searched. Twelve articles from 10 distinct studies were identified for a total of 992 patients. Five QoL measures were used. One study reported only on pre-surgical QoL, six only on post-surgical QoL and three studies reported on both pre- and post-surgical QoL. Timing for the administration of post-surgical QoL surveys varied. The literature on QoL in Stage I non-small-cell lung cancer patients is very sparse. Additional research is needed to explore the impact of different surgical approaches on QoL.

Combined virtual-assisted lung mapping (VAL-MAP) with CT-guided localization in thoracoscopic pulmonary segmentectomy. Yang SM1, Lin CK2, Chen LW3, Chen YC4, Huang HC5, Ko HJ6, Chen CM3, Sato M7. Asian J Surg. 2018 Jul 20. pii: S1015-9584(18)30467-6. doi: 10.1016/j.asjsur.2018.06.005. [Epub ahead of print]
BACKGROUND/OBJECTIVE: Virtual assisted lung mapping (VAL-MAP) is a bronchoscopic lung marking technique developed to assist in navigational lung resection. It can be used for nodule localization and segmental identification. This article presents our initial experience of thoracoscopic pulmonary segmentectomy using combined VAL-MAP and computed tomography (CT)-guided localization. **MATERIAL AND METHODS:** Markings with India Ink were made bronchoscopically, before surgery, using a virtual bronchoscopy system (LungPoint® Planner) without fluoroscopy guidance. Post VAL-MAP CT scans localized the actual markings. All data on patients, markings, and outcomes were retrospectively collected, and the contribution of VAL-MAP to the operation was graded by the surgeon. **RESULTS:** From March 2017 to September 2017, 24 consecutive patients received the VAL-MAP marking procedure before thoracoscopic segmentectomy. Nineteen patients also received pre-operative CT-guided percutaneous localization after VAL-MAP; fifteen patients received CT-guided localization with dye (patent blue V) and microcoil, and four patients received with dye only. Of the 101 marking attempts made in all the patients, 71 (70.3%) were identified as contributing to the surgery. No clinically evident complications were associated with the procedure. A total of 24 segmentectomies were thoracoscopically conducted for 18 cases of lung cancer and six cases of benign diseases.
CONCLUSION: The combination of VAL-MAP and CT-guided percutaneous localization contribute to precise thoracoscopic pulmonary segmentectomy.

Challenges in Predicting Recurrence after Resection of Node Negative Non-Small Cell Lung Cancer. Thornblade LW1, Mulligan MS1, Odem-Davis K2, Hwang B1, Waworuntu RL1, Wolff EM1,

Kessler L3, Wood DE1, Farjah F4. Ann Thorac Surg. 2018 Jul 19. pii: S0003-4975(18)31005-1. doi: 10.1016/j.athoracsur.2018.06.022. [Epub ahead of print]
BACKGROUND: One-in-five patients with completely resected early-stage non-small cell lung cancer (NSCLC) will recur within two years. Risk-stratification may facilitate a personalized approach to the use of adjuvant therapy and surveillance imaging. We developed a prediction model for recurrence based on five clinical variables (tumor size & grade, visceral pleural and lymphovascular invasion, and sublobar resection), and tested the hypothesis that the addition of several new molecular markers of poor long-term outcome (vascular endothelial growth factor-C; miR-486; miR-30d) would enhance prediction.
METHODS: We performed a retrospective cohort study of patients with completely resected, node-negative NSCLC (2011-2014, follow-up through 2016) using the Lung Cancer Biospecimen Resource Network. Cox regression was used to estimate the two-year risk of recurrence. Our primary measure of model performance was optimism corrected c-statistic. **RESULTS:** Among 173 patients (mean tumor size 3.6 cm; 12% sublobar resection; 32% poorly differentiated; 16% lymphovascular invasion; 26% visceral pleural invasion), the two-year recurrence rate was 23% (95% confidence interval [CI] 17-31%). A prediction model using five known risk-factors for recurrence performed only slightly better than chance in predicting recurrence (optimism corrected c-statistic 0.54, 95% CI: 0.51-0.68). The addition of biomarkers did not improve the model's ability to predict recurrence (corrected c-statistic 0.55, 95% CI: 0.52-0.71). **CONCLUSIONS:** We were unable to predict lung cancer recurrence using a risk-prediction model based on five well-known clinical risk-factors and several biomarkers. Further research should consider novel predictors of recurrence in order to stratify patients with completely resected early-stage NSCLC according to their risk of recurrence.

Surgical wound-site inflammation: video-assisted thoracic surgery versus thoracotomy. Menna C1, De Falco E2, Teodonio L1, et al. Interact Cardiovasc Thorac Surg. 2018 Jul 27. doi: 10.1093/icvts/ivy231. [Epub ahead of print]
OBJECTIVES: Mechanical trauma occurring during pulmonary resection through both video-assisted thoracic surgery (VATS) or thoracotomy causes profound alterations in cytokines and the cellular network. The aim of this study was to analyse biological changes occurring in both the microenvironment (wound site) and macroenvironment (systemic circulation) following pulmonary lobectomy via the VATS or thoracotomic approach. **METHODS:** From October 2016 to July 2017, 30 patients with clinical Stage I lung cancer were recruited. In 12 cases (the VATS group), surgery was performed through a video-assisted thoracoscopic approach and in 15 cases (the thoracotomy group) through a muscle-sparing minithoracotomy. Following the skin incision, the wound was irrigated with a saline solution (20 ml) and then collected. After the pulmonary resection, the surgical incision was re-irrigated. The number of polymorphonuclears, granulocytes and lymphocytes in the fluids was determined by the fluorescence activated cell sorting (FACS) analysis. Cytokine profiles of interleukin (IL)-6, tumour necrosis factor (TNF)-α, IL-1 and IL-8 from sera and fluids were detected by the enzyme linked immunosorbent assay (ELISA) assay. Functional results were evaluated through spirometry, and pain was assessed using the visual analogue scale. **RESULTS:** In the postoperative fluids of the VATS group, fewer polymorphonuclears were seen compared to the thoracotomy group ($P = 0.001$), as well as a decreased percentage of granulocytes ($P = 0.01$) and a parallel increased lymphocytes fraction ($P = 0.001$). Only the systemic IL-1β levels were significantly lower in postoperative sera of the VATS group ($P = 0.038$). No differences were observed regarding other cytokines. **CONCLUSIONS:** The local microenvironment during VATS differs from that of thoracotomy by not producing the same inflammatory phenotype. The clinical efficacy of a less invasive surgical approach is confirmed by a reduced inflammation of the systemic and local districts.

Ado-Trastuzumab Emtansine for Patients With HER2-Mutant Lung Cancers: Results From a Phase II Basket Trial. Li BT1, Shen R1, Buonocore D1, et al. J Clin Oncol. 2018 Jul 10:JCO2018779777. doi: 10.1200/JCO.2018.77.9777. [Epub ahead of print]
PURPOSE: Human epidermal growth factor receptor 2 (HER2, ERBB2)-activating mutations occur in 2% of lung cancers. We assessed the activity of ado-trastuzumab emtansine, a HER2-targeted antibody-drug conjugate, in a cohort of patients with HER2-mutant lung cancers as part of a phase II basket trial. **PATIENTS AND METHODS:** Patients received ado-trastuzumab emtansine at 3.6 mg/kg intravenously every 3 weeks until progression. The primary end point was overall response rate using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. A Simon two-stage optimal design was used. Other end points included progression-free survival and toxicity. HER2 testing was performed on tumor tissue by next generation sequencing, fluorescence in situ hybridization, immunohistochemistry, and protein mass spectrometry. **RESULTS:** We treated 18 patients with advanced HER2-mutant lung adenocarcinomas. The median number of prior systemic therapies was two (range, zero to four prior therapies). The partial response rate was 44% (95% CI, 22% to 69%), meeting the primary end point. Responses were seen in patients with HER2 exon 20 insertions and point mutations in the kinase, transmembrane, and extracellular domains. Concurrent HER2 amplification was observed in two patients. HER2 immunohistochemistry ranged from 0 to 2+ and did not predict response, and responders had low HER2 protein expression measured by mass spectrometry. The median progression-free survival was 5 months (95% CI, 3 to 9 months). Toxicities included grade 1 or 2 infusion reactions, thrombocytopenia, and elevated hepatic transaminases. No patient stopped therapy as a result of toxicity or died on study. **CONCLUSION:** Ado-trastuzumab emtansine is an active agent in patients with HER2-mutant lung cancers. This is the first positive trial in this molecular subset of lung cancers. Further use and study of this agent are warranted.

A phase II study of carboplatin, pemetrexed, and bevacizumab followed by erlotinib and bevacizumab maintenance for non-squamous non-small cell lung cancer with wild-type EGFR (HOT1101). Takashina T1,2, Asahina H3, Oizumi S1,4, et al. Int J Clin Oncol. 2018 Jul 19. doi: 10.1007/s10147-018-1318-z. [Epub ahead of print]
BACKGROUND: This study evaluated the efficacy and safety of switch maintenance erlotinib and bevacizumab after induction therapy with carboplatin/pemetrexed/bevacizumab for non-squamous non-small cell lung cancer (NSCLC) with wild-type EGFR. **METHODS:** Enrolled patients had treatment-naïve, advanced non-squamous NSCLC with wild-type EGFR. Carboplatin [area under the curve (AUC) 5.0], pemetrexed (500 mg/m2) and bevacizumab (15 mg/kg) were administered on day 1 every 3 weeks for 4-6 cycles. Maintenance therapy with erlotinib (150 mg/body) on day 1 through 21 plus bevacizumab on day 1 every 3 weeks was continued until disease progression or unacceptable toxicity. The primary endpoint was 6-month progression-free survival (PFS); secondary endpoints included overall survival (OS), overall response rate (ORR), toxicity, and quality of life (QOL). **RESULTS:** Fifty-one patients were enrolled between September 2011 and June 2014. The median number of cycles for induction and maintenance therapy was 4 (range 1-6) and 4 (range 1-20). Twenty-nine patients (58%) received maintenance therapy. The 6-month PFS rate was 59.5% [95% confidence interval (CI) 45.0-72.6%]. The ORR was 48.0% (95% CI 34.8-61.5%), and disease control rate was 86.0% (95% CI 73.8-93.0%). The median PFS and OS were 6.5 months (95% CI 5.8-7.2 months) and 21.4 months (95% CI 15.9-26.9 months), respectively. Although grades ≥ 3 adverse events were observed in 33 patients (66.0%), most were hematologic; there was no febrile neutropenia. QOL was maintained throughout treatment.

CONCLUSIONS: Carboplatin/pemetrexed/bevacizumab followed by erlotinib and bevacizumab maintenance showed modest efficacy and was well tolerated in non-squamous NSCLC patients with wild-type EGFR.

Patient-reported outcomes in a phase II, North American study of alectinib in patients with ALK-positive, crizotinib-resistant, non-small cell lung cancer. Ou SI1, Socinski MA2, Gadgeel S3, et al. ESMO Open. 2018 Jul 12;3(5):e000364. doi: 10.1136/esmoopen-2018-000364. eCollection 2018.
BACKGROUND: In a phase II North American study (NP28761; NCT01871805), the anaplastic lymphoma kinase (ALK) inhibitor alectinib demonstrated both systemic and central nervous system (CNS) efficacy with good tolerability in patients with ALK-positive non-small cell lung cancer. We describe patient-reported outcomes (PROs) from the NP28761 study. **PATIENTS AND METHODS:** PROs and health-related quality of life (HRQoL) benefits were assessed using two self-administered questionnaires (the European Organisation for Research and Treatment of Cancer 30-Item Quality of Life Questionnaire-Core (EORTC QLQ-C30), and the 13-item EORTC QLQ-lung cancer-specific module) at enrolment and every 6 weeks until week 66, disease progression or death. **RESULTS:** Clinically meaningful mean improvements (≥10 point change from baseline) were observed in 10 domains, including global health status (GHS), role and social functioning, fatigue, pain, dyspnoea, and appetite loss. A clinically meaningful improvement was observed in GHS from the first assessment (6 weeks) until week 60. Alectinib demonstrated a rapid effect, with a median time to symptom improvement, using the composite endpoint of cough, dyspnoea and pain in the chest, of 1.4 months (6.1 weeks) (95% CI 1.4 to 1.6) and a median time to symptom deterioration of 5.1 months (22.1 weeks) (95% CI 2.8 to 6.8). Patients with CNS metastases at baseline experienced comparable HRQoL over the duration of the study as patients without CNS metastases. Exploratory analysis showed that the occurrence of an objective response may be associated with a better HRQoL. **CONCLUSIONS:** Patients treated with alectinib in this phase II study achieved clinically meaningful improvements in HRQoL and symptoms and had delayed time to symptom deterioration.

Entrectinib: an orally available, selective tyrosine kinase inhibitor for the treatment of NTRK, ROS1, and ALK fusion-positive solid tumors. Liu D1, Offin M2, Harnicar S1, Li BT2, Drilon A2. Ther Clin Risk Manag. 2018 Jul 20;14:1247-1252. doi: 10.2147/TCRM.S147381. eCollection 2018.
Entrectinib is a potent small-molecule tyrosine kinase inhibitor that targets oncogenic rearrangements in NTRK, ROS1, and ALK. The consolidated results of 2 Phase I trials demonstrated activity in tyrosine kinase inhibitor-naïve patients along with substantial intracranial activity. In ROS1-rearranged lung cancers, entrectinib results in durable disease control and prolonged progression-free survival. The drug is well tolerated and has a safety profile that includes adverse events mediated by on-target tropomyosin-related kinase A/B/C inhibition.

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC). Brahmer JR1, Govindan R2, Anders RA3, Antonia SJ4, Sagorsky S5, Davies MJ6, Dubinett SM7, Ferris A8, Gandhi L9, Garon EB10, Hellmann MD11, Hirsch FR12, Malik S13, Neal JW14, Papadimitrakopoulou VA15, Rimm DL16, Schwartz LH17, Sepesi B18, Yeap BY19, Rizvi NA20, Herbst RS21.
Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for over 85% of all cases. Until recently, chemotherapy - characterized by some benefit but only rare durable responses - was the only treatment option for patients with NSCLC whose tumors lacked targetable mutations. By contrast, immune checkpoint inhibitors have demonstrated distinctly durable responses and represent the advent of a new treatment approach for patients with NSCLC. Three immune checkpoint inhibitors, pembrolizumab, nivolumab and atezolizumab, are now

approved for use in first- and/or second-line settings for selected patients with advanced NSCLC, with promising benefit also seen in patients with stage III NSCLC. Additionally, durvalumab following chemoradiation has been approved for use in patients with locally advanced disease. Due to the distinct features of cancer immunotherapy, and rapid progress in the field, clinical guidance is needed on the use of these agents, including appropriate patient selection, sequencing of therapies, response monitoring, adverse event management, and biomarker testing. The Society for Immunotherapy of Cancer (SITC) convened an expert Task Force charged with developing consensus recommendations on these key issues. Following a systematic process as outlined by the National Academy of Medicine, a literature search and panel voting were used to rate the strength of evidence for each recommendation. This consensus statement provides evidence-based recommendations to help clinicians integrate immune checkpoint inhibitors into the treatment plan for patients with NSCLC. This guidance will be updated following relevant advances in the field.

Efficacy of pemetrexed and carboplatin with or without bevacizumab in lung adenocarcinoma patients with EGFR non-T790M mutations after progression on first-line EGFR-tyrosine kinase inhibitors. Jiang Z1, Zhang Y1, Yang Y1, Yue Z1, Pan Z1. Thorac Cancer. 2018 Jul 20. doi: 10.1111/1759-7714.12814. [Epub ahead of print]

BACKGROUND: The purpose of this study was to compare the effects of pemetrexed and carboplatin plus bevacizumab (PC + B) versus pemetrexed and carboplatin (PC) in lung adenocarcinoma patients with EGFR non-T790M mutations after progression on first-line EGFR-tyrosine kinase inhibitors (TKIs). **METHODS:** Patients with EGFR-positive lung adenocarcinoma who had received second-line PC with or without bevacizumab harboring EGFR non-T790M mutations after progression on first-line EGFR-TKIs between April 2015 and 2017 at Tianjin Medical University Cancer Institute and Hospital were enrolled in the study. The primary endpoint was progression-free survival and secondary endpoints were overall survival, objective response rate, disease control rate, and safety. **RESULTS:** A total of 85 patients were eligible for the study: 55 and 30 cases were enrolled in the PC and PC + B groups, respectively. The median progression-free survival was prolonged with PC + B compared to PC (median 8.2 vs. 5.1 months; P = 0.037). The objective response rate was improved with PC + B compared to PC (46.7% vs. 25.5%; P = 0.047) and overall survival prolonged with PC + B compared to PC (median 26.3 vs. 19.2 months; P = 0.012). Safety was similar to previous studies of bevacizumab in non-small cell lung cancer: one patient experienced grade 3 hypertension and proteinuria but did not require the discontinuation of therapy. **CONCLUSION:** The addition of bevacizumab to PC was superior to PC alone as second-line therapy in patients with advanced non-T90M EGFR-positive lung adenocarcinoma. However, this result needs to be confirmed by prospective clinical trials.

Long-term survival follow-up of atezolizumab in combination with platinum-based doublet chemotherapy in patients with advanced non-small-cell lung cancer. Liu SV1, Camidge DR2, Gettinger SN3, et al. Eur J Cancer. 2018 Jul 24;101:114-122. doi: 10.1016/j.ejca.2018.06.033. [Epub ahead of print]

BACKGROUND: Before the availability of immunotherapy, chemotherapy was standard first-line therapy for non-small-cell lung cancer (NSCLC) lacking actionable gene alterations. Preclinical evidence suggests chemotherapy is immunomodulatory, supporting chemotherapy/immunotherapy combinations. Atezolizumab, anti-programmed death ligand-1 (PD-L1) antibody, blocks programmed cell death protein-1 and B7.1 interaction with PD-L1. GP28328 (NCT01633970) assessed atezolizumab with chemotherapy in multiple tumours; we report results for advanced, treatment-naïve NSCLC. **METHODS:** Patients received atezolizumab plus carboplatin with paclitaxel (Arm C: atezo/cb/pac), pemetrexed (Arm D: atezo/cb/pem, maintenance pemetrexed permitted), or nab-paclitaxel (Arm E: atezo/cb/nab-pac), four-six

cycles, then atezolizumab maintenance. Primary end-point was safety; secondary end-points were objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). **RESULTS:** Seventy-six NSCLC patients were enrolled (n = 25, 25 and 26 for Arms C, D and E, respectively). Common treatment-related grade III/IV adverse events were neutropenia (36% atezo/cb/pac, 36% atezo/cb/pem, 42% atezo/cb/nab-pac) and anaemia (16% atezo/cb/pac, 16% atezo/cb/pem, 31% atezo/cb/nab-pac). Confirmed ORRs were 36% atezo/cb/pac, 68% atezo/cb/pem (one complete response [CR]) and 46% atezo/cb/nab-pac (four CRs). Median PFS was 7.1 months, (95% confidence interval [CI]: 4.2-8.3), 8.4 months (95% CI: 4.7-11) and 5.7 months (95% CI: 4.4-14.8), respectively. Median OS was 12.9 months (95% CI: 8.8-21.3), 18.9 months (95% CI: 9.9-27.4) and 17.0 months (95% CI: 12.7-not evaluable), respectively. **CONCLUSION:** Atezolizumab with chemotherapy was well tolerated with encouraging efficacy, though the analysis was limited by small numbers. NSCLC chemotherapy combination studies are ongoing. CLINICALTRIALS.

Association Between Imaging Findings of Airway Obstruction Adjacent to Lung Tumors and the Onset of Interstitial Lung Disease After Nivolumab. Nakahama K1, Tamiya A2, Isa SI3, et al. In Vivo. 2018 Jul-Aug;32(4):887-891. doi: 10.21873/invivo.11324.
BACKGROUND: Compared to conventional cytotoxic chemotherapy, immune checkpoint inhibitors have shown a significant efficacy in the treatment of lung cancer. Although interstitial lung disease (ILD) is an important adverse event in immunotherapy, risk factors for ILD remain unclear. **PATIENTS AND METHODS:** In this multicenter cohort study (UMIN000025908), 201 patients who were treated with nivolumab were retrospectively reviewed. Associations between the incidence of ILD and patient characteristics were evaluated. ILD grade and progression-free survival were analyzed according to the presence or absence of imaging findings of airway obstruction adjacent to lung tumors (IAOT). **RESULTS:** In the multivariate analysis, the odds ratio (OR) of ILD for patients with a history of radiation pneumonitis or IAOT was 3.96 (p=0.012) and 6.59 (p=0.004), respectively. ILD occurred in six (37.5%) out of 16 patients with IAOT and 19 (10.3%) out of 185 patients without IAOT. Three out of the six patients with ILD and IAOT had ILD of grade 4 or more. The median progression-free survival of patients with and without IAOT was 0.9 and 3.2 months, respectively (p<0.001). **CONCLUSION:** IAOT was strongly associated with the occurrence of ILD after therapy with nivolumab.

A Combination Of Approved Antibodies Overcomes Resistance Of Lung Cancer To Osimertinib By Blocking Bypass Pathways. Romaniello D1, Mazzeo L2, Mancini M3, et al. Clin Cancer Res. 2018 Jul 2. pii: clincanres.0450.2018. doi: 10.1158/1078-0432.CCR-18-0450. [Epub ahead of print]
PURPOSE: Because of emergence of resistance to osimertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI), no targeted treatments are available for patients with lung cancer who lose sensitivity due to new mutations or bypass mechanisms. We examined in animals and in vitro an alternative therapeutic approach making use of antibodies. **EXPERIMENTAL DESIGN:** An osimertinib-sensitive animal model of lung cancer, which rapidly develops drug resistance, has been employed. To overcome compensatory hyper-activation of ERK, which we previously reported, an anti-EGFR antibody (cetuximab) was combined with other antibodies, as well as with a sub-therapeutic dose of osimertinib, and cancer cell apoptosis was assayed. **RESULTS:** Our animal studies identified a combination of three clinically approved drugs, cetuximab, trastuzumab (an anti-HER2 mAb) and osimertinib (low dose), as an effective and long-lasting treatment, able to prevent onset of resistance to osimertinib. A continuous schedule of concurrent treatment was sufficient for effective tumor inhibition and for prevention of relapses. Studies employing cultured cells and analyses of tumor extracts indicated that the combination of two mAbs and a sub-therapeutic TKI dose sorted EGFR and HER2 for degradation, cooperatively enhanced apoptosis, inhibited activation of ERK, and reduced abundance of several bypass proteins, namely MET, AXL and HER3. **CONCLUSIONS:** Our in vitro assays and animal studies identified an

effective combination of clinically approved drugs, which might overcome resistance to irreversible TKIs in clinical settings. The results we present attribute the long-lasting effect of the drug combination to simultaneous blockade of several well-characterized mechanisms of drug resistance.

Pathologic Features of Response to Neoadjuvant Anti-PD-1 in Resected Non-Small Cell Lung Carcinoma: A Proposal for Quantitative Immune-Related Pathologic Response Criteria (irPRC). Cottrell TR1, Thompson ED1,2,3, Forde PM2,3, et al. Ann Oncol. 2018 Jul 6. doi: 10.1093/annonc/mdy218. [Epub ahead of print]

BACKGROUND: Neoadjuvant anti-PD-1 may improve outcomes for patients with resectable NSCLC and provides a critical window for examining pathologic features associated with response. Resections showing major pathologic response (MPR) to neoadjuvant therapy, defined as ≤ 10% residual viable tumor (RVT), may predict improved long-term patient outcome. However, %RVT calculations were developed in the context of chemotherapy (%cRVT). An immune-related %RVT (%irRVT) has yet to be developed. **PATIENTS AND METHODS:** The first trial of neoadjuvant anti-PD-1 (nivolumab, NCT02259621) was just reported. We analyzed hematoxylin and eosin-stained slides from the post-treatment resection specimens of the 20 patients with non-small cell lung carcinoma who underwent definitive surgery. Pre-treatment tumor biopsies and pre-resection radiographic 'tumor' measurements were also assessed. **RESULTS:** We found that the regression bed (the area of immune-mediated tumor clearance) accounts for the previously noted discrepancy between CT imaging and pathologic assessment of residual tumor. The regression bed is characterized by (1) immune activation-dense tumor infiltrating lymphocytes with macrophages and tertiary lymphoid structures; (2) massive tumor cell death-cholesterol clefts; and (3) tissue repair-neovascularization and proliferative fibrosis (each feature enriched in major pathologic responders vs. non-responders, $p < 0.05$). This distinct constellation of histologic findings was not identified in any pre-treatment specimens. Histopathologic features of the regression bed were used to develop "Immune-Related Pathologic Response Criteria" (irPRC), and these criteria were shown to be reproducible amongst pathologists. Specifically, %irRVT had improved inter-observer consistency compared to %cRVT [median per-case %RVT variability 5% (0-29%) vs. 10% (0-58%), $p = 0.007$] and a two-fold decrease in median standard deviation across pathologists within a sample (4.6 vs. 2.2, $p = 0.002$). **CONCLUSIONS:** irPRC may be used to standardize pathologic assessment of immunotherapeutic efficacy. Long-term follow-up is needed to determine irPRC reliability as a surrogate for recurrence-free and overall survival.

Long Term Outcomes of a Phase II Trial of Chemotherapy with Consolidative Radiation Therapy for Oligometastatic Non-Small Cell Lung Cancer. Petty WJ1, Urbanic JJ2, Ahmed T3, et al. Int J Radiat Oncol Biol Phys. 2018 Jul 9. pii: S0360-3016(18)31401-9. doi: 10.1016/j.ijrobp.2018.06.400. [Epub ahead of print]

PURPOSE: Recent data indicate consolidative radiation therapy (CRT) improves progression free survival (PFS) for patients with oligometastatic non-small cell lung cancer (NSCLC). Data regarding long term outcomes are limited. **METHODS AND MATERIALS:** In 2010, this prospective, multi-center, single arm, phase II trial was initiated and enrolled patients with oligometastatic NSCLC. Oligometastatic disease was defined as a maximum number of five metastatic lesions for all disease sites including no more than three active extracranial metastatic lesions. Limited mediastinal lymph node involvement was allowed. Patients achieving a partial response or stable disease after 3-6 cycles of platinum based chemotherapy were treated with CRT to the primary and metastatic sites of disease followed by observation alone. Primary endpoint was PFS with secondary endpoints of local control, overall survival, and safety. **RESULTS:** Twenty nine patients were enrolled between October 2010 and October 2015, and twenty seven were eligible for consolidative radiation therapy. The study was closed early due to slow accrual but met its primary endpoint for success which was PFS greater than 6 months ($P < .0001$). The

median PFS (95% CI) was 11.2 months (7.6-15.9 months) and the median OS was 28.4 months (14.5-45.8 months). Survival outcomes were not significantly different for patients with brain metastases (P = .87 for PFS; P = .12 for OS) or lymph node involvement (P = .74 for PFS; P = .86 for OS). **CONCLUSIONS:** For patients with oligometastatic NSCLC, chemotherapy followed by consolidative radiation therapy without maintenance chemotherapy was associated with encouraging long term outcomes.

The incidence of brain metastases in stage IV ROS1-rearranged non-small cell lung cancer and rate of central nervous system progression on crizotinib. Patil T1, Smith DE2, Bunn PA3, Aisner DL4, Le AT3, Hancock M3, Purcell WT3, Bowles DW3, Camidge DR3, Doebele RC3. J Thorac Oncol. 2018 Jul 5. pii: S1556-0864(18)30772-X. doi: 10.1016/j.jtho.2018.07.001. [Epub ahead of print]
INTRODUCTION: Central nervous system (CNS) metastases in lung cancer are a frequent cause of morbidity and mortality. There are conflicting data on the incidence of CNS metastases in stage IV ROS1+ non-small cell lung cancer (NSCLC) and rate of CNS progression on crizotinib. **METHODS:** A retrospective review of 579 patients with stage IV NSCLC between June 2008 to December 2017 was performed. Brain metastases and oncogene status (ROS1, ALK, EGFR, KRAS, BRAF, and other) were recorded. We measured progression free survival (PFS) and time to CNS progression (P-CNS) in ROS1+ and ALK+ patients on crizotinib. **RESULTS:** We identified 33 ROS1+ and 115 ALK+ patients with stage IV NSCLC. The incidence of brain metastases for treatment-naïve, stage IV ROS1+ and ALK+ NSCLC was 36% (12/33) and 34% (39/115) respectively. There were no statistically significant differences in incidence of brain metastases across ROS1, ALK, EGFR, KRAS, BRAF or other mutations. Complete survival data was available for 19 ROS1+ and 83 ALK+ patients. Median PFS for ROS1+ and ALK+ patients was 11 and 8 months (p = 0.304). The CNS was the first and sole site of progression in 47% (9/19) of ROS1+ and 33% ALK+ (28/83) patients with no differences between these groups (p = 0.610). **CONCLUSIONS:** Brain metastases are common in treatment-naïve stage IV ROS1+ NSCLC, though the incidence does not differ from other oncogene cohorts. The CNS is a common first site of progression in ROS1+ patients on crizotinib. This study reinforces the importance of developing CNS-penetrant TKIs for patients with ROS1+ NSCLC.

Use of nivolumab in elderly patients with advanced squamous non-small-cell lung cancer: results from the Italian cohort of an expanded access programme. Grossi F1, Crinò L2, Logroscino A3, et al. . Eur J Cancer. 2018 Sep;100:126-134. doi: 10.1016/j.ejca.2018.05.015. Epub 2018 Jul 13.
AIM: This analysis evaluated the efficacy and safety of nivolumab, an immune checkpoint inhibitor, in elderly patients with stage IIIB or IV squamous non-small-cell lung cancer (NSCLC) enrolled in the expanded access programme (EAP) in Italy. **METHODS:** Nivolumab was available on physician request. Safety data included adverse events (AEs). Efficacy data included investigator-assessed tumour response, progression date and survival information. Results were analysed for patients aged <65, 65-<75 and ≥75 years and for the overall population. **RESULTS:** A total of 371 patients with squamous NSCLC were enrolled at 96 centres between April 2015 and September 2015; 34% (n = 126), 47% (n = 175) and 19% (n = 70) were aged <65, 65-<75 and ≥75 years, respectively. Efficacy was similar among patients aged <65, 65-<75 and ≥75 years and the overall population (objective response rates: 18%, 18%, 19% and 18%, respectively; disease control rates: 49%, 47%, 43% and 47%, respectively). Median overall survival was reduced in patients aged ≥75 years (5.8 months) versus patients aged <65; years (8.6 months), patients aged 65-<75 years (8.0 months) and the overall population (7.9 months). The incidence of grade 3-4 treatment-related AEs was low in patients aged 65, 65-<75 and ≥75 years and the overall population (3%, 9%, 3%, 6%, respectively). Discontinuation rates due to treatment-related AEs were low irrespective of age (4-5%). **CONCLUSIONS:** These EAP results suggest that elderly patients with advanced squamous NSCLC benefit from nivolumab, with tolerability similar to that in the overall population.

A Case-control Study Supporting the Use of Liquid Biopsy in the Targeted Therapy for Lung Cancer Dai LJ1, Wang C, Ding ZY. Asian Pac J Cancer Prev. 2018 Jul 27;19(7):1761-1766.
BACKGROUNDS: Targeted therapy for lung cancer depends on the genetic testing. Liquid biopsy provides a valuable source for the genetic testing. However, direct evidence was lacking for whether liquid biopsy could guide the targeted therapy. **METHODS:** In this retrospective study, the admitted patients from Jan 2015 to Feb 2016 were screened through a pre-established database. Patients with metastatic, pathologically-confirmed, and treatment naïve non-small cell lung cancer who were prescribed with epithelial growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) from the guidance of liquid biopsy were enrolled (Liquid group). The mutation status in tumors was not mandatory. During the same period, patients medicated with TKI based on tumor samples were included in the Control group. They were enrolled in an age-, gender-, performance-, smoking-, and histology-matched manner. **RESULTS:** We screened 536 patients and enrolled 26 patients in the Liquid group. Another 26 patients were enrolled in a 1:1 ratio in the Control group. In the Liquid group, a high consistence (84.6%) in EGFR mutation status between liquid and tumor was observed. The best response was partial response in 19 patients (73.1 %), and followed by stable disease in 6 patients (23.1 %). The median progression-free survival was 10.0 months (95%CI: 4.2-15.8 months). In the Control group, a similar disease control rate (88.4%, P=0.603) and comparable PFS (8.6 months, 95% CI: 7.6-10.4 months, P=0.714, HR=0.657, 95% CI: 0.309-1.396) was found. In the Liquid group, 3 of 4 patients with discordant results between tumor and liquid biopsy showed treatment responses favoring the liquid biopsy. **CONCLUSION:** This study provided direct evidence supporting the liquid biopsy for guiding the targeted therapy for lung cancer.

Combined effect of cabozantinib and gefitinib in crizotinib-resistant lung tumors harboring ROS1 fusions. Kato Y1, Ninomiya K1, Ohashi K1,2, et al. Cancer Sci. 2018 Jul 27. doi: 10.1111/cas.13752. [Epub ahead of print]
The ROS1 tyrosine kinase inhibitor (TKI) crizotinib has shown dramatic effects in patients with non-small cell lung cancer (NSCLC) harboring ROS1 fusion genes. However, patients inevitably develop resistance to this agent. Therefore, a new treatment strategy is required for lung tumors with ROS1 fusion genes. Two lung cancer cell lines, HCC78 harboring SLC34A2-ROS1 and ABC-20 harboring CD74-ROS1, were used as cell line-based resistance models. Crizotinib-resistant HCC78R cells were established from HCC78. We comprehensively screened the resistant cells using a phosphor-receptor tyrosine kinase array and RNA sequence analysis by next-generation sequencing (NGS). HCC78R cells showed upregulation of HB-EGF and activation of EGFR phosphorylation and the EGFR signaling pathway. Recombinant HB-EGF or EGF rendered HCC78 cells or ABC-20 cells resistant to crizotinib. RNA sequence analysis by NGS revealed the upregulation of AXL in HCC78R cells. HCC78R cells showed marked sensitivity to EGFR-TKIs or anti-EGFR antibody treatment in vitro. Combinations of an AXL-inhibitor, cabozantinib or gilteritinib, and an EGFR-TKI were more effective against HCC78R cells than monotherapy with an EGFR-TKI or AXL inhibitor. The combination of cabozantinib and gefitinib effectively inhibited the growth of HCC78R tumors in an in vivo xenograft model of NOG mice. The results of this study indicated that HB-EGF/EGFR and AXL play roles in crizotinib resistance in lung cancers harboring ROS1 fusions. The combination of cabozantinib and EGFR-TKI may represent a useful alternative treatment strategy for patients with advanced NSCLC harboring ROS1 fusion genes. This article is protected by copyright. All rights reserved.

Exploratory analysis using machine learning to predict for chest wall pain in patients with stage I non-small-cell lung cancer treated with stereotactic body radiation therapy. Chao HH1, Valdes G1,2, Luna JM1, Heskel M1, Berman AT1, Solberg TD1,2, Simone CB 2nd3. J Appl Clin Med Phys. 2018 Jul 10. doi: 10.1002/acm2.12415. [Epub ahead of print]
BACKGROUND AND PURPOSE: Chest wall toxicity is observed after stereotactic body radiation therapy (SBRT) for peripherally located lung tumors. We utilize machine learning algorithms to identify toxicity predictors to develop dose-volume constraints. **MATERIALS AND METHODS:** Twenty-five patient, tumor, and dosimetric features were recorded for 197 consecutive patients with Stage I NSCLC treated with SBRT, 11 of whom (5.6%) developed CTCAEv4 grade ≥2 chest wall pain. Decision tree modeling was used to determine chest wall syndrome (CWS) thresholds for individual features. Significant features were determined using independent multivariate methods. These methods incorporate out-of-bag estimation using Random forests (RF) and bootstrapping (100 iterations) using decision trees. **RESULTS:** Univariate analysis identified rib dose to 1 cc < 4000 cGy (P = 0.01), chest wall dose to 30 cc < 1900 cGy (P = 0.035), rib Dmax < 5100 cGy (P = 0.05) and lung dose to 1000 cc < 70 cGy (P = 0.039) to be statistically significant thresholds for avoiding CWS. Subsequent multivariate analysis confirmed the importance of rib dose to 1 cc, chest wall dose to 30 cc, and rib Dmax. Using learning-curve experiments, the dataset proved to be self-consistent and provides a realistic model for CWS analysis. **CONCLUSIONS:** Using machine learning algorithms in this first of its kind study, we identify robust features and cutoffs predictive for the rare clinical event of CWS. Additional data in planned subsequent multicenter studies will help increase the accuracy of multivariate analysis.

Stereotactic body radiation therapy versus conventionally fractionated radiation therapy for early stage non-small cell lung cancer. Haque W1, Verma V2, Polamraju P3, Farach A4, Butler EB4, Teh BS4. Radiother Oncol. 2018 Jul 18. pii: S0167-8140(18)33395-4. doi: 10.1016/j.radonc.2018.07.008. [Epub ahead of print]
PURPOSE: To date, no published randomized trials have shown stereotactic body radiation therapy (SBRT) to offer superior outcomes to conventionally fractionated radiation therapy (CFRT) for early-stage non-small cell lung cancer (NSCLC). The largest study to date, this investigation of a contemporary national database sought to evaluate practice patterns and survival between CFRT and SBRT.
METHODS: The National Cancer Database was queried (2004-2015) for histologically-confirmed cT1-2aN0M0 NSCLC undergoing definitive CFRT or SBRT. Multivariable logistic regression ascertained factors associated with SBRT administration. Kaplan-Meier analysis evaluated overall survival (OS) before and following propensity matching. Cox proportional hazards modeling determined variables associated with OS. **RESULTS:** Of 23,088 patients, 2286 (10%) patients received CFRT and 20,802 (90%) SBRT. SBRT was less often delivered in African-Americans, patients with lower incomes, urban location, greater comorbidities, at non-academic centers, in larger tumors, and squamous histology ($p < 0.05$ for all). Patients treated with SBRT had a higher median OS (38.8 months vs. 28.1 months, $p < 0.001$). At median follow-up of 44.6 months, the median OS for the SBRT group was 38.8 months, versus 28.1 months for CFRT ($p < 0.001$). These findings persisted following propensity matching. Subgroup analyses demonstrated improved OS in multiple subcohorts (T2, Charlson comorbidity score 2-3, squamous histology). SBRT was also independently associated with OS on Cox multivariate analysis ($p < 0.001$). **CONCLUSIONS:** The largest such study to date (comprising of over 23,000 patients), this investigation demonstrates the survival benefit to ablative radiotherapy for early-stage NSCLC. Maturation of comparative prospective trials is eagerly awaited.

A National Cancer Database Analysis of Radiofrequency Ablation versus Stereotactic Body Radiotherapy in Early-Stage Non-Small Cell Lung Cancer. Lam A1, Yoshida EJ2, Bui K3, Fernando D3, Nelson K3, Abi-Jaoudeh N3. J Vasc Interv Radiol. 2018 Jul 27. pii: S1051-0443(18)31163-1. doi: 10.1016/j.jvir.2018.04.029. [Epub ahead of print]
PURPOSE: To compare overall survival (OS) after radiofrequency (RF) ablation and stereotactic body radiotherapy (SBRT) at high-volume centers in patients with early-stage non-small cell lung cancer (NSCLC). **MATERIALS AND METHODS:** Cases in the National Cancer Database of stage 1a and 1b NSCLC treated with primary RF ablation or SBRT from 2004 to 2014 were included. Patients treated at low-volume centers, defined as facilities below the 95th percentile in volume of cases performed, were excluded. Outcomes measured include OS and rate of 30-day readmission. The Kaplan-Meier method was used to estimate OS. The log-rank test was used to compare survival curves. Propensity score matched cohort analysis was performed. $P < .05$ was considered statistically significant. **RESULTS:** The final cohort comprised 4,454 cases of SBRT and 335 cases of RF ablation. Estimated median survival and follow-up were 38.8 months and 42.0 months, respectively. Patients treated with RF ablation had significantly more comorbidities ($P < .001$) and higher risk for an unplanned readmission within 30 days (hazard ratio = 11.536; $P < .001$). No difference in OS for the unmatched groups was found on multivariate Cox regression analysis ($P = .285$). No difference was found in the matched groups with 1-, 3-, and 5-year OS of 85.5%, 54.3%, and 31.9% in the SBRT group vs 89.3%, 52.7%, and 27.1% in the RF ablation group ($P = .835$). **CONCLUSIONS:** No significant difference in OS was seen between patients with early-stage NSCLC treated with RF ablation and SBRT.

Stereotactic body radiation therapy (SBRT) for central early stage non-small cell lung cancer: results of a prospective phase I/II trial. Roach MC1, Robinson CG1, DeWees TA2, et al. J Thorac Oncol. 2018 Jul 26. pii: S1556-0864(18)30812-8. doi: 10.1016/j.jtho.2018.07.017. [Epub ahead of print]
INTRODUCTION: We report results from a prospective phase I/II trial for patients with centrally-located, early-stage non-small cell lung cancer (NSCLC) receiving stereotactic body radiation therapy (SBRT). **METHODS:** Eligible patients were medically inoperable with biopsy-proven NSCLC within 2 cm of the proximal bronchial tree or 5 mm of the mediastinal pleura or parietal pericardium. Phase I had 4 dose levels using 5 fractions: 9, 10, 11, and 12 Gy per fraction. The primary phase II objective was to determine if the maximum tolerated dose in phase I achieved local control >80% at 2 years. **RESULTS:** Seventy-four patients were enrolled; 23 to phase I and 51 to phase II. Two phase I patients treated with 10 Gy x5 developed unrelated acute grade 3 lung toxicities which resolved. The phase II dose level selected was 11 Gy x5 fractions. The median follow-up for living phase II patients was 27 months (range: 9-58). Two-year local control using 11 Gy x5 fractions was 85% (95% CI: 62-95%). Two-year overall survival was 43% (95% CI: 28-57%). Three patients (6%, 95% CI: 1-17%) experienced acute grade 3 and 4 cardiac or pulmonary toxicities. Of the 41 patients evaluable for late cardiac and pulmonary toxicity, 11 (27%, 95% CI: 14-43%) developed grade 3, 5 (12%, 95% CI: 4-26%) developed grade 4, and 1 (4%, 95% CI: 0-13%) died of grade 5 toxicity. **CONCLUSION:** SBRT for central NSCLC using 11 Gy x5 fractions is tolerable and has excellent local control, but is associated severe late toxicity in some patients.

Stereotactic Ablative Body Radiotherapy for Primary Non-Small-Cell Lung Cancer: Achieving Local Control with a Lower Biologically Effective Dose. Zhu S1, Lightsey JL1, Hoppe BS1, et al. Cancer Invest. 2018 Jul 24:1-7. doi: 10.1080/07357907.2018.1479415. [Epub ahead of print]
We conducted a retrospective study of stereotactic ablative radiotherapy (SABR) for 94 patients with non-small-cell lung cancer at our institution. The patients were treated with either 50 Gy in five treatments or 48 Gy in four treatments, corresponding to biologically effective doses (BED) of 100 Gy or 105.6 Gy, respectively. The results demonstrate that, with relatively low BEDs, we can achieve excellent local control with minimal toxicity.

Clinical Outcomes After Lung Stereotactic Body Radiation Therapy in Patients With or Without a Prior Lung Resection. Hou Y1, Hermann G1, Lewis JH1,2, et al. Am J Clin Oncol. 2018 Jul;41(7):695-701. doi: 10.1097/COC.0000000000000344.

OBJECTIVES: Tumor control (TC), toxicity and survival, following stereotactic body radiation therapy (SBRT) were compared between patients with and without a prior lung resection (PLR). **MATERIALS AND METHODS:** The study is comprised of 130 patients with 141 peripheral tumors treated with SBRT at our institution from 2009 to 2013. Primary TC and lobar control (LC) were defined per RTOG 0236. Toxicity was scored using Common Terminology Criteria for Adverse Events version 4.0. Survival/TC and toxicity were compared between patients with and without PLR using the Kaplan-Meier method and cumulative incidence, respectively. Fine and Gray regression was used for univariable/multivariable analysis for radiation pneumonitis (RP). **RESULTS:** Of the 130 patients with median age 70 years (range, 42 to 93 y), 50 had undergone PLR (median time between PLR and SBRT: 33 mo; range, 1 to 206), including pneumonectomy (12%), lobectomy (46%), wedge resection (42%). With a median follow-up of 21 months in survivors, the PLR group had better TC (1-y 100% vs. 93%; P<0.01) and increased grade ≥2 (RP; 1-y 12% vs. 1%; P<0.01). OS was not significantly different between the 2 groups (1-y 91% vs. 85%; P=0.24). On univariable/multivariable analyses, biologically effective dose was associated with TC (hazard ratios, 0.97; 95% confidence interval, 0.94-0.999; P=0.04). Chemotherapy use was associated with grade ≥2 RP for all patients (hazard ratios, 14.92; 95% confidence interval, 5.68-39.21; P<0.0001) in multivariable analysis. PLR was not associated with increased RP in multivariable analysis. **CONCLUSIONS:** Patients with PLR who receive lung SBRT for lung tumors have high local control and relatively low toxicity. SBRT is an excellent option to treat second lung tumors or pulmonary metastases in patients with PLR.

The influence of fractionated radiotherapy on the stability of spinal bone metastases: a retrospective analysis from 1047 cases. Sprave T1,2, Hees K3, Bruckner T3, et al. Radiat Oncol. 2018 Jul 24;13(1):134. doi: 10.1186/s13014-018-1082-2.

BACKGROUND: The effect of radiotherapy, in particular the application of different multi-fraction schedules in the management of unstable spinal bone metastases (SBM), is incompletely understood. This study aims to compare the radiological response regarding various dose and fractionation schedules of radiotherapy in the palliative treatment of SBM. **METHODS:** We retrospectively assessed 1047 patients with osteolytic SBM, treated with palliative radiotherapy at our department between 2000 and 2015. Lung cancer (40.2%), breast (16.7%) and renal cancer (15.2%) were the most common solid tumors in this study. Different common multi-fraction regimen (5x4Gy, 10x3Gy, 14 × 2.5Gy and 20x2Gy) were compared with regard to radiological response and recalcification at 3 and 6 months after radiotherapy. The Taneichi score was used for classification of osteolytic SBM. **RESULTS:** Median follow up was 6.3 months. The median overall survival (OS) in the short-course radiotherapy (SCR) group using less than 10 treatment fractions was 5.5 months vs. 9.5 months in the long-course radiotherapy (LCR) group using in excess of 10 fractions (log rank p < .0001). Overall survival (OS) in the SCR group after 3 and 6 months was 66.8 and 49.1%, respectively vs 80.9 and 61.5%, respectively in the LCR group. 17.6% (n = 54/306) and 31.1% (n = 89/286) of unstable SBM were classified as stable in the SCR group at 3 and 6 months post radiotherapy, respectively (p < .001 for both). In the LCR group, 24.1% (n = 28/116) and 34.2% (n = 38/111) of unstable SBM were stabilized after 3 and 6 months, respectively (p < .001 for both). **CONCLUSIONS:** Our study shows no significant difference in stabilization achieving recalcification rates between multi-fraction schedules (SCR vs. LCR) in the palliative management of unstable SBM. Both groups with multi-fraction regimen demonstrate a stabilizing effect following 3 and 6 months after radiotherapy.

Repeat stereotactic body radiotherapy (SBRT) for local recurrence of non-small cell lung cancer and lung metastasis after first SBRT. Ogawa Y1, Shibamoto Y2, Hashizume C3, et al. Radiat Oncol. 2018 Jul 28;13(1):136. doi: 10.1186/s13014-018-1080-4.
BACKGROUND: This study evaluated the safety and efficacy of repeat SBRT for local recurrence of stage I non-small-cell lung cancer (NSCLC) and solitary lung metastasis. **METHODS:** Thirty-one patients with in-field local relapse of NSCLC (n = 23) or lung metastasis (n = 8) underwent repeat SBRT. All patients had grade 2 or lower radiation pneumonitis after the first SBRT. Local recurrence was diagnosed with CT and FDG-PET in 17 patients and by biopsy in 14. The median interval between the first and second SBRT was 18 months (range, 4-80). The first SBRT dose was mainly 48-52 Gy in 4 fractions (n = 25) according to the institutional protocols. Second SBRT doses were determined based on the tumor size and distance to organs at risk, and were mostly 48-52 Gy in 4 fractions (n = 13) or 60 Gy in 8 fractions (n = 13). **RESULTS:** At 3 years, overall survival and local control rates were 36 and 53%, respectively, for all 31 patients. Four patients showed no further recurrence for > 5 years (63-111 months) after the second SBRT. Radiation pneumonitis after the second SBRT was grade 2 in 4 patients, and no grade 3 pneumonitis was observed. **CONCLUSION:** Repeat SBRT was safe. Local control and survival rates were higher than expected. SBRT should be an important treatment option for local recurrence of NSCLC or lung metastasis after previous local SBRT.

Concurrent daily Cisplatin and high dose radiotherapy in patients with stage III non-small cell lung cancer. Dieleman EMT1, Uitterhoeve ALJ2, van Hoek MW2, et al. Int J Radiat Oncol Biol Phys. 2018 Jul 25. pii: S0360-3016(18)31641-9. doi: 10.1016/j.ijrobp.2018.07.188. [Epub ahead of print]
PURPOSE: To determine survival, local and distant control, toxicity and prognostic factors in patients with stage III non-small cell lung cancer (NSCLC) treated with concurrent chemoradiotherapy (CCRT). **METHODS:** 18F-FDG PET-CT staged, stage IIIA and IIIB NSCLC consecutive patients (n = 154) were retrospectively selected (2005-2015). CCRT consisted of daily low-dose Cisplatin (6 mg/m2) combined with 24 fractions of 2.75 Gy to a total dose of 66 Gy. **RESULTS:** During a median follow-up period of 22 months (range 1-92 months) the median overall survival was 36 months. 1-, 2- ,3- and 5-year survival rates were 79% (95%CI:73-86), 61% (95%CI:54-70), 52% (95%CI:43-60) and 40%(95%CI:31-51), respectively. The local relapse-free survival at 5 years was 55% (95%CI:44-69). Metastasis free survival at 5 years was 53% (95%CI:44-65). The incidence of severe gastrointestinal disorders (grade 3-5) was 11% among which radiation esophagitis grade 3 was 8,4%. The incidence of severe respiratory, thoracic and mediastinal disorders (grade 3-5) was 8,4% among which radiation pneumonitis grade 3 was 1,3%. Predictors of overall survival were lymph node gross tumor volume (GTV) (HR: 1.007, 95%CI: 1.000-1.012) and gender (HR: 0.500, 95%CI: 0.320-0.870 in favor of women. While lymph node GTV was an predictor of treatment toxicity (HR: 1.010, 95%CI: 1.000-1.013), GTV tumor was the predictor for distant metastasis during follow-up (HR: 1.002, 95%CI: 1.001-1.003). **CONCLUSION:** CCRT with daily low-dose cisplatin for locally advanced stage III NSCLC resulted in promising overall survival (3-year survival rate of 52% and a 5-year survival rate of 40%) with low toxicity. Lymph node GTV, tumor GTV and gender were predictors of overall survival, treatment toxicity and distant metastasis.

SMALL CELL LUNG CANCER - SCLC

Guideline for the Initial Management of Small Cell Lung Cancer (Limited and Extensive Stage) and the Role of Thoracic Radiotherapy and First-line Chemotherapy.
Sun A1, Durocher-Allen LD2, Ellis PM3, Ung YC4, Goffin JR5, Ramchandar K6, Darling G7. Clin Oncol (R Coll Radiol). 2018 Jul 11. pii: S0936-6555(18)30291-7. doi: 10.1016/j.clon.2018.06.008. [Epub ahead of print]

AIMS: We investigated the efficacy of adding radiotherapy to chemotherapy in patients with extensive stage small cell lung cancer (ES-SCLC) and the appropriate timing, dose and schedule of treatment for patients with ES-SCLC or limited stage SCLC (LS-SCLC). **MATERIALS AND METHODS:** The guideline was developed by Cancer Care Ontario's Program in Evidence-Based Care and by the Lung Cancer Disease Site Group through a systematic review of randomised controlled trials. **KEY RECOMMENDATIONS:** In patients with LS-SCLC (stage I, II and III), the addition of thoracic radiotherapy to standard chemotherapy is recommended. However, there is no clear evidence to inform definitive recommendations for optimal timing, sequential versus concurrent therapies and optimal dose or regimen. In patients with LS-SCLC, etoposide-cisplatin is the preferred regimen for adults who are being treated with combined modality therapy with curative intent. In patients with ES-SCLC (stage IV), there is insufficient evidence to recommend the addition of thoracic radiotherapy to standard chemotherapy as a standard practice for survival benefit; however, it could be considered on a case-by-case basis to reduce local recurrence. In patients with ES-SCLC, a platinum agent plus etoposide is the preferred regimen for adult patients who are being treated with combined modality therapy. Cisplatin and irinotecan represents an alternative treatment option to this, but is associated with increased rates of adverse events such as diarrhoea.

Phase II Study of Maintenance Pembrolizumab in Patients with Extensive-Stage Small Cell Lung Cancer (SCLC).

Gadgeel SM1, Pennell NA2, Fidler MJ3, et al. J Thorac Oncol. 2018 Jul 17. pii: S1556-0864(18)30600-2. doi: 10.1016/j.jtho.2018.05.002. [Epub ahead of print]

OBJECTIVE: The aim of this study was to assess the efficacy of maintenance pembrolizumab in patients with extensive-stage SCLC after treatment with platinum and etoposide. **METHODS:** Patients with extensive-stage SCLC with a response or stable disease after induction chemotherapy were eligible. Pembrolizumab at a dose of 200 mg administered intravenously every 3 weeks was initiated within 8 weeks of the last cycle of chemotherapy. The primary end point of the study was progression-free survival (PFS) from study registration, with overall survival (OS) as a key secondary end point. Available tumor tissue was assessed for expression of programmed death ligand 1 (PD-L1) both in the tumor cells and in the surrounding stroma. Blood for circulating tumor cells was collected before the first, second, and third cycles of pembrolizumab. **RESULTS:** Of the 45 patients enrolled, 56% were male and 22% had treated brain metastases. The median PFS was 1.4 months (95% confidence interval [CI]: 1.3-2.8), with a 1-year PFS of 13%. The median OS was 9.6 months (95% CI: 7.0-12), with a 1-year OS of 37%. Of the 30 tumors that could be assessed, three had PD-L1 expression (≥1%) in the tumor cells. A total of 20 tumors could be assessed for PD-L1 expression in the stroma. The median PFS in the eight patients with tumors positive for expression of PD-L1 at the stromal interface was 6.5 months (95% CI: 1.1-12.8) compared with 1.3 months (95% CI: 0.6-2.5) in 12 patients with tumors negative for this marker. No unexpected toxicities were observed. **CONCLUSION:** Maintenance pembrolizumab did not appear to improve median PFS compared with the historical data. However, the 1-year PFS rate of 13% and OS rate of 37% suggest that a subset of patients did benefit from pembrolizumab.

Effects of thoracic radiotherapy timing and duration on progression-free survival in limited-stage small cell lung cancer.

Zhao S1,2, Zhou T2,3,4, Ma S2,3,4, et al. Cancer Med. 2018 Jul 17. doi: 10.1002/cam4.1616. [Epub ahead of print]

Concurrent chemoradiotherapy (CRT) has been recommended and applied widely as the standard treatment for limited-stage small cell lung cancer (LS-SCLC). However, controversies remain regarding the optimal timing and treatment duration of thoracic radiotherapy (TRT), and their effects on patient survival. To evaluate prognostic values of TRT timing and duration on progression-free survival (PFS) in

LS-SCLC and their dependence on TRT fractionation and clinicopathological characteristics, we retrospectively analyzed 197 LS-SCLC patients receiving CRT from 2000 to 2016 at Sun Yat-sen University Cancer Center. Based on the optimal cut-off values of TRT timing and duration generated by Cutoff Finder, patients were divided into early TRT/late TRT group and short TRT/long TRT group respectively. Univariate and multivariate Cox analysis were performed to assess correlations of TRT timing, duration, fractionation, and clinicopathological characteristics with PFS. Univariate analysis revealed that early-initiated TRT (P = 2.54 × 10-4) and short TRT (P = .001) significantly correlated with longer PFS. Their PFS benefits persisted in patients receiving hyperfractionated TRT and etoposide-cisplatin (EP) chemotherapy, but were less prominent in those receiving once-daily TRT and non-EP chemotherapy. Multivariate analysis further identified early initiated TRT (P = .004) and short TRT (P = .017) as independent prognostic factors for longer PFS in LS-SCLC. Our study confirmed that early-initiated TRT and short TRT had positive prognostic roles in LS-SCLC, especially in patients receiving hyperfractionated TRT and etoposide-cisplatin chemotherapy. TRT fractionation was not an independent prognostic factor in LS-SCLC.

Whole brain radiation therapy alone versus radiosurgery for patients with 1-10 brain metastases from small cell lung cancer (ENCEPHALON Trial): study protocol for a randomized controlled trial. Bernhardt D1,2, Hommertgen A3,4, Schmitt D3,4, et al. Trials. 2018 Jul 16;19(1):388. doi: 10.1186/s13063-018-2745-x.

BACKGROUND: Conventional whole brain radiotherapy (WBRT) has been established as the treatment standard in patients with cerebral metastases from small-cell lung cancer (SCLC), however, it has only modest efficacy and limited prospective data is available for WBRT as well as local treatments such as stereotactic radiosurgery (SRS). **METHODS/DESIGN:** The present single-center prospective randomized study, conducted at Heidelberg University Hospital, compares neurocognitive function, as objectively measured by significant deterioration in Hopkins Verbal Learning Test - Revised total recall at 3 months. Fifty-six patients will be randomized to receive either SRS of all brain metastases (up to ten lesions) or WBRT. Secondary endpoints include intracranial progression (local tumor progression and number of new cerebral metastases), extracranial progression, overall survival, death due to brain metastases, local (neurological) progression-free survival, progression-free survival, changes in other cognitive performance measures, quality of life and toxicity. **DISCUSSION:** Recent evidence suggests that SRS might be a promising treatment option for SCLC patients with brain metastases. The present trial is the first to prospectively investigate the treatment response, toxicity and neurocognition of WBRT and SRS in SCLC patients. **TRIAL REGISTRATION:** Clinicaltrials.gov NCT03297788 . Registered September 29, 2017.

Development of targeted therapy and immunotherapy for treatment of small cell lung cancer. Saito M1,2,3, Shiraishi K1, Goto A4, Suzuki H3, Kohno T1, Kono K2. Jpn J Clin Oncol. 2018 Jul 1;48(7):603-608. doi: 10.1093/jjco/hyy068.

Targeted therapy against druggable genetic aberrations has shown a significantly positive response rate and longer survival in various cancers, including lung cancer. In lung adenocarcinoma (LADC), specific thyroxin kinase inhibitors against EGFR mutations and ALK fusions are used as a standard treatment regimen and show significant positive efficacy. On the other hand, targeted therapy against driver gene aberrations has not been adapted yet in small cell lung cancer (SCLC). This is because driver genes and druggable aberrations are rarely identified by next generation sequencing in SCLC. Recent advances in the understanding of molecular biology have revealed several candidate therapeutic targets. To date, poly [ADP-ribose] polymerase (PARP), enhancer of zeste homologue 2 (EZH2) or delta-like canonical Notch ligand 3 (DLL3) are considered to be druggable targets in SCLC. In addition, another candidate of personalized therapy for SCLC is immune blockade therapy of programmed death-1 (PD-1) and its

ligand, PD-L1. PD-1/PD-L1 blockade therapy is not a standard therapy for SCLC, so many clinical trials have been performed to investigate its efficacy. Herein, we review gene aberrations exploring the utility of targeted therapy and discuss blockade of immune checkpoints therapy in SCLC.

Biological effects of BMP7 on small-cell lung cancer cells and its bone metastasis. Shen W1, Pang H1, Xin B1, Duan L1, Liu L1, Zhang H1. Int J Oncol. 2018 Jul 4. doi: 10.3892/ijo.2018.4469. [Epub ahead of print]
Small-cell lung cancer (SCLC) is typically fatal if untreated. It is characterized by early and widespread metastases, and has the ability to rapidly develop resistance to chemotherapy. Bone morphogenetic protein 7 (BMP7), a member of the BMP family of signaling molecules, has been implicated in various types of cancer, particularly prostate cancer and breast cancer. However, there is little knowledge of the function of BMP7 in SCLC. The aim of the present study was to investigate the biological function of recombinant human (rh)BMP7 on SCLC cells and the underlying molecular basis for this regulatory mechanism. The effect of rhBMP7 on SCLC cell lines and associated signaling pathways was investigated. Results suggested that rhBMP7 significantly inhibited the proliferation, motility and invasion of SBC-3 and SBC-5 cells. However, rhBMP7 exhibited no effect on the apoptosis of SBC-5 cells, but promoted apoptosis of SBC-3 cells. Furthermore, cell cycle analysis revealed that rhBMP7 was able to increase the proportion of cells in G1 phase and decrease the S phase proportion. Total and membrane BMP receptor (BMPR)IA and BMPRIB were highly expressed in SBC-5 cells, whereas cytoplasmic BMPRIA and BMPRIB expression was higher in SBC-3 cells. However, activin A receptor type I expression was higher in SBC-3 cells in total and cytoplasmic proteins. Furthermore, following stimulation with rhBMP7, Smad2, Smad4 and p21 were downregulated. We hypothesized that rhBMP7 inhibited the progressiveness of SCLC cells by inducing G1 phase arrest and inhibiting S phase entry. The results of the present study indicated that BMP7 serves a key function in regulating the progression of SCLC.

PALLIATIVE AND SUPPORTIVE CARE

Intra-individual study of mindfulness: ecological momentary perspective in post-surgical lung cancer patients. Shiyko MP1, Siembor B2, Greene PB3, Smyth J4, Burkhalter JE5. J Behav Med. 2018 Jul 10. doi: 10.1007/s10865-018-9942-7. [Epub ahead of print]
The period of recovery following a lung-cancer surgery presents unique challenges and psychological demands. The study utilized ecological momentary assessments (EMA) to repeatedly sample mindfulness states in a sample of mindfulness-untrained individuals following hospital discharge. Intra- and inter-individual variability was assessed to examine cancer patients' natural capacity to exhibit mindfulness states during two weeks of recovery. Fifty nine stage I lung cancer patients (61% women, mean age = 66.1, SD = 7.9) completed EMA twice a day for two weeks. Mean level of mindfulness in the sample was low and equaled .49 (SD = .51) on the 5 point scale, with older participants being less likely to endorse mindful states. Net variability in mindfulness, defined as the person-based standard deviation in momentary scores, equaled .42 (SD = .26), ranging for 0 to 1.3 and indicating very modest variability for most participants. Results of the multi-level variance partitioning model revealed 41.4% of variance in mindfulness scores at the inter-individual, 2.4% on the temporal (i.e., .2% weekly and 2.2% daily), and 56.2% on the momentary levels. Findings indicate that, for cancer patients recovering from surgery, the innate ability to exhibit mindfulness is limited. From the methodological standpoint, consideration of intra-individual variability has implications for conceptualization and design of EMA studies.

Predictors of physical and functional loss in advanced stage lung cancer patients receiving platinum chemotherapy. Kinsey E1, Ajazi E2, Wang X3, Johnston MAM4, Crawford J5. J Thorac Oncol. 2018 Jul 4. pii: S1556-0864(18)30676-2. doi: 10.1016/j.jtho.2018.05.029. [Epub ahead of print]
INTRODUCTION: Muscle wasting has detrimental effects including increased mortality. Identifying patients at risk can guide treatment efforts. **METHODS:** POWER 1 and 2 were randomized, double blind, placebo-controlled, multinational Phase III trials of 600 lung cancer patients initiating chemotherapy to assess the efficacy of enobosarm on prevention and treatment of muscle loss. We performed a secondary analysis restricted to the control group using a cumulative logit model for ordinal outcome to determine which baseline characteristics predicted physical and functional loss during chemotherapy. **RESULTS:** Fifty three percent of patients had loss of lean body mass and 49% had loss of stair climb power (SCP) at day 84 of treatment. Of the 322 placebo patients, 232 with observable outcome and baseline covariates were included for LBM analysis and 236 for SCP analysis. More advanced disease predicted higher probability of greater physical loss (OR 1.96, 95%CI 1.14-3.36). Three factors predicted higher probability of SCP loss including taxane chemotherapy (OR 1.73, 95%CI 1.06-2.83), tobacco use before (OR 2.15, 95%CI 1.10-4.18), and SCP at baseline (OR 1.01, 95%CI 1.004-1.015). Higher BMI was a protective factor for functional loss (OR 0.85, 95%CI 0.73-0.98). A higher ECOG PS trended toward being predictive for greater probability of both physical (0.767) and functional loss (0.070), but the results were not statistically significant. **CONCLUSIONS:** Approximately 50% of patients with advanced lung cancer on chemotherapy had ongoing loss of muscle mass and muscle function. Advanced stage predicted physical loss. Tobacco use and taxane chemotherapy predicted functional loss. BMI was a protective factor for functional loss. We identified predictors of physical and functional loss that could be used as therapeutic targets or to guide treatment efforts.

Morning Fatigue Severity Profiles in Oncology Outpatients Receiving Chemotherapy. Wright F1, Dunn LB, Paul SM, Conley YP, Levine JD, Hammer MJ, Cooper BA, Miaskowski C, Kober KM. Cancer Nurs. 2018 Jul 17. doi: 10.1097/NCC.0000000000000626. [Epub ahead of print]
BACKGROUND: Morning fatigue is a distinct symptom experienced during chemotherapy that demonstrates significant interindividual variability. **OBJECTIVES:** The aims of this study were to identify subgroups with distinct morning fatigue profiles and evaluate how these subgroups differed by demographic, clinical, and symptom characteristics. **METHODS:** Outpatients (N = 1332) with breast, gastrointestinal, gynecological, or lung cancer completed questionnaires 6 times over 2 cycles of chemotherapy. Morning fatigue was assessed with the Lee Fatigue Scale. Latent profile analysis was used to identify distinct morning fatigue profiles. **RESULTS:** Four morning fatigue profiles (ie, very low, low, high, and very high) were identified. In the high and very high classes, all 6 morning fatigue scores were higher than the clinical cutoff score. Compared with those in the very low and low classes, patients in the very high class were younger and not married/partnered; lived alone; had higher incomes, higher comorbidity, and higher body mass index; and did not exercise regularly. Across the 4 classes, functional status and attentional function scores decreased and anxiety, depression, sleep disturbance, morning fatigue, and evening fatigue scores increased across the 2 cycles. **CONCLUSION:** Results provide insights into modifiable risk factors for morning fatigue. These risk factors can be used to develop more targeted interventions. **IMPLICATIONS FOR PRACTICE:** Patients in the high and very high morning fatigue classes experienced high symptom and comorbidity burdens and significant decrements in functional status. Using this information, clinicians can identify patients who are at an increased risk for higher levels of morning fatigue and prescribe interventions to improve this devastating symptom.

Combined aerobic exercise and high-intensity respiratory muscle training in patients surgically treated for non-small cell lung cancer: a pilot randomized clinical trial. Messaggi-Sartor M1,2,

Marco E3,2,4, Martínez-Téllez E5, et al. Eur J Phys Rehabil Med. 2018 Jul 6. doi: 10.23736/S1973-9087.18.05156-0. [Epub ahead of print]
BACKGROUND: Lung resection surgery further decreases exercise capacity and negatively affects respiratory muscle function in patients with non-small cell lung cancer (NSCLC). The best design for exercise interventions in these patients has not been determined. **AIM:** To assess the impact of aerobic exercise and high-intensity respiratory muscle training on patient outcomes following lung cancer resection surgery. **DESIGN:** Prospective, single-blind, pilot randomized controlled trial. **SETTING:** Outpatient cardiopulmonary rehabilitation unit of two university hospitals. **POPULATION:** Thirty-seven patients with NSCLC after tumor resection. **METHODS:** Patients were randomly assigned to exercise training or usual post-operative care. The training program consisted of aerobic exercises and high-intensity respiratory muscle training (24 supervised sessions, 3 per week, 8 weeks). Primary outcome was exercise capacity assessed with peak oxygen uptake (VO2peak) during cardiopulmonary exercise test. Secondary outcomes included changes in respiratory muscle strength, levels of serum insulin growth factor I (IGF-I) and IGF binding protein 3 (IGFBP-3), and quality of life assessed with the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) questionnaire. **RESULTS:** The 8-week training program was associated with significant improvement in VO2peak (2.13 mL/Kg/min [95%CI 0.06 to 4.20]), maximal inspiratory and expiratory pressures (18.96 cmH2O [95% CI 2.7 to 24.1] and 18.58 cmH2O [95% CI 4.0 to 33.1], respectively) and IGFBP-3 (0.61 μg/mL [%95 CI 0.1 to 1.12]). No significant differences were observed in the EORTC QLQ-C30. **CONCLUSIONS:** An 8-week exercise program consisting of aerobic exercise and high-intensity respiratory muscle training improved exercise capacity, respiratory muscle strength, and serum IGFBP-3 levels in NSCLC patients after lung resection. There was no impact on the other outcomes assessed. **CLINICAL REHABILITATION IMPACT:** A combination of aerobic exercise and respiratory muscle training could be included in the rehabilitation program of deconditioned patients with NSCLC after lung resection surgery.

A longitudinal investigation of internalized stigma, constrained disclosure, and quality of life across 12 weeks in lung cancer patients on active oncologic treatment. Williamson TJ1, Choi AK1, Kim JC1, Garon EB2, Shapiro JR3, Irwin MR4, Goldman JW5, Bornyazan K5, Carroll JM5, Stanton AL6. J Thorac Oncol. 2018 Jul 5. pii: S1556-0864(18)30769-X. doi: 10.1016/j.jtho.2018.06.018. [Epub ahead of print]
INTRODUCTION: Internalized lung cancer stigma (i.e., feelings of regret, shame, and self-blame about one's lung cancer) is related to poorer psychological outcomes. Less is known about how internalized stigma relates to physical and functional outcomes or how constrained disclosure (i.e., avoidance of or discomfort about disclosing one's lung cancer status to others) relates to well-being. Furthermore, no study has examined whether internalized stigma and constrained disclosure predict changes in well-being for lung cancer patients. This longitudinal study characterized relationships of internalized stigma and constrained disclosure with emotional and physical/functional outcomes. **METHODS:** Participants (N=101, 52.4% male, 63.4% currently/formerly smoked) were lung cancer patients on active medical treatment who completed questionnaires on stigma and well-being at study entry and at 6- and 12-week follow-up. Multivariable linear regressions characterized relationships of internalized stigma and constrained disclosure with emotional and physical/functional well-being at study entry and across time. **RESULTS:** Participants who currently or formerly smoked reported higher levels of internalized stigma (but not constrained disclosure), compared to never smokers ($p<.001$). Higher internalized stigma and constrained disclosure were uniquely associated with poorer emotional and physical/functional well-being at study entry (all $p<.05$), beyond sociodemographic characteristics, time elapsed since diagnosis, and smoking status. Higher internalized stigma predicted significant declines in emotional well-being across 6 and 12 weeks (all $p<.01$) and declines in physical/functional well-being across 6 weeks ($p<.05$).

CONCLUSIONS: Internalized lung cancer stigma and constrained disclosure relate to emotional and physical/functional maladjustment. Findings carry implications for provider- and patient-focused interventions to reduce internalized stigma and promote well-being.

COMPLEMENTARY & ALTERNATIVE THERAPY

Maekmoondong-tang in treatment of postoperative cough in patients with lung cancer: Study protocol for a randomized, double-blind, placebo-controlled, multicenter trial. Cheon C1, Kang S1, Ko Y1, Kim M2, Jang BH1, Shin YC1, Ko SG1. Medicine (Baltimore). 2018 Jul;97(29):e11541. doi: 10.1097/MD.0000000000011541.
BACKGROUND: Cough is a common symptom that occurs in 25% of patients after lung cancer surgery. It might last a long time and degrade the quality of life of patients. Maekmoondong-tang (Bakumondo-to in Japanese or Mai-Men-Dong-Tang in Chinese) is a herbal medicine which has been widely used for respiratory diseases with cough in Korea, China, and Japan. **AIMS:** The aim of the present study is to evaluate the efficacy and safety of Maekmoondong-tang for postoperative cough in patient with lung cancer. **METHODS/DESIGN:** This study is a randomized, double-blind, placebo-controlled, multicenter trial of Maekmoondong-tang. A total of 96 participants will be enrolled and allocated to 2 parallel groups: the Maekmoondong-tang group and the placebo group from 5 university hospitals. The participants will be administered either Maekmoondong-tang or a placebo 3 times a day for 4 weeks. The primary outcome measurement is the change in the Leicester Cough Questionnaire (LCQ) score. The secondary outcome measurements are the changes in the cough visual analog scale and Yin Deficiency Scale. The participants will visit 4 times in total for 4 weeks of trial period. **DISCUSSION:** The present study will be the first multicener study to evaluate the efficacy and safety of Maekmoondong-tang for postoperative cough in patient with lung cancer surgery. The results of this study will provide a new treatment for cough using herbal medicine and will be a reference for planning clinical trial of herbal medicine in patient with cough.

Complementary Medicine, Refusal of Conventional Cancer Therapy, and Survival Among Patients With Curable Cancers. Johnson SB1, Park HS1, Gross CP2, Yu JB1,2. JAMA Oncol. 2018 Jul 19. doi: 10.1001/jamaoncol.2018.2487. [Epub ahead of print]
IMPORTANCE: There is limited information on the association among complementary medicine (CM), adherence to conventional cancer treatment (CCT), and overall survival of patients with cancer who receive CM compared with those who do not receive CM. **OBJECTIVES:** To compare overall survival between patients with cancer receiving CCT with or without CM and to compare adherence to treatment and characteristics of patients receiving CCT with or without CM. **DESIGN, SETTING, AND PARTICIPANTS:** This retrospective observational study used data from the National Cancer Database on 1 901 815 patients from 1500 Commission on Cancer-accredited centers across the United States who were diagnosed with nonmetastatic breast, prostate, lung, or colorectal cancer between January 1, 2004, and December 31, 2013. Patients were matched on age, clinical group stage, Charlson-Deyo comorbidity score, insurance type, race/ethnicity, year of diagnosis, and cancer type. Statistical analysis was conducted from November 8, 2017, to April 9, 2018. **EXPOSURES:** Use of CM was defined as "Other-Unproven: Cancer treatments administered by nonmedical personnel" in addition to at least 1 CCT modality, defined as surgery, radiotherapy, chemotherapy, and/or hormone therapy. **MAIN OUTCOMES AND MEASURES:** Overall survival, adherence to treatment, and patient characteristics. **RESULTS:** The entire cohort comprised 1 901 815 patients with cancer (258 patients in the CM group and 1 901 557 patients in the control group). In the main analyses following matching, 258 patients (199 women and 59 men; mean age, 56 years [interquartile range, 48-64 years]) were in the CM group, and 1032 patients (798 women and 234 men; mean age, 56 years [interquartile range, 48-64 years]) were in the control group.

Patients who chose CM did not have a longer delay to initiation of CCT but had higher refusal rates of surgery (7.0% [18 of 258] vs 0.1% [1 of 1031]; P < .001), chemotherapy (34.1% [88 of 258] vs 3.2% [33 of 1032]; P < .001), radiotherapy (53.0% [106 of 200] vs 2.3% [16 of 711]; P < .001), and hormone therapy (33.7% [87 of 258] vs 2.8% [29 of 1032]; P < .001). Use of CM was associated with poorer 5-year overall survival compared with no CM (82.2% [95% CI, 76.0%-87.0%] vs 86.6% [95% CI, 84.0%-88.9%]; P = .001) and was independently associated with greater risk of death (hazard ratio, 2.08; 95% CI, 1.50-2.90) in a multivariate model that did not include treatment delay or refusal. However, there was no significant association between CM and survival once treatment delay or refusal was included in the model (hazard ratio, 1.39; 95% CI, 0.83-2.33). **CONCLUSIONS AND RELEVANCE:** In this study, patients who received CM were more likely to refuse additional CCT, and had a higher risk of death. The results suggest that mortality risk associated with CM was mediated by the refusal of CCT.

Lentinan as an immunotherapeutic for treating lung cancer: a review of 12 years clinical studies in China. Zhang Y1, Zhang M1, Jiang Y1,2, et al. J Cancer Res Clin Oncol. 2018 Jul 24. doi: 10.1007/s00432-018-2718-1. [Epub ahead of print]
PURPOSE: Lentinan is a polysaccharide extracted from Shiitake mushrooms that have been used to improve general health for thousands of years in Asia. Lentinan injection is a clinically approved drug in several countries in Asia. The purpose of this study is to review the structure, preclinical and clinical studies, and molecular mechanisms of lentinan. Most importantly, the clinical effectiveness of lentinan as an adjuvant therapeutic drug in treating patients with lung cancer in China during the past 12 years is analyzed statistically. **METHODS:** We carried out literature search of randomized controlled trials (RCTs) published from 2004 to 2016 based on CNKI (China National Knowledge Infrastructure), VIP (Chongqing VIP Chinese Scientific Journals Database) and Wanfang database, and 38 eligible RCTs of lentinan-associated lung cancer treatment were identified, containing 3,117 patients. **RESULTS:** The structure and function relationship and underlying molecular mechanism of lentinan as an immunostimulant has been summarized. The mean value of overall response rate in treating lung cancer was increased from 43.3% of chemotherapy alone to 56.9% of lentinan plus chemotherapy [p < 0.001, 95% confidence interval (CI) 0.102-0.170]. Compared with chemotherapy alone, lentinan plus chemotherapy showed more efficacy in treating lung cancer (pooled RR 0.79, 95% CI 0.74-0.85) and no statistical heterogeneity was found among studies (I2 = 11%). **CONCLUSION:** Clinical data presented in the past 12 years shows that lentinan is effective not only in improving quality of life, but also in promoting the efficacy of chemotherapy during lung cancer treatment.

MISCELLANEOUS WORKS

Radon Exposure-induced Genetic Variations in Lung Cancers among Never Smokers. Choi JR1, Koh SB2, Kim HR3, Lee H4, Kang DR1. J Korean Med Sci. 2018 Jun 20;33(29):e207. doi: 10.3346/jkms.2018.33.e207. eCollection 2018 Jul 16.
BACKGROUND: Lung cancer in never smokers (LCINS) differs etiologically and clinically from lung cancer attributed to smoking. After smoking, radon exposure is the second leading cause and the primary risk factor of lung cancer among never smokers. Exposure to radon can lead to genetic and epigenetic alterations in tumor genomes affecting genes and pathways involved in lung cancer development. The present study sought to explore genetic alterations associated with LCINS exposed to radon gas indoors. **METHODS:** Genetic associations were assessed via a case-control study of LCINS (39 cases and 30 controls) using next generation sequencing. Associations between genetic mutations and high exposure to radon were investigated by OncoPrint and heatmap graphs. Bioinformatic analysis was conducted using various tools. According radon exposure levels, we divided subjects in two groups of cases and controls.

RESULTS: We found that ABL2 rs117218074, SMARCA4 rs2288845, PIK3R2 rs142933317, MAPK1 rs1803545, and androgen receptor (AR) rs66766400 were associated with LCINS exposed to high radon levels. Among these, Chromodomain helicase DNA-binding protein 4 (CHD4) rs74790047, TSC2 rs2121870, and AR rs66766408 were identified as common exonic mutations in both lung cancer patients and normal individuals exposed to high levels of radon indoor. **CONCLUSION:** We identified that CHD4 rs74790047, TSC2 rs2121870, and AR rs66766408 are found to be common exonic mutations in both lung cancer patients and normal individuals exposed to radon indoors. Further analysis is needed to determine whether these genes are completely responsible for LCINS exposed to residential radon.

Safety and Efficacy of Retreating with Immunotherapy After Immune-Related Adverse Events in Patients with NSCLC.

Santini FC1, Rizvi H2, Plodkowski AJ3, et al. Cancer Immunol Res. 2018 Jul 10. pii: canimm.0755.2017. doi: 10.1158/2326-6066.CIR-17-0755. [Epub ahead of print]

Consideration of retreatment following recovery from an irAE is a common clinical scenario, but the safety and benefit of retreatment is unknown. We identified patients with advanced non-small cell lung cancer (NSCLC) treated with anti-PD-L1 who had treatment held due to serious irAEs and divided them into two groups: those retreated with anti-PD-L1 (retreatment cohort) or those in whom anti-PD-L1 was stopped (discontinuation cohort). Of 482 patients with NSCLC treated with anti-PD-L1, 68 (14%) developed a serious irAE requiring treatment interruption. Of these, 38 (56%) were retreated and 30 (44%) had treatment discontinued. In the retreatment cohort, 18 (48%) patients had no subsequent irAEs, 10 (26%) had recurrence of the initial irAE, and 10 (26%) had a new irAE. Most recurrent/new irAEs were mild (58% grade 1-2) and manageable (84% resolved or improved to grade 1). Two treatment-related deaths occurred. Recurrent/new irAEs were more likely if the initial irAE required hospitalization, but the initial grade and time to retreatment did not influence risk. Among those with no observed partial response prior to the irAE, PFS and OS were longer in the retreatment cohort. Conversely, for those with objective responses prior to the irAE, PFS and OS were similar in the retreatment and discontinuation cohorts. Among patients with early objective responses prior to a serious irAE, outcomes were similar whether or not they were retreated. Together, these data suggest that benefit may occur with retreatment in patients with irAEs who had no treatment response prior to irAE onset.

Lung Cancer Stigma Across the Social Network: Patients' and Caregivers' Perspectives.

Occhipinti S1, Dunn J2, O'Connell DL3, Garvey G4, Valery PC5, Ball D6, Fong KM7, Vinod S8, Chambers S9. J Thorac Oncol. 2018 Jul 5. pii: S1556-0864(18)30766-4. doi: 10.1016/j.jtho.2018.06.015. [Epub ahead of print]

OBJECTIVE: To examine the personal experiences of people with lung cancer and of their caregivers and how stigma manifests throughout the patient's social network. **METHODS:** Qualitative thematic analysis conducted on interviews with 28 lung cancer patients and caregivers. Telephone interviews were conducted and transcribed verbatim. Data analysis was guided by contemporary stigma theory. **RESULTS:** Patients and caregivers reported high levels of felt stigma and concomitant psychological distress in response to the diagnosis of lung cancer. Three overarching themes emerged: the nexus of lung cancer and smoking; moralization; attacking the link between lung cancer and smoking. Stigma was inevitably linked to smoking and this formed the hub around which other themes were organised. Caregivers reported feeling invisible and noted a lack of support systems for families and caregivers. As well, there was evidence that caregivers experienced stigma-by-association as members of the patients' close networks. Both groups responded ambivalently to stigmatizing antismoking advertisements. **CONCLUSIONS:** The qualitative analysis demonstrated the complex interplay of the social and the personal domains in the experience and outcomes of stigma in lung cancer. There is a significant potential for caregivers of lung cancer patients to experience exacerbations of psychosocial distress as a

consequence of widely shared negative views about lung cancer and its prognosis. It remains for researchers and practitioners to incorporate such complexity in addressing stigma and psychosocial distress in both patients and caregivers.

Treatment of tobacco dependence: current state of the art. Kathuria H1, Leone FT2, Neptune ER3. Curr Opin Pulm Med. 2018 Jul;24(4):327-334. doi: 10.1097/MCP.0000000000000491.
PURPOSE OF REVIEW: The Centers for Medicare and Medicaid Services' requirement to integrate tobacco treatment with lung cancer screening (LCS) has served as a catalyst for motivating pulmonary medicine clinicians to improve upon their ability to effectively treat tobacco dependence. To do so, clinicians need to be well versed in the behavioral and pharmacologic tools that promote smoking cessation. **RECENT FINDINGS:** The current review outlines current strategies for treating tobacco dependence, focusing on the important interplay between counseling and pharmacotherapy. Studies that have been found to be particularly effective in patients with smoking-related lung disease and in the LCS setting are reviewed. New therapies that are in the pipeline, as well as novel strategies aimed at improving both adoption and effectiveness of existing therapies, are discussed. **SUMMARY:** Treating tobacco dependence improves mortality and quality of life far more than the limited therapies available to treat smoking-related lung disease. Novel strategies to making tobacco treatment services more widely available, particularly to vulnerable patient populations, are needed to further decrease smoking-related morbidity and mortality. The Affordable Care Act's greater focus on prevention represents a moment of opportunity for healthcare providers and systems to engage in these efforts.

Acceptance of the Advanced Practice Nurse in Lung Cancer Role by Healthcare Professionals and Patients: A Qualitative Exploration. Serena A1, Dwyer AA2, Peters S3, Eicher M4. J Nurs Scholarsh. 2018 Jul 22. doi: 10.1111/jnu.12411. [Epub ahead of print]
PURPOSE: The purpose of this study was to explore the acceptance of a novel role, the advanced practice nurse in lung cancer (APNLC), from the perspective of patients and healthcare professionals in a country lacking a regulatory oversight for advanced practice nursing (APN) roles. **METHODS AND DESIGN:** This study utilized a qualitative methodology using focus groups and semistructured nterviews. Participants were purposively sampled in a Swiss academic medical center. Two focus groups were conducted: the first included nurses (n = 5) and the social worker, while the second targeted physicians (n = 6). The APNLC and patients (n = 4) were interviewed using semistructured interviews. Data were analyzed using thematic content analysis. **FINDINGS:** Three main themes were identified: APNLC role identification, APNLC role-specific contributions, and APNLC flexible service. Physicians and patients clearly recognized the APNLC role, noting contributions to continuity of care, psychosocial support, and enabling symptom self-management. Nurses perceived the APNLC role as overlapping with the oncology nurse role. Flexibility in providing care was seen as the strength of the APNLC role, yet this also posed organizational challenges. **CONCLUSIONS:** The new role appears to be well accepted by patients and physicians, yet barriers posed by nursing colleagues remain challenging. **CLINICAL RELEVANCE:** Based on existing literature and the present findings, we propose a model to guide future implementation and enhance acceptance of the APNLC role. This model comprises three actions: (a) formalizing nursing role expectations, (b) providing appropriate support and resources, and (c) promoting a national plan for APN regulation.

Time to treatment and survival in veterans with lung cancer eligible for curative intent therapy. Ha D1, Ries AL2, Montgrain P3, Vaida F4, Sheinkman S5, Fuster MM3. Respir Med. 2018 Aug;141:172-179. doi: 10.1016/j.rmed.2018.07.005. Epub 2018 Jul 17.
BACKGROUND: The Institute of Medicine emphasizes care timeliness as an important quality metric. We assessed treatment timeliness in stage I-IIIA lung cancer patients deemed eligible for curative intent

therapy and analyzed the relationship between time to treatment (TTT) and timely treatment (TT) with survival. **METHODS:** We retrospectively reviewed consecutive cases of stage I-IIIA lung cancer deemed eligible for curative intent therapy at the VA San Diego Healthcare System between 10/2010-4/2017. We defined TTT as days from chest tumor board to treatment initiation and TT using guideline recommendations. We used multivariable (MVA) Cox proportional hazards regressions for survival analyses. **RESULTS:** In 177 veterans, the median TTT was 35 days (29 days for chemoradiation, 36 for surgical resection, 42 for definitive radiation). TT occurred in 33% or 77% of patients when the most or least timely guideline recommendation was used, respectively. Patient characteristics associated with longer TTT included other cancer history, high simplified comorbidity score, stage I disease, and definitive radiation treatment. In MVA, TTT and TT [HR 0.53 (95% CI 0.27, 1.01) for least timely definition] were not associated with OS in stage I-IIIA patients, or disease-free survival in subgroup analyses of 122 stage I patients [HR 1.49 (0.62, 3.59) for least timely definition]. **CONCLUSION:** Treatment was timely in 33-77% of veterans with lung cancer deemed eligible for curative intent therapy. TTT and TT were not associated with survival. The time interval between diagnosis and treatment may offer an opportunity to deliver or improve other cancer care.

Evaluating the Completeness of ClinicalTrials.gov. Stergiopoulos S1, Getz KA1, Blazynski C2. Ther Innov Regul Sci. 2018 Jul 26:2168479018782885. doi: 10.1177/2168479018782885. [Epub ahead of print]
BACKGROUND: To date, although studies have been conducted to assess compliance with listing clinical trial information, to our knowledge there is nothing in the literature examining the completion and accuracy of clinical trial site information on ClinicalTrials.gov. **METHODS:** We compared clinical trial information originating from ClinicalTrials.gov to a widely subscribed and well-established commercial clinical trial database, Informa Pharma Intelligence's Trialtrove, as Trialtrove includes information from ClinicalTrials.gov among its more than 30,000 sources. We assessed breast cancer, non-small cell lung cancer, type 2 diabetes mellitus, and pain clinical trials submitted to ClinicalTrials.gov . We compared the number of trials associated with each disease indication for each database, and we conducted a head-to-head comparison of certain data fields of clinical trial information found in both databases for clinical trials with identical National Clinical Trial (NCT) numbers. **RESULTS:** As of January 17, 2017, Trialtrove captured 31% more clinical trials (10,786 trials) in the selected disease indications than did ClinicalTrials.gov (7,419 trials) using identical Medical Subject Headings (MeSH) terms for breast cancer, non-small cell lung cancer, type 2 diabetes mellitus, and pain. Clinical trial site information was identical in 48% of clinical trials, while country information was identical in 82% of clinical trials, and patient enrollment figures identical for 86% of clinical trials. Clinical trial status, Phase, and start year differed across the 2 datasets. **CONCLUSION:** This study provides a baseline to compare the completeness of trial information required by the NIH and HHS with respect to reporting practices on ClinicalTrials.gov. While one cannot determine which database is more accurate: ClinicalTrials.gov or Trialtrove, wide variation exists in clinical trial site and country information for trials with identical NCT numbers suggesting that caution should be used when relying solely on ClinicalTrials.gov to assess the clinical trial landscape.

Impact of the Affordable Care Act (ACA) Medicaid Expansion on Cancer Admissions and Surgeries. Eguia E1,2, Cobb AN1,2, Kothari AN2, Molefe A3, Afshar M4, Aranha GV5, Kuo PC6. Ann Surg. 2018 Jul 12. doi: 10.1097/SLA.0000000000002952. [Epub ahead of print]
OBJECTIVE: This study aims to evaluate the trends in cancer (CA) admissions and surgeries after the Affordable Care Act (ACA) Medicaid expansion. **METHODS:** This is a retrospective study using HCUP-SID analyzing inpatient CA (pancreas, esophagus, lung, bladder, breast, colorectal, prostate, and gastric) admissions and surgeries pre- (2010-2013) and post- (2014) Medicaid expansion. Surgery was

defined as observed resection rate per 100 cancer admissions. Nonexpansion (FL) and expansion states (IA, MD, and NY) were compared. A generalized linear model with a Poisson distribution and logistic regression was used with incidence rate ratios (IRR) and difference-in-differences (DID). **RESULTS:** There were 317, 858 patients in our sample which included those with private insurance, Medicaid, or no insurance. Pancreas, breast, colorectal, prostate, and gastric CA admissions significantly increased in expansion states but decreased in nonexpansion states. (IRR 1.12, 1.14, 1.11, 1.34, 1.23; P<.05) Lung and colorectal CA surgeries (IRR 1.30, 1.25; P<.05) increased, while breast CA surgeries (IRR 1.25; P<.05) decreased less in expansion states. Government subsidized, or self-pay patients had greater odds of undergoing lung, bladder, and colorectal CA surgery (OR 0.45 vs 0.33; 0.60 vs 0.48; 0.47 vs 0.39; P<.05) in expansion states after reform. **CONCLUSIONS:** In states that expanded Medicaid coverage under the ACA, the rate of surgeries for colorectal and lung CA increased significantly, while breast CA surgeries decreased less. Parenthetically, these cancers are subject to population screening programs. We conclude that expanding insurance coverage results in enhanced access to cancer surgery.

More Frequent Surveillance Following Lung Cancer Resection Is Not Associated With Improved Survival: A Nationally Representative Cohort Study. McMurry TL1, Stukenborg GJ1, Kessler LG2, et al. Ann Surg. 2018 Jul 12. doi: 10.1097/SLA.0000000000002955. [Epub ahead of print]
OBJECTIVE: To evaluate whether an association exists between the intensity of surveillance following surgical resection for non-small cell lung cancer (NSCLC) and survival. **BACKGROUND:** Surveillance guidelines following surgical resection of NSCLC vary widely and are based on expert opinion and limited evidence. **METHODS:** A Special Study of the National Cancer Database randomly selected stage I to III NSCLC patients for data reabstraction. For patients diagnosed between 2006 and 2007 and followed for 5 years through 2012, registrars documented all postsurgical imaging with indication (routine surveillance, new symptoms), recurrence, new primary cancers, and survival, with 5-year follow-up. Patients were placed into surveillance groups according to existing guidelines (3-month, 6-month, annual). Overall survival and survival after recurrence were analyzed using Cox Proportional Hazards Models. **RESULTS:** A total of 4463 patients were surveilled with computed tomography scans; these patients were grouped based on time from surgery to first surveillance. Groups were similar with respect to age, sex, comorbidities, surgical procedure, and histology. Higher-stage patients received more surveillance. More frequent surveillance was not associated with longer risk-adjusted overall survival [hazard ratio for 6-month: 1.16 (0.99, 1.36) and annual: 1.06 (0.86-1.31) vs 3-month; P value 0.14]. More frequent imaging was also not associated with postrecurrence survival [hazard ratio: 1.02/month since imaging (0.99-1.04); P value 0.43]. **CONCLUSIONS:** These nationally representative data provide evidence that more frequent postsurgical surveillance is not associated with improved survival. As the number of lung cancer survivors increases over the next decade, surveillance is an increasingly important major health care concern and expenditure.