Caring Ambassadors Lung Cancer Program
Literature Review, January 2019

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Interleukin-6 and insulin-like growth factor-1 synergistically promote the progression of NSCLC.
Tang H1, Bai Y1, Pan G1, Wang X1, Wei Y2, Yang Z1, Zhao J1. Autoimmunity. 2018 Dec;51(8):399-407. doi: 10.1080/08916934.2018.1550079. Epub 2019 Jan 3.
The signaling pathways of interleukin-6 (IL-6) and insulin-like growth factor 1 (IGF-1) play an important role in the progression of lung cancer, and this study aimed to explore whether they can synergistically promote the progression of non-small cell lung cancer (NSCLC). We found that IL-6, glycoprotein 130 (GP130), IGF-1 and IGF-1R were highly expressed in NSCLC (p = .000), and there was the correlation between GP130, IGF-1, and IGF-1R (p < .01). The overall survival of patients with the co-expression of GP130 and IGF-1R was significantly shorter (p = .0360). Co-stimulation of IL-6 and IGF-1 resulted in significantly enhanced in cell proliferation, (p < .05), invasion (p < .05), cycle (p < .05), apoptosis (p < .05), and the expression of signal molecules (GP130, IGF-1R, p-AKT, and p-ERK1/2) (all p < .05) in NSCLC cells. This experiment revealed that IL-6 and IGF-1 can synergistically promote the progression of NSCLC. The high expression of GP130 and IGF-1R is an independent risk factor for poor prognosis patients, and it is helpful to find a more accurate target for targeted therapy in NSCLC.

Circulating miRNA-21 and miRNA-23a expression signature as potential biomarkers for early detection of non-small-cell lung cancer. Hetta HF1,2, Zahran AM3, Shafik EA3, et al. Microrna. 2019 Jan 15. doi: 10.2174/1573399815666190115151500. [Epub ahead of print]
BACKGROUND AND AIM: Lung cancer (LC) is a major cancer killer worldwide, and 5-yr survival is extremely poor (≤15%), accentuating the need for more effective diagnostic and therapeutic strategies. Studies have shown cell-free microRNAs (miRNAs) circulating in the serum and plasma with specific expression in cancer, indicating the potential of using miRNAs as biomarkers for cancer diagnosis and therapy. This study aimed to identify differentially-expressed two miRNAs in the plasma of non-small cell lung cancer (NSCLC) patients that might be a clinically useful tool for lung cancer early detection. miRNA-21 is one of the most abundant oncomirs. miRNA-23a functions as an oncogene in several human cancers, however, its clinical value has not been investigated in NSCLC. **MATERIALS AND METHODS:** A case-control study was conducted in Assiut University Hospital, Egypt, from 2017 to

2018. Plasma samples were obtained from 45 NSCLC patients. The expression level of miR-21 and miRNA-23a was detected by qRT-PCR and compared to 40 healthy control subjects. The relation between both miRNAs and clinicopathological parameters was evaluated. **RESULTS:** The expression level of miR-21 and miRNA-23a was significantly up-regulated (36.9±18.7 vs 1.12±0.84 and 24.7±19.09 vs 1.16±0.45) in NSCLC compared to matched controls (P<0.0001each). There was a significant difference in the level of plasma miRNA-21 and miRNA-23a expression between the different grades of the disease (P=0.032 and P=0.001, respectively). The plasma miRNA-21 and miRNA-23a levels in the lung cancer patients with distant metastasis (n=20) were significantly higher than those in the patients without metastasis (n=25) (P<0.0001 each), the expression of miR-21 and miRNA-23a was significantly associated with tumor size (P=0.001, P= 0.0001, respectively), but not significantly related to lymph node metastasis (P= 0.687 and 0.696 respectively). A positive correlation was observed between miRNA-21 and miRNA-23a (r = 0.784, P<0.01), There was no significant difference in the plasma miRNA-21 and miRNA-23a levels in the lung cancer patients with different histopathological types. **CONCLUSION:** miR-21 and miR-23a might play an oncogenic role in LC and is a poor prognostic factor. Switching off miRNA-21 and miRNA-23a may improve the treatment of LC. Our results must be verified by large-scale prospective studies with standardized meth¬odology.

[**Identification of Key Genes and Pathways in Female Lung Cancer Patients Who Never Smoked by a Bioinformatics Analysis.**](#) Shi K1,2, Li N3, Yang M3, Li W1,2. J Cancer. 2019 Jan 1;10(1):51-60. doi: 10.7150/jca.26908. eCollection 2019.
Smoking is considered the major risk factor for lung cancer, but only a small portion of female lung adenocarcinoma patients are associated with smoking. Thus, identifying crucial genes and pathways related to nonsmoking female lung cancer patients is of great importance. Gene expression profiles were downloaded from the Gene Expression Omnibus (GEO) and the Cancer Genome Atlas (TCGA) databases. The R software packages were applied to screen the differentially expressed genes (DEGs). GO term enrichment and KEGG pathway analyses were carried out using DAVID tools. The protein-protein interaction (PPI) network was constructed by Cytoscape software. In total, 487 downregulated and 199 upregulated DEGs were identified. The down-regulated DEGs were mainly enriched for behavior and response to wounding, and the upregulated DEGs were significantly enriched for multicellular organismal metabolic process and cell division. The KEGG pathway analysis revealed that the downregulated DEGs were significantly enriched for cell adhesion molecules and neuroactive ligand-receptor interaction, while the upregulated DEGs were mainly enriched for cell cycle and the p53 signaling pathway. The top 10 hub genes and top 3 gene interaction modules were selected from the PPI network. Of the ten hub genes, a high expression of five genes was related to a poor OS in female lung cancer patients who never smoked, including IL6, CXCR2, FPR2, PPBP and HBA1. However, a low expression of GNG11, LRRK2, CDH5, CAV1 and SELE was associated with a worse OS for the female lung cancer patients who never smoked. In conclusion, our study provides novel insight for a better understanding of the pathogenesis of nonsmoking female lung cancer, and these identified DEGs may serve as biomarkers for diagnostics and treatment.

SCREENING, DIAGNOSIS BIOMARKER TESTING AND STAGING

[**Impact of Slice Thickness on the Predictive Value of Lung Cancer Screening Computed Tomography in the Evaluation of Coronary Artery Calcification.**](#) Christensen JL1, Sharma E1, Gorvitovskaia AY1, et al. J Am Heart Assoc. 2019 Jan 8;8(1):e010110. doi: 10.1161/JAHA.118.010110.
BACKGROUND: Image reconstruction thickness may impact quantitative coronary artery calcium scoring (CACS) from lung cancer screening computed tomography (LCSCT), limiting its application in practice. **METHODS AND RESULTS:** We evaluated Agatston-based quantitative CACS from 1.25-mm

LCSCT and cardiac computed tomography for agreement in 87 patients. We then evaluated Agatston-based quantitative CACS from 1.25-, 2.5-, and 5.0-mm slice thickness LCSCT for agreement in 258 patients. Secondary analysis included the impact of slice thickness on predictive value of 4-year outcomes. Median age of patients who underwent 1.25-mm LCSCT and cardiac computed tomography was 63 years (interquartile interval, 57, 68). CACS from 1.25-mm LCSCT and cardiac computed tomography demonstrated a strong Pearson correlation, R=0.9770 (0.965, 0.985), with good agreement. The receiver operating characteristic curve areas under the curve for cardiac computed tomography and LCSCT were comparable at 0.8364 (0.6628, 1.01) and 0.8208 (0.6431, 0.9985), respectively (P=0.733). Median age of patients who underwent LCSCT with 3 slice thicknesses was 66 years (interquartile interval, 63, 73). Compared with CACS from 1.25-mm scans, CACS from 2.5- and 5.0-mm scans demonstrated strong Pearson correlations, R=0.9949 (0.9935, 0.996) and R=0.9478 (0.9338, 0.959), respectively, though bias was largely negative for 5.0-mm scans. Receiver operating characteristic curve areas under the curve for 1.25-, 2.5-, and 5.0-mm scans were comparable at 0.7040 (0.6307, 0.7772), 0.7063 (0.6327, 0.7799), and 0.7194 (0.6407, 0.7887), respectively (P=0.6487). When using individualized high-risk thresholds derived from respective receiver operating characteristic curves, all slice thicknesses demonstrated similar prognostic value. **CONCLUSIONS:** Slice thickness is an important consideration when interpreting Agatston CACS from LCSCTs. Despite the absence of ECG gating, it appears reasonable to report CACS from either 1.25- or 2.5-mm slice thickness LCSCT to help stratify cardiovascular risk. Conversely, 5.0-mm scans largely underidentify calcium, limiting practical use within the established CACS values used to categorize cardiovascular risk.

[Lung cancer screening: Practice guidelines and insurance coverage are not enough.](#) McDonnell KK1, Estrada RD1, Dievendorf AC1, Blew L1, Sercy E2, Khan S2, Hardin JW3, Warden D1, Eberth JM3. J Am Assoc Nurse Pract. 2019 Jan;31(1):33-45. doi: 10.1097/JXX.0000000000000096.
BACKGROUND AND PURPOSE: Low-dose computed tomography (LDCT) is expected to increase early detection of lung cancer and improve survival. The growth in the number of advanced nurse practitioners (NPs) in primary care settings increases the likelihood that an NP will serve as a patient's provider. This study's purpose was to examine knowledge, attitudes, and practices regarding LDCT among NPs who work in primary care settings. **METHODS:** An explanatory, sequential, mixed-method design used a 32-item questionnaire, followed by a semi-structured telephone interview. The development of the survey and interview questions were guided by a conceptual framework representing a temporal sequence for behavior change and potential barriers to guideline adherence. **CONCLUSIONS:** Nurse practitioners believe that shared decision making with their high-risk patients about LDCT is within their scope of their practice. Working in time-constrained primary care settings, NPs have limited abilities to improve the uptake of LDCT. Substantial patient barriers exist that deter follow through on providers' recommendation. Disseminating guidelines and authorizing health insurance reimbursement is insufficient. **IMPLICATIONS FOR PRACTICE:** Research is needed that investigates the screening process so that barriers can be closely studied. Culture change is needed where early detection has greater value for insurers, providers, and patients.

[Safety and diagnostic performance of pulmonologists performing electromagnetic guided percutaneous lung biopsy (SPiNperc).](#) Mallow C1, Lee H1, Oberg C2, et al. Respirology. 2019 Jan 24. doi: 10.1111/resp.13471. [Epub ahead of print]
BACKGROUND AND OBJECTIVE: Percutaneous lung biopsy for diagnostic sampling of peripheral lung nodules has been widely performed by interventional radiologists under computed tomography (CT) guidance. New technology allows pulmonologists to perform percutaneous lung biopsies using electromagnetic (EM) guided technology. With the adoption of this new technique, the safety, feasibility

and diagnostic yield need to be explored. The goal of this study was to determine the safety, feasibility and diagnostic yield of EM-guided percutaneous lung biopsy performed by pulmonologists. **METHODS:** We conducted a retrospective, multicentre study of 129 EM-guided percutaneous lung biopsies that occurred between November 2013 and March 2017. The study consisted of seven academic and three community medical centres. **RESULTS:** The average age of participants was 65.6 years, BMI was 26.3 and 50.4% were females. The majority of lesions were in the right upper lobe (37.2%) and left upper lobe (31.8%). The mean size of the lesions was 27.31 mm and the average distance from the pleura was 13.2 mm. Practitioners averaged two fine-needle aspirates and five core biopsies per procedure. There were 23 (17.8%) pneumothoraces, of which 16 (12.4%) received small-bore chest tube placement. The diagnostic yield of percutaneous lung biopsy was 73.7%. When EM-guided bronchoscopic sampling was also performed during the same procedural encounter, the overall diagnostic yield increased to 81.1%. **CONCLUSION:** In this large multicentred series, the use of EM guidance for percutaneous lung biopsies was safe and feasible, with acceptable diagnostic yield in the hands of pulmonologists. A prospective multicentre trial to validate these findings is currently underway (NCT03338049).

[**Molecular Testing for EGFR Mutations and ALK Rearrangements in the Cytological Specimens From the Patients With Non-Small Cell Lung Cancer.**](#) Wang X1, Chen S, Emerson RE, et al. Appl Immunohistochem Mol Morphol. 2019 Jan 25. doi: 10.1097/PAI.0000000000000701. [Epub ahead of print]

OBJECTIVE: The aim of this study was to investigate epidermal growth factor receptor (EGFR) gene mutations and anaplastic lymphoma kinase (ALK) gene rearrangements using cytological specimens from the patients with a diagnosis of primary or metastatic lung non-small cell carcinoma. **MATERIALS AND METHODS:** A total 307 cases were submitted for EGFR mutational analysis and 265 cases for ALK analysis. The cytological specimen sources included lung, lymph node, liver, bone, adrenal gland, mesentery mass, and body fluids/bronchial brushing. EGFR mutations in the exons 18 to 21 were analyzed with Qiagen EGFR Pyro Kits. Fluorescence in situ hybridization (FISH) studies for ALK rearrangement inv(2)(p21; p23) were performed on the paraffin-embedded cell block sections utilizing dual-color Vysis LSI ALK Break Apart Probe Kit. **RESULTS:** Among 307 fine needle aspirate cases for EGFR analysis, 302 cases (269 from cell blocks, 33 from direct smears) had sufficient material for EGFR test. Five cases failed due to inadequate cellularity. Twenty six of 302 (8.6%) cases were positive for EGFR mutations. A total of 265 cases submitted for ALK analysis included 240 cases of fine needle aspirate, 25 cases of pleural fluid/pericardial fluid/bronchial washings. Eight cases failed because of low cellularity, whereas 257 of 265 cases had sufficient material for ALK FISH study. Nine of 257 cases (3.5%) revealed ALK rearrangement by FISH. **CONCLUSIONS:** The current study demonstrates that cytological specimens can yield sufficient material for EGFR mutations and ALK rearrangement test. Our study reveals that 8.6% of EGFR mutation rate and 3.5% of ALK rearrangement rate in the cytology specimens from the patients with primary or metastatic lung non-small cell carcinoma.

[**Comparison of cardiovascular effects of crizotinib and chemotherapy in ALK-positive advanced non-small-cell lung cancer.**](#)
Wilner KD1, Usari T2, Polli A2, Kim EE3. Future Oncol. 2019 Jan 17. doi: 10.2217/fon-2018-0869. [Epub ahead of print]

AIM: We analyzed cardiac function in two Phase III studies of previously treated (PROFILE 1007) or untreated (PROFILE 1014) ALK-positive advanced non-small-cell lung cancer. **PATIENTS & METHODS:** Adverse events associated with cardiac failure were compared between treatment arms in each study separately. Cardiac function was assessed prospectively by multigated acquisition scans or echocardiograms. **RESULTS:** In PROFILE 1007 and 1014, incidence of cardiac failure adverse events was 0% (crizotinib) versus 0.6% (chemotherapy) and 2.3% versus 0.6%, respectively. In crizotinib versus

chemotherapy arms, respectively, >20% left ventricular ejection fraction decreases occurred in 0/19 (0%) versus 1/16 (6.3%) patients from PROFILE 1007 and 4/150 (2.7%) versus 10/150 (6.7%) patients from PROFILE 1014. **CONCLUSION:** These analyses did not reveal any clinically meaningful changes in myocardial function with crizotinib in patients with ALK-positive non-small-cell lung cancer. Clinicaltrials.gov identifier: PROFILE 1007, NCT00932893; PROFILE 1014, NCT01154140.

[**Biomarkers for immune checkpoint inhibitors in advanced nonsmall cell lung cancer.**](#) Pirker R1. Curr Opin Oncol. 2019 Jan;31(1):24-28. doi: 10.1097/CCO.0000000000000496.
PURPOSE OF REVIEW: Immune checkpoint inhibitors have been established as a new class of anticancer drugs for patients with advanced nonsmall cell lung cancer. Predictive biomarkers might help to select those patients who will derive the greatest benefit from these expensive drugs. This review summarizes the current status of predictive biomarkers for immune checkpoint inhibitors in advanced nonsmall cell lung cancer. **RECENT FINDING:** Programmed death ligand 1 (PD-L1) staining on tumor cells and immune cells has been studied as a predictive biomarker for immune checkpoint inhibitors. Higher PD-L1 levels appeared to be associated with greater benefit from these drugs in many studies, although such an association was absent in some studies. Tumor mutational load was associated with benefit from the combination of nivolumab plus ipilimumab. Immune checkpoint inhibitors combined with first-line chemotherapy improved survival compared to chemotherapy alone. These improvements were clinically relevant also in patients with PD-L1 expression in less than 1% of tumor cells. **SUMMARY:** PD-L1 expression on tumor and immune cells and tumor mutational load allow better selection of patients for treatment with immune checkpoint inhibitors as single agents. The role of PD-L1 for the selection of patients for chemoimmuntherapy remains to be seen.

[**Shared Decision-making and Lung Cancer Screening: Let's Get the Conversation Started.**](#) Tanner NT1, Silvestri GA2. Chest. 2019 Jan;155(1):21-24. doi: 10.1016/j.chest.2018.10.013. Epub 2018 Oct 22.
Screening with low-dose CT scan has been shown to reduce mortality from lung cancer in those at risk based on age and smoking history. While lung cancer screening (LCS) is recommended by the United States Preventative Services Task Force and many professional societies, it has been recognized that the decision to be screened is complex due to a close balance of risk and benefit; therefore, shared decision-making is considered an essential component of effective LCS. The Centers for Medicare and Medicaid Services provides coverage for LCS following a mandated shared-decision making (SDM) visit. Here we review the concept of SDM, facilitators and barriers, evidence and knowledge gaps, and novel considerations for SDM within LCS.

[**Health-related quality of life and anxiety in the PAN-CAN lung cancer screening cohort.**](#)
Taghizadeh N1, Tremblay A1, Cressman S2, et al. BMJ Open. 2019 Jan 17;9(1):e024719. doi: 10.1136/bmjopen-2018-024719.
OBJECTIVES: The impact of lung cancer screening with low-dose chest CT (LDCT) on participants' anxiety levels and health-related quality of life (HRQoL) is an important consideration in the implementation of such programmes. We aimed to describe changes in anxiety and HRQoL in a high-risk Canadian cohort undergoing LDCT lung cancer screening. **METHODS:** 2537 subjects who had 2% or greater lung cancer risk over 6 years using a risk prediction tool were recruited from eight centres across Canada in the Pan-Canadian Early Detection of Lung Cancer Study (2008-2010). We compared HRQoL and anxiety levels before and after screening of 1237 participants with LDCT (excluding a subset of 1300 participants who also underwent autofluorescence bronchoscopy screening), as well as after investigations performed because of a positive screening examination. The 12-item short-form Physical and Mental Component Scales (SF-12), EQ-5D-3L scores and State Trait Anxiety Inventory-State anxiety were used at each assessment. **RESULTS:** Overall, there were no clinically significant differences in HRQoL

outcomes between baseline and each of the survey time points following initial screening. No mean change in anxiety in the overall cohort was noted following baseline LDCT, but more participants had clinically significant increase in anxiety versus decrease after baseline screening (increase >minimal clinically important difference (MCID) (n=180) vs decrease >MCID (n=50), p<0.001). This finding persisted but to a lesser degree at the 12 month time point (increase >MCID (n=146) vs decrease >MCID (n=87), p<0.001). **CONCLUSIONS:** CT screening for lung cancer has no major overall impact on HRQoL among participants, although a minority of participants (number-needed-to-harm=7 after baseline screening and 18 at 1 year) demonstrated clinically significant increased anxiety levels.

[Expediting Comprehensive Molecular Analysis to Optimize Initial Treatment of Lung Cancer Patients with Minimal Smoking History.](#) Dagogo-Jack I1, Robinson H2, Mino-Kenudson M3, Farago AF4, Kamesan V4, Iafrate AJ2, Shaw AT4, Lennerz JK2. J Thorac Oncol. 2019 Jan 17. pii: S1556-0864(19)30024-3. doi: 10.1016/j.jtho.2018.12.032. [Epub ahead of print]
PURPOSE: Lung cancer patients with tumors harboring actionable alterations can achieve very durable responses to first-line targeted therapy. However, identifying targetable alterations using next-generation sequencing (NGS) is a complex and time-intensive process. As actionable genetic alterations are enriched in lung cancers arising in patients with limited smoking history, we designed a workflow to expedite NGS testing for this group. **PATIENTS AND METHODS:** We developed a protocol to allow for next-day extraction of nucleic acids from frozen tissue. Specimens were designated as high priority during sequencing. We determined the interval between biopsy and NGS results to evaluate whether the workflow reduced the pre-analytical period and in-laboratory turnaround time and allowed for rapid initiation of genotype-matched therapy. **RESULTS:** Between 1/2017 and 5/2018, twenty-one patients participated in the expedited sequencing program. The median interval between biopsy and NGS results was 10.7 days. Six patients received results within one week of biopsy. Performing molecular analysis on frozen tissue and prioritizing sequencing and analysis of these specimens reduced the pre-analytical period from 3.5 to 1.3 days (p<0.0001) and shortened in-laboratory turnaround time by 3 days (11.8 vs 8.4 business days, p<0.0001). Ninety-three percent of patients with an actionable molecular alteration received first-line targeted therapy. The median time-to-initiation of treatment was 19.7 days from biopsy. **CONCLUSION:** Sequencing and analyzing nucleic acids from frozen tissue is a practical strategy for shortening the time to matched therapy. The significant advantage of upfront treatment with targeted therapies in subsets of lung cancer patients provides rationale for developing workflows that accelerate comprehensive molecular analysis.

[Targeted Incentive Programs For Lung Cancer Screening Can Improve Population Health And Economic Efficiency.](#) Kim DD1, Cohen JT2, Wong JB3, Mohit B4, Fendrick AM5, Kent DM6, Neumann PJ7. Health Aff (Millwood). 2019 Jan;38(1):60-67. doi: 10.1377/hlthaff.2018.05148.
Because an intervention's clinical benefit depends on who receives it, a key to improving the efficiency of lung cancer screening with low-dose computed tomography (LDCT) is to incentivize its use among the current or former smokers who are most likely to benefit from it. Despite its clinical advantages and cost-effectiveness, only 3.9 percent of the eligible population underwent LDCT screening in 2015. Using individual lung cancer mortality risk, we developed a policy simulation model to explore the potential impact of implementing risk-targeted incentive programs, compared to either implementing untargeted incentive programs or doing nothing. We found that compared to the status quo, an untargeted incentive program that increased overall LDCT screening from 3,900 (baseline) to 10,000 per 100,000 eligible people would save 12,300 life-years and accrue a net monetary benefit (NMB) of $771 million over a lifetime horizon. Increasing screening by the same amount but targeting higher-risk people would yield an additional 2,470-6,600 life-years and an additional $210-$560 million NMB, depending on the extent of the risk-targeting. Risk-targeted incentive programs could include provider-level bonuses, health plan

premium subsidies, and smoking cessation programs to maximize their impact. As clinical medicine becomes more personalized, targeting and incentivizing higher-risk people will help enhance population health and economic efficiency.

Barriers to Lung Cancer Screening Engagement from the Patient and Provider Perspective.

Wang GX1, Baggett TP1, Pandharipande PV1, Park ER1, Percac-Lima S1, Shepard JO1, Fintelmann FJ1, Flores EJ1. Radiology. 2019 Feb;290(2):278-287. doi: 10.1148/radiol.2018180212. Epub 2019 Jan 8.
Lung cancer remains the leading cause of cancer mortality in the United States. Lung cancer screening (LCS) with low-dose CT reduces mortality among high-risk current and former smokers and has been covered by public and private insurers without cost sharing since 2015. Patients and referring providers confront numerous barriers to participation in screening. To best serve in multidisciplinary efforts to expand LCS nationwide, radiologists must be knowledgeable of these challenges. A better understanding of the difficulties confronted by other stakeholders will help radiologists continue to collaboratively guide the growth of LCS programs in their communities. This article reviews barriers to participation in LCS for patients and referring providers, as well as possible solutions and interventions currently underway.

The Importance of Smoking Cessation on Surgical Outcome in Primary Lung Cancer.
Fukui M1, Suzuki K2, Matsunaga T1, Oh S1, Takamochi K1. Ann Thorac Surg. 2019 Jan 2. pii: S0003-4975(18)31871-X. doi: 10.1016/j.athoracsur.2018.12.002. [Epub ahead of print]
BACKGROUND: Smoking cessation is important in the management of patients who require pulmonary resection. However the impact of short term smoking cessation on the surgical outcome remains unclear. **METHODS:** A retrospective study was conducted on patients with stage I-III primary lung cancer who underwent resection between 2012 and 2016. The rate of surgical mortality and morbidity were evaluated according to smoking status. The relationship between the preoperative interval of smoking cessation and pulmonary complications after surgery was also examined. **RESULTS:** This study included 666 patients, of which 256 (38.4%) were never smokers and 410 (61.6%) were smokers. There were significant differences between the smokers and never smokers regarding the 90-day mortality rate (2.0% vs 0%, p=0.025), and respiratory complications (22.3% vs 3.5%, p<0.001). A multivariate analysis indicated that smoking (OR 2.8, p = 0.017), FEV 1.0/ FVC < 0.7 (OR 2.6, p = 0.001), %DLCO < 40% (OR 4.2, p =<0.001), and clinical stage of lung cancer (OR 2.3, p = 0.005) were predictors of pulmonary complications after pulmonary resection. In comparison to never smokers, the odds ratios for pulmonary complications at each cessation interval (Current smoker/ cessation for -1month/ 1-3 months/ 3-6 months/ 6-12 months/ > 12 months) were 12.9 (p < 0.001)/ 10.3 (p < 0.001)/ 8.5 (p < 0.001)/ 6.3 (p=0.011)/ 6.0 (p = 0.003)/ 5.0 (p < 0.001). **CONCLUSIONS:** A longer period of cessation might be more effective for reducing the risk of pulmonary complications. Smoking cessation at any time is valuable for lung cancer surgery.

The Reach and Feasibility of an Interactive Lung Cancer Screening Decision Aid Delivered by Patient Portal.
Dharod A1,2, Bellinger C3, Foley K2, Case LD4, Miller D1,2. Appl Clin Inform. 2019 Jan;10(1):19-27. doi: 10.1055/s-0038-1676807. Epub 2019 Jan 9.
OBJECTIVE: Health systems could adopt population-level approaches to screening by identifying potential screening candidates from the electronic health record and reaching out to them via the patient portal. However, whether patients would read or act on sent information is unknown. We examined the feasibility of this digital health outreach strategy. **METHODS:** We conducted a single-arm pragmatic trial in a large academic health system. An electronic health record algorithm identified primary care patients who were potentially eligible for lung cancer screening (LCS). Identified patients were sent a patient portal invitation to visit a LCS interactive Web site which assessed screening eligibility and included a decision aid. The primary outcome was screening completion. Secondary outcomes included

the proportion of patients who read the invitation, visited the interactive Web site, and completed the interactive Web site. **RESULTS:**   We sent portal invitations to 1,000 patients. Almost all patients (86%, 862/1,000) read the invitation, 404 (40%) patients visited the interactive Web site, and 349 patients (35%) completed it. Of the 99 patients who were confirmed screening eligible by the Web site, 81 made a screening decision (30% wanted screening, 44% unsure, 26% declined screening), and 22 patients had a chest computed tomography completed. **CONCLUSION:** The digital outreach strategy reached the majority of patient portal users. While the study focused on LCS, this digital outreach approach could be generalized to other health needs. Given the broad reach and potential low cost of this digital strategy, future research should investigate best practices for implementing the system.

[**Opinions and Practices of Lung Cancer Screening by Physician Specialty.**](#) Henderson LM1, Marsh MW2, Benefield TS3, et al. N C Med J. 2019 Jan-Feb;80(1):19-26. doi: 10.18043/ncm.80.1.19.
BACKGROUND: In response to the National Lung Screening Trial, numerous professional organizations published guidelines recommending annual lung cancer screening with low-dose computed tomography (LDCT) for high-risk patients. Prior studies found that physician attitudes and knowledge about lung cancer screening directly impacts the number of screening exams ordered. **METHODS:** In 2015, we surveyed 34 pulmonologists and 186 primary care providers (PCPs) to evaluate opinions and practices of lung cancer screening in a large academic medical center. We compared PCP and pulmonologist responses using t-tests and $\chi2$ tests. **RESULTS:** The overall survey response rate was 40% (39% for PCPs and 50% for pulmonologists). Pulmonologists were more likely than PCPs to report lung cancer screening as beneficial for patients (88.2% versus 37.7%, $P < .0001$) and as being cost-effective (47.1% versus 14.3%, $P = .02$). More pulmonologists (76%) reported ordering a LDCT for screening in the past 12 months compared to PCPs (41%, $P = .012$). Pulmonologists and PCPs reported similar barriers to referring patients for lung cancer screening, including patient costs (82.4% versus 77.8%), potential for emotional harm (58.8% versus 58.3%), high false positive rate (47.1% versus 69.4%), and likelihood for medical complications (47.1% versus 59.7%). **LIMITATIONS:** Our results are generalizable to academic medical centers and responses may be susceptible to recall bias, non-response bias, and social desirability bias. **CONCLUSION:** We found significant differences in opinions and practices between PCPs and pulmonologists regarding lung cancer screening referrals and perceived benefits. As lung cancer screening continues to emerge in clinical practice, it is important to understand these differences across provider specialty to ensure screening is implemented and offered to patients appropriately.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[**A National Analysis of Long-term Survival Following Thoracoscopic Versus Open Lobectomy for Stage I Non-small-cell Lung Cancer.**](#) Yang CJ1, Kumar A1, Klapper JA1, Hartwig MG1, Tong BC1, Harpole DH Jr1, Berry MF2, D'Amico TA1. Ann Surg. 2019 Jan;269(1):163-171. doi: 10.1097/SLA.0000000000002342.
OBJECTIVE: The objective of this study was to compare the long-term survival of open versus thoracoscopic (VATS) lobectomy for early stage non-small-cell lung cancer (NSCLC).
BACKGROUND: Data from national studies on long-term survival for VATS versus open lobectomy are limited. **METHODS:** Outcomes of patients who underwent open versus VATS lobectomy for clinical T1-2, N0, M0 NSCLC in the National Cancer Data Base were evaluated using propensity score matching. **RESULTS:** The median follow-up of 7114 lobectomies (5566 open and 1548 VATS) was 52.0 months. The VATS approach was associated with a better 5-year survival when compared to the open approach (66.0% vs. 62.5%, $P = 0.026$). Propensity score matching resulted in 1464 open and 1464 VATS patients

who were well matched by 14 common prognostic covariates including tumor size and comorbidities. After propensity score matching, the VATS approach was associated with a shorter median length of stay (5 vs. 6 days, P < 0.001). The VATS approach was not significantly different compared with the open approach with regard to nodal upstaging (11.6% vs 12.3%, P = 0.53), 30-day mortality (1.7% vs 2.3%, P = 0.50) and 5-year survival (66.3% vs 65.8%, P = 0.92). **CONCLUSIONS:** In this national analysis, VATS lobectomy was used in the minority of patients with stage I NSCLC. VATS lobectomy was associated with shorter length of stay and noninferior long-term survival when compared with open lobectomy. These results support previous findings from smaller single- and multi-institutional studies that suggest that VATS does not compromise oncologic outcomes when used for early-stage lung cancer and suggest the need for broader implementation of VATS techniques.

[Short-Term Readmissions After Open, Thoracoscopic, and Robotic Lobectomy for Lung Cancer Based on the Nationwide Readmissions Database.](#) [Bailey KL1, Merchant N1, Seo YJ1, Elashoff D2,](#) Benharash P1,3, Yanagawa J4,5. World J Surg. 2019 Jan 2. doi: 10.1007/s00268-018-04900-0. [Epub ahead of print]
BACKGROUND: Readmission after surgery is an established surrogate indicator of quality of care. We aimed to compare short-term readmission rates and patient outcomes between open, video-assisted thoracoscopic (VATS), and robotic lobectomies in the Nationwide Readmissions Database (NRD). **METHODS:** Adults who underwent open, VATS, or robotic lobectomy for lung cancer from 2010 to 2014 were evaluated. Propensity-matched analysis was used to assess differences in readmission characteristics, GDP-adjusted cost, and mortality. **RESULTS:** Of the 129,539 lobectomies for lung cancer, 74,493 (57.5%) were open, 48,185 (37.2%) VATS, and 6861 (5.3%) robotic. Open surgery was associated with significantly higher readmission rate (10.5 vs 9.3%, p < 0.001), mortality (2 vs 1.2%, p < 0.001), index hospitalization cost [$21,846 (16,158-31,034) vs $20,779 (15,619-27,920), p < 0.001], and length of stay [6 (5-9) vs 4 (3-7) days, p < 0.001] compared to minimally invasive surgery. The robotic approach had similar mortality, readmission rate, and length of stay compared to VATS, but higher index cost [$23,870 (18,372-31,300) vs $20,279 (15,275-27,375), p < 0.001] and incidence of pulmonary complication (35.9 vs 31.6%, p < 0.001). The robotic approach was associated with greater direct discharges to home. **CONCLUSIONS:** Analysis of the NRD revealed significantly reduced readmission rates, better clinical outcomes, and lower cost in the minimally invasive approach compared to open surgery. Although VATS and robotic surgery had similar readmission and mortality rates, VATS is associated with significantly reduced risk of short-term complications and lower cost.

[Sevoflurane Effect on Cognitive Function and the Expression of Oxidative Stress Response Proteins in Elderly Patients undergoing Radical Surgery for Lung Cancer.](#) Qin Y1, Ni J1, Kang L1, Zhong Z1, Wang L1, Yin S1. J Coll Physicians Surg Pak. 2019 Jan;29(1):12-15. doi: 10.29271/jcpsp.2019.01.12.
OBJECTIVE: To investigate the effects of sustained inhalation of sevoflurane on cognitive function and the expression of oxidative stress response proteins such as NADPH oxidase subunits NOX2 and NOX4 in elderly patients undergoing radical surgery for lung cancer. **STUDY DESIGN:** An experimental study. **PLACE AND DURATION OF STUDY:** Department of Anesthesiology, Suzhou Kowloon Hospital, Shanghai Jiao Tong University School of Medicine, China, from February 2016 to October 2017. **METHODOLOGY:** Elderly patients who underwent radical surgery for lung cancer were divided into the sevoflurane group and the propofol group, with 52 cases in each group. Sustained inhalation of sevoflurane and propofol was administered to maintain anesthesia in the respective groups. Cognitive function and lung function parameters were compared between the two groups. Serum S100 β levels and expression of NOX2 and NOX4 proteins in peripheral blood mononuclear cells of the two groups were determined. **RESULTS:** At 24 hours after surgery, the lung function indices of the sevoflurane group such as FEV1, FVC and VC were higher than those of the propofol group (p<0.001, p=0.008 and

p=0.002, respectively). At the end of the surgery and at 24 hours after surgery, the MMSE scores of the sevoflurane group were higher than the propofol group (all p<0.001). S100☐ levels were lower than the propofol group (p=0.003 and p<0.001, respectively). Levels of NADPH oxidase subunits NOX2 and NOX4 proteins in peripheral blood mononuclear cells of the sevoflurane group were lower than the propofol group (p=0.033, p<0.001, p<0.001and p<0.001, respectively). **CONCLUSION:** Compared with intravenous anesthesia with propofol, general anesthesia with sevoflurane inhalation has little effect on the short-term cognitive function in elderly patients undergoing radical surgery for lung cancer, and can effectively improve lung function. The mechanism may be related to the reduction of the expression of NOX2 and NOX4 proteins.

[**Survival and resected lymph nodes number during sublobectomy for N0 Non-Small Cell Lung Cancer ≤ 2cm.**](#) Ding H1, Wang H2, Xu L2, Song N2, Jiang G2. Ann Thorac Surg. 2019 Jan 22. pii: S0003-4975(19)30083-9. doi: 10.1016/j.athoracsur.2018.12.024. [Epub ahead of print]
BACKGROUND: To investigate the association between survival and the number of examined lymph nodes following sublobar resection for node-negative non-small cell lung cancer ≤2 cm. **METHODS:** The Surveillance, Epidemiology, and End Results database was used to identify patients diagnosed with non-small cell lung cancer ≤2 cm from 2004 to 2014 and underwent wedge resection or segmentectomy. Patients were stratified by the procedure (wedge resection, segmentectomy), the size of tumors (≤1 cm, 1-2 cm) and the number of lymph nodes examined (0, 1-3, 4-9, 10+). The relationship between the number of resected lymph nodes and Overall Survival (OS)/Lung Cancer-Specific Survival (LCSS) was analyzed. **RESULTS:** 2298 patients with wedge resection and 566 patients with segmentectomy were identified. Segmentectomy was performed for bigger tumors (1.43 vs 1.38 cm) and associated with more lymph nodes resected (median number, 3 vs 1). Multivariable analysis after propensity score matching revealed that lymph nodes resection improved survival for patients undergoing wedge resection while not for those undergoing segmentectomy. In wedge resection group, 1-3 nodes resected improved OS and 4-9 nodes improved OS and LCSS compared to those without nodes evaluated for lesions ≤1 cm. No survival benefit was observed when 10+ nodes were resected. For lesions 1-2 cm, incremental improvement in survival appeared with the increase of examined lymph node number. More than 16 nodes resected conferred no additional survival benefit compared to those with 10-16 nodes resected. **CONCLUSIONS:** In wedge resection, 4-9 and 10-16 lymph nodes should be examined for lesions ≤1 cm and 1-2 cm, respectively. In segmentectomy, lymph node resection did not confer survival benefits for lesions ≤2 cm.

NSCLC – SYSTEMIC THERAPIES (CHEMOTHERAPY, TARGETED THERAPY, AND IMMUNOTHERAPY)

[**Phase 1b trial of nintedanib in combination with bevacizumab in patients with advanced solid tumors.**](#) Paluri R1, Madan A1, Li P1, Jones B1, Saleh M1, Jerome M1, Miley D1, Keef J1, Robert F2. Cancer Chemother Pharmacol. 2019 Jan 2. doi: 10.1007/s00280-018-3761-y. [Epub ahead of print]
PURPOSE: Vascular endothelial growth factor (VEGF) inhibitors have produced demonstrable but limited benefit for various cancers. One mechanism of resistance includes revascularization, secondary to upregulation of alternative pro-angiogenic platelet-derived growth factor receptor and fibroblast growth factor receptor pathways. Nintedanib is an oral, triple kinase inhibitor that blocks these pathways and may improve anti-tumor activity by overcoming resistance to anti-VEGF therapies. The primary objective of this first in-human study was to evaluate the safety and tolerability of nintedanib in combination with bevacizumab. **METHODS:** Patients were treated with escalating doses of nintedanib (150 mg or 200 mg oral twice daily) and bevacizumab (15 mg/kg once intravenously every 3 weeks) until disease progression or unacceptable toxicity using standard 3 + 3 phase 1 design. Plasma levels of angiogenic biomarkers were correlated with clinical outcomes. **RESULTS:** Eighteen patients with advanced tumors [lung (n = 9), colon (n = 8), and cervical (n = 1)] previously treated with at least two lines of chemotherapy

including bevacizumab (n = 9, 50%) were enrolled. The highest dose of nintedanib was 200 mg twice a day with no observed dose-limiting toxicities (DLT). Common adverse events (AE) were fatigue (grade 1-3) and diarrhea (grade 1-2). Durable clinical response was observed in 55% patients pretreated with bevacizumab (1 complete and 4 stable response). Better disease control was correlated with higher than median baseline values for VEFGR2 and E-selectin, and lower levels for SDF-1α. **CONCLUSION:** Nintedanib was well-tolerated with bevacizumab with no DLT. Significant clinical activity was observed, including in bevacizumab-pretreated patients, suggesting nintedanib can overcome bevacizumab resistance.

[Afatinib in patients with metastatic or recurrent HER2-mutant lung cancers: a retrospective international multicentre study.](#) Lai WV1, Lebas L2, Barnes TA3, et al. Eur J Cancer. 2019 Jan 24;109:28-35. doi: 10.1016/j.ejca.2018.11.030. [Epub ahead of print]
INTRODUCTION: HER2 mutations occur in 1-3% of lung adenocarcinomas. With increasing use of next-generation sequencing at diagnosis, more patients with HER2-mutant tumours present for treatment. Few data are available to describe the clinical course and outcomes of these patients when treated with afatinib, a pan-HER inhibitor. **METHODS:** We identified patients with metastatic or recurrent HER2-mutant lung adenocarcinomas treated with afatinib among seven institutions across Europe, Australia, and North America between 2009 and 2017. We determined the partial response rate to afatinib, types of HER2 mutations, duration of response, time on treatment, and survival. **RESULTS:** We collected information on 27 patients with stage IV or recurrent HER2-mutant lung adenocarcinomas treated with afatinib. Of 23 patients evaluable for response, three partial responses were noted (13%, 95% confidence interval [CI] 4-33%). In addition, 57% of patients (13/23) had stable disease, and 30% (7/23) had progressive disease. We documented partial responses in patients with HER2 exon 20 insertions, including two with YVMA insertion and one with VAG insertion. Two patients with partial responses were previously treated with trastuzumab and pertuzumab. Median duration of response to afatinib was 6 months (range 5-10); median time on treatment was 3 months (range 1-30) and median overall survival from the date of diagnosis of metastatic or recurrent disease was 23 months (95% CI 18-53 months). **CONCLUSIONS:** Afatinib is modestly active in patients with HER2-mutant lung adenocarcinomas, including responses after progression on prior HER2-targeted therapies. However, investigations into the biology of HER2-mutant lung adenocarcinomas and development of better HER2-directed therapies are warranted.

[ALK Inhibitors in the Treatment of ALK Positive NSCLC.](#) Khan M1,2, Lin J1, Liao G1, et al. Front Oncol. 2019 Jan 9;8:557. doi: 10.3389/fonc.2018.00557. eCollection 2018.
BACKGROUND: ALK inhibitors have shown positive advance in the treatment of ALK+ NSCLC. They have achieved better results in prolonging the progression free survival and improving quality of life in comparison to chemotherapy. We have assembled the evidence related to the efficacy and safety of these agents in the treatment of ALK positive NSCLC. **MATERIALS AND METHODS:** A comprehensive search was conducted using electronic databases of PubMed, Medline and Cochrane Library to identify the studies involving comparison of ALK inhibitors to chemotherapy and Next generation ALK inhibitors to crizotinib. PFS was the primary outcome while other outcomes like ORR, adverse events, quality of life and OS were also analyzed and compared. Hazard ratios and odds ratios obtained were analyzed using fixed effect or random effects model in Review Manager Software. **RESULTS:** A total of 12 studies (n = 3,297) met the criteria for inclusion in this review and meta-analysis. ALK inhibitors including crizotinib, ceritinib and alectinib revealed significantly better PFS (HR 0.42 [0.35, 0.50; p < 0.00001]), ORR (Overall OR 6.59 [4.86, 8.94; p < 0.00001] as compared to chemotherapy in the first line as well as second line treatment settings. Intracranial response rate was better with ALK inhibitors (ceritinib and alectinib) as compared to chemotherapy OR 6.51 [2.86, 14.83; p < 0.00001]. No significant increase in

grade 3 or 4 adverse events was observed with crizotinib (OR 1.21 [0.82, 1.77; p = 0.34]) or ceritinib (OR 1.49 [0.86, 2.57; p = 0.17]) when compared to chemotherapy individually. Quality of life indicators assessed were significantly improved with ALK inhibitors. Next generation agents (ceritinib, alectinib and brigatinib) revealed significant improvement in PFS (HR 0.50 [0.43, 0.57; p < 0.00001]), ORR (OR 1.57 [1.21, 2.04; p = 0.0006]) in comparison to crizotinib. Next generation agents (Alectinib and brigatinib) yielded better response intra-cranially than crizotinib in terms of objective response rate (OR 5.87 [3.49, 9.87; p < 0.00001]) and time to CNS progression (HR 0.25 [0.13, 0.46; p < 0.0001]). Alectinib by far resulted in fewer adverse events than chemotherapy or crizotinib. **CONCLUSIONS:** Overall ALK inhibitors are safe and effective treatment option in ALK+ non-small cell lung cancer. Of the ALK inhibitors, Next generation agents in particular alectinib and brigatinib are safer and more effective intra-cranially and can be preferred as first option.

[Brigatinib: Novel ALK Inhibitor for Non-Small-Cell Lung Cancer.](#) Spencer SA1, Riley AC1, Matthew A1, Di Pasqua AJ1. Ann Pharmacother. 2019 Jan 13:1060028018824578. doi: 10.1177/1060028018824578. [Epub ahead of print]
OBJECTIVE: We review here the pharmacology, pharmacokinetics, efficacy, safety, dosage and administration, potential drug-drug interactions and place in therapy of brigatinib for abnormal anaplastic lymphoma kinase (ALK) specific non-small-cell lung cancer (NSCLC). **DATA SOURCES:** A literature search using PubMed was conducted using the terms brigatinib and ALK positive NSCLC from January 2013 to November 2018. **STUDY SELECTION AND DATA EXTRACTION:** All English-language articles evaluating brigatinib were analyzed for this review. **DATA SYNTHESIS:** Brigatinib was granted approval for the treatment of patients with metastatic ALK+ NSCLC who have progressed on or are intolerant to crizotinib. It is administered at a dose of 90 mg orally once daily for the first 7 days then, if tolerated, increased to a dose of 180 mg orally once daily. Common adverse effects include nausea, fatigue, diarrhea, increased creatine phosphokinase levels, headache, dyspnea, and hypertension. Serious treatment-emergent adverse effects were pulmonary related. Relevance to Patient Care and Clinical Practice: This article discusses the clinical trials that led to the accelerated approval of brigatinib for its ability to overcome crizotinib-resistant mutations and for its increased central nervous system penetration properties. **CONCLUSION:** Brigatinib was granted accelerated approval for the treatment of patients with metastatic ALK+ NSCLC who have progressed on or are intolerant to crizotinib. In a subset of NSCLC patients, brigatinib increases survival for approximately 1 year; however, side effects were detected.

[An Open-Label Phase II Trial of Bevacizumab plus Docetaxel and Gemcitabine in Advanced, Previously Untreated Nonsquamous Non-Small Cell Lung Cancer.](#) Patil PD1, Shapiro M2, Hashemi Sadraei N3, Pennell NA1. Oncologist. 2019 Jan 2. pii: theoncologist.2018-0857. doi: 10.1634/theoncologist.2018-0857. [Epub ahead of print]
LESSONS LEARNED: The combination of bevacizumab with docetaxel-gemcitabine resulted in unacceptable toxicity, particularly a high rate of pulmonary toxicity (30%).Despite promising efficacy, excessive toxicity of this regimen does not support its use in patients with advanced nonsquamous non-small cell lung cancer. **BACKGROUND:** Prior to immunotherapy, standard treatment for advanced non-small cell lung cancer (NSCLC) was platinum doublet chemotherapy. In a previous phase II study, docetaxel-gemcitabine demonstrated comparable efficacy and tolerability to platinum doublets. In this phase II trial, we evaluated the efficacy and tolerability of adding bevacizumab to docetaxel- gemcitabine in patients with advanced nonsquamous NSCLC. **METHODS:** Patients with untreated advanced nonsquamous NSCLC were treated with up to six cycles of docetaxel-gemcitabine-bevacizumab, followed by bevacizumab until progression. The primary endpoint for this study was 1-year progression-free survival (PFS); secondary endpoints were safety, overall response rate (ORR) and overall survival

(OS). The planned sample size was 46 patients. **RESULTS:** A total of 13 patients were enrolled and received a median of six cycles of chemotherapy and four cycles of bevacizumab. The treatment was poorly tolerated, with five patients requiring dose reduction and four discontinuing treatment for toxicity. Grade 3-5 nonhematologic toxicity was seen in 10 patients, and 4 (30%) were hospitalized with pulmonary toxicity possibly related to study drugs. At this point, enrollment was halted for safety concerns. The 12-month PFS was 8%. In 11 evaluable patients, ORR was 72%, median PFS 6 months, and median OS was 11 months. **CONCLUSION:** Docetaxel, gemcitabine, and bevacizumab at this dose and schedule resulted in excessive toxicity. Despite promising efficacy, in light of efficacious and safe alternative therapies, this regimen should not be used to treat advanced NSCLC.

[Academic oncology clinicians' understanding of biosimilars and information needed before prescribing.](#) Cook JW1, McGrath MK1, Dixon MD1, Switchenko JM2, Harvey RD1, Pentz RD3. Ther Adv Med Oncol. 2019 Jan 6;11:1758835918818335. doi: 10.1177/1758835918818335. eCollection 2019. **BACKGROUND:** With increasing numbers of oncology biosimilars in the approval pipeline, it is important to investigate oncology clinicians' understanding of biosimilars and what information they need prior to adoption. **METHODS:** Between January and May 2018, 77 oncology clinicians (52 physicians, 16 pharmacists, and 9 advanced practice providers) completed a survey covering three domains: clinician understanding, prescription preferences, and patient involvement. An in-depth interview was designed based on themes identified in the first 50 surveys: cost, safety and efficacy, patient preference, and disease stage. Participants were chosen to participate in the interview based on outlying responses to survey questions. **RESULTS:** When asked to define a biosimilar, 74% (57/77) of respondents could not give a satisfactory definition, and 40.3% (31/77) considered a biosimilar the same as a generic drug. The most important factor in biosimilar prescription was safety and efficacy (4.51 out of 5) followed closely by cost differences (4.34 out of 5). A 40% increase (53.2-94.8%) in clinicians' prescribing likelihood was seen after a biosimilar is designated as interchangeable. Participants in this study were split regarding the importance of shared decision-making with patients [50.7% (39/77) important or extremely important, 39.0% (30/77) somewhat or not at all important]. Clinicians were also split concerning the role that pharmacists should play in the decision to prescribe or substitute biosimilars. **CONCLUSION:** Understanding of biosimilars is low, and educational needs are high. The information that clinicians deem important to assess, such as safety, efficacy and cost, will need to be provided before they are comfortable prescribing biosimilars.

[Influence of Vitamin D in Advanced Non-Small Cell Lung Cancer Patients Treated with Nivolumab.](#) Cusato J1, Genova C2, Tomasello C3, et al. Cancers (Basel). 2019 Jan 21;11(1). pii: E125. doi: 10.3390/cancers11010125.
Nivolumab is one of the most commonly used monoclonal antibodies for advanced non-small cell lung cancer treatment, to the extent that the presence of its anti-antibody is considered a negative prognostic factor. Vitamin D (VD) modulates expression of the genes involved in drug metabolism and elimination. Immune system regulation and immunodeficiency is frequent in non-small cell lung cancer patients. To date, no data have been reported about the relationship between nivolumab and VD. The aim of this study was to quantify plasma 25-hydroxyVD (25-VD) and 1,25-VD, nivolumab, and its anti-antibody before starting treatment (baseline) and at 15, 45 and 60 days of therapy. VD-pathway-associated gene single nucleotide polymorphisms (SNPs) were also evaluated. Molecules were quantified through enzyme-linked immunosorbent assay, and SNPs through real-time PCR. Forty-five patients were enrolled. Median nivolumab concentrations were 12.5 ug/mL, 22.3 ug/mL and 27.1 ug/mL at 15, 45 and 60 days respectively. No anti-nivolumab antibodies were found. Correlations were observed between nivolumab concentrations and 25-VD levels. Nivolumab concentrations were affected by VD-pathway-related gene SNPs. VDBP AC/CC genotype and baseline 25-VD < 10 ng/mL predicted a nivolumab concentration cut-

off value of <18.7ug/mL at 15 days, which was associated with tumor progression. This is the first study showing VD marker predictors of nivolumab concentrations in a real-life context of non-small cell lung cancer treatment.

[Immune-related adverse events predict the therapeutic efficacy of anti-PD-1 antibodies in cancer patients.](#) Rogado J1, Sánchez-Torres JM1, Romero-Laorden N1, et al. Eur J Cancer. 2019 Jan 22;109:21-27. doi: 10.1016/j.ejca.2018.10.014. [Epub ahead of print]

BACKGROUND: Cancer immune therapy has shown remarkable benefit in the treatment of a range of cancer types, although it may initiate autoimmune-related disorders in some patients. We have attempted to establish whether the incidence of irAEs after the use of anti-PD-1 antibodies nivolumab or pembrolizumab in advanced malignancies is associated with anti-PD-1 treatment efficacy. **PATIENTS AND METHODS:** We studied patients treated with single-agent nivolumab or pembrolizumab for advanced cancer. irAEs (immune-related adverse events) were identified clinically and graded as per the Common Terminology Criteria for Adverse Events version 4.0. Efficacy was evaluated with objective response rate (ORR, immune-Response Evaluation Criteria in Solid Tumours [RECIST] criteria) progression-free survival (PFS) and overall survival (OS). Tests were performed to determine the association between irAEs and ORR, PFS or OS. **RESULTS:** We identified 106 patients. Primary diagnoses were lung cancer (n = 77), melanoma (n = 8), head and neck carcinoma (n = 7), renal carcinoma (n = 5), Hodgkin's lymphoma (n = 3), urothelial carcinoma (n = 3) and gallbladder adenocarcinoma, hepatocellular carcinoma and Merkel cell carcinoma (n = 1 each). IrAEs were observed in 40 patients (37.7%). The most frequent irAEs were hypothyroidism (n = 15), nephritis (n = 5) and hyperthyroidism (n = 4). Objective response was observed in 44 patients (41.5%), and median PFS was 5.5 months (0.5-31 months). Thirty-three of the 40 patients with irAEs had objective response (82.5%) in contrast with 11 of the 66 cases without irAEs (16.6%) (OR 23.5, P < 0.000001). PFS in patients with irAEs was 10 months and 3 months in those without irAEs (HR 2.2, P = 0.016). OS in patients with irAEs was 32 months and 22 in those without irAEs, without statistically significant differences. **CONCLUSION:** In advanced cancer treated with single-agent anti-PD-1 antibodies, patients with irAEs showed a markedly improved efficacy over patients without irAEs (ORR of 82.5% and PFS of 10 months vs ORR of 16.6% and PFS of 3 months). Future studies of anti-PD-1 immune-therapy should address this association to explore the underlying biological mechanisms of efficacy.

NSCLC - RADIOTHERAPY

[Safety of Electromagnetic Navigation Bronchoscopy in Patients With COPD: Results From the NAVIGATE Study.](#) Towe CW1, Nead MA2, Rickman OB3, Folch EE4, Khandhar SJ5, Perry Y1, Linden PA1. J Bronchology Interv Pulmonol. 2019 Jan;26(1):33-40. doi: 10.1097/LBR.0000000000000522.

BACKGROUND: Electromagnetic navigation bronchoscopy (ENB) aids in the localization of lung lesions for biopsy and/or to guide fiducial or dye marking for stereotactic radiation or surgical localization. This study assessed ENB safety in patients with chronic obstructive pulmonary disease (COPD) and/or poor lung function. **METHODS:** NAVIGATE is a prospective, multicenter, observational study of ENB. This substudy analyzed the 1-month follow-up of the first 1000 enrolled subjects. COPD was determined by medical history. Pulmonary function testing (PFT) results were collected if available within 30 days of the procedure. Procedure-related complications were captured. **RESULTS:** The analysis included 448 subjects with COPD and 541 without COPD (COPD data missing in 11). One-month follow-up was completed in 93.3%. Subjects with COPD tended to be older, male, and have history of tobacco exposure, asthma, and recent pneumonia. Nodule size, location, and procedure time were similar between groups. There was no statistically significant difference in the procedure-

related composite complication rate between groups (7.4% with COPD, 7.8% without COPD, P=0.90). Common Terminology Criteria for Adverse Events scale grade ≥2 pneumothorax was not different between groups (2.7% with COPD, 3.7% without COPD, P=0.47). COPD was not a significant multivariate predictor of complications. Severity of forced expiratory volume in 1 second (FEV1) or diffusing capacity of the lung for carbon monoxide impairment was not associated with increased composite procedure-related complications (ppFEV1 P=0.66, ppDLCO P=0.36). **CONCLUSION:** In this analysis, complication rates following ENB procedures were not increased in patients with COPD or poor pulmonary function. Because pneumothorax risk is not elevated, ENB may be the preferred method to biopsy peripheral lung lesions in patients with COPD and/or poor pulmonary function testing.

[**PD-L1 Expression in Circulating Tumor Cells Increases during Radio(chemo)therapy and Indicates Poor Prognosis in Non-small Cell Lung Cancer.**](#) Wang Y1,2, Kim TH2,3, Fouladdel S2,4, et al. Sci Rep. 2019 Jan 24;9(1):566. doi: 10.1038/s41598-018-36096-7.
Zhang Z1,2, Soni P5, Qin A4, Zhao L6, Azizi E2,4, Lawrence TS5, Ramnath N4, Cuneo KC7,8, Nagrath S9,10,11.
Preclinical studies demonstrated that radiation up-regulates PD-L1 expression in tumor cells, providing a rationale for combining PD-1/PD-L1 inhibitors with radiation. However this has not been validated in patients with non-small cell lung cancer due to the difficulty to obtain serial biopsies. Measuring PD-L1 expression in circulating tumor cells (CTCs), may allow real-time monitoring of immune activation in tumor. In this study, whole blood from non-metastatic NSCLC patients was collected before, during, and after radiation or chemoradiation using a microfluidic chip. PD-L1 expression in CTCs was assessed by immunofluorescence and qPCR and monitored through the course of treatment. Overall, PD-L1(+) CTCs were detected in 25 out of 38 samples (69.4%) with an average of 4.5 cells/ml. After initiation of radiation therapy, the proportion of PD-L1(+) CTCs increased significantly (median 0.7% vs. 24.7%, P < 0.01), indicating up-regulation of PD-L1 in tumor cells in response to radiation. In addition, patients positive for PD-L1 (≥5% of CTCs positive for PD-L1) at baseline had shorter PFS. Gene expression analysis revealed that higher levels of PD-L1 were associated with poor prognosis. Therefore, CTCs can be used to monitor dynamic changes of PD-L1 during radiation therapy which is potentially prognostic of response to treatment.

[**Overall survival according to immunotherapy and radiation treatment for metastatic non-small-cell lung cancer: a National Cancer Database analysis.**](#) Foster CC1, Sher DJ2, Rusthoven CG3, Verma V4, Spiotto MT5,6, Weichselbaum RR5, Koshy M5,6. Radiat Oncol. 2019 Jan 28;14(1):18. doi: 10.1186/s13014-019-1222-3.
BACKGROUND: Preclinical studies suggest enhanced anti-tumor activity with combined radioimmunotherapy. We hypothesized that radiation (RT) + immunotherapy would associate with improved overall survival (OS) compared to immunotherapy or chemotherapy alone for patients with newly diagnosed metastatic non-small-cell lung cancer (NSCLC). **METHODS:** The National Cancer Database was queried for patients with stage IV NSCLC receiving chemotherapy or immunotherapy from 2013 to 2014. RT modality was classified as stereotactic radiotherapy (SRT) to intra- and/or extracranial sites or non-SRT external beam RT (EBRT). OS was analyzed using the Kaplan-Meier method and Cox proportional hazards models. **RESULTS:** In total, 44,498 patients were included (13% immunotherapy, 46.8% EBRT, and 4.7% SRT). On multivariate analysis, immunotherapy (hazard ratio [HR]:0.81, 95% confidence interval [CI]:0.78-0.83) and SRT (HR:0.78, 95%CI:0.70-0.78) independently associated with improved OS; however, the interaction term for SRT + immunotherapy was insignificant (p = 0.89). For immunotherapy patients, the median OS for no RT, EBRT, and SRT was 14.5, 10.9, and 18.2 months, respectively (p < 0.0001), and EBRT (HR:1.37, 95%CI:1.29-1.46) and SRT (HR:0.78, 95%CI:0.66-0.93) associated with OS on multivariate analysis. In the SRT subset, median OS for immunotherapy and

chemotherapy was 18.2 and 14.3 months, respectively (p = 0.004), with immunotherapy (HR:0.82, 95%CI:0.69-0.98) associating with OS on multivariate analysis. Furthermore, for patients receiving SRT, biologically effective dose (BED) > 60 Gy was independently associated with improved OS (HR:0.79, 95%CI:0.70-0.90, p < 0.0001) on multivariate analysis with a significant interaction between BED and systemic treatment (p = 0.008). **CONCLUSIONS:** Treatment with SRT associated with improved OS for patients with metastatic NSCLC irrespective of systemic treatment. The high survival for patients receiving SRT + immunotherapy strongly argues for evaluation in randomized trials.

[**Predictive factors for response and survival in a cohort of oligometastatic patients treated with Stereotactic Body Radiation Therapy.**](#) Franceschini D1, De Rose F2, Franzese C2, et al. Int J Radiat Oncol Biol Phys. 2019 Jan 7. pii: S0360-3016(18)34231-7. doi: 10.1016/j.ijrobp.2018.12.049. [Epub ahead of print]
PURPOSE: To evaluate patients, treatment or disease characteristics that could predict response to SBRT and survival in a database of oligometastatic patients from different solid tumors. Matherial and Methods Patients treated with SBRT for oligometastatic disease between 2014 and 2015 were included. Patients were defined as oligometastatic if they were affected by maximum 5 active lesions in 3 different sites. They had to be treated with SBRT with radical intent. **RESULTS:** 358 patients were included in the study. With a median follow up of 31.83 months local control at 6 and 24 months was 94.6% and 78.9%. Distant progression was recorded in 279 patients (77.9%). PFS at 6 and 24 months was 66.1% and 18.4%. At last follow up, 195 patients (54.5%) were still alive, in 59 cases with no evidence of disease. Median overall survival (OS) was 34.7 months (95%CI 29.66-43.83). OS at 6 and 24 months was 96.07% and 63.57%. At multivariable analysis the presence of lung metastases [HR 0.50 (0.33 - 0.75), p=0.001] and nodal metastases [HR 0.44 (0.24 - 0.78), p=0.005] were related with longer OS. Primary lung cancer [HR 1.89 (1.14-3.13), p=0.013], increasing age [HR 1.02 (1.01-1.04), p=0.002], presence of metastatic sites other than the irradiated ones [HR 2.19 (1.39 - 3.43), p= 0.001] were all independent predictors of shorter OS. Local response was associated with OS. **CONCLUSION:** SBRT for oligometastatic patients is effective. Local response is strongly correlated with patients' prognosis, underlying its relevance also in a metastatic setting.

[**Modern Radiation Further Improves Survival in Non-Small Cell Lung Cancer: An Analysis of 288,670 Patients.**](#) Cheng M1, Jolly S2, Quarshie WO3, Kapadia N4, Vigneau FD3, Kong FS5. J Cancer. 2019 Jan 1;10(1):168-177. doi: 10.7150/jca.26600. eCollection 2019.
BACKGROUND: Radiation therapy plays an increasingly important role in the treatment of patients with non-small-cell lung cancer (NSCLC). The purpose of the present study is to assess the survival outcomes of radiotherapy treatment compared to other treatment modalities and to determine the potential role of advanced technologies in radiotherapy on improving survival. **METHODS:** We used cancer incidence and survival data from the Surveillance, Epidemiology, and End Results database linked to U.S. Census data to compare survival outcomes of 288,670 patients with stage I-IV NSCLC treated between 1999 and 2008. The primary endpoint was overall survival. **RESULTS:** Among the 288,670 patients diagnosed with stage I-IV NSCLC, 92,374 (32%) patients received radiotherapy-almost double the number receiving surgery (51,961, 18%). Compared to other treatment groups and across all stages of NSCLC, patients treated with radiotherapy showed greater median and overall survival than patients without radiation treatment (p < 0.0001). Radiotherapy had effectively improved overall survival regardless of age, gender, and histological categorization. Radiotherapy treatment received during the recent time period 2004 - 2008 is correlated with enhanced survival compared to the earlier time period 1999 - 2003. **CONCLUSION:** Radiation therapy was correlated with increased overall survival for all patients with primary NSCLC across stages. Combined surgery and radiotherapy treatment also correlates with improved survival, signaling the value of bimodal or multimodal treatments. Population-based

increases in overall survival were seen in the recent time period, suggesting the potential role of advanced radiotherapeutic technologies in enhancing survival outcomes for lung cancer patients.

Definitive Radiation for Stage I lung cancer in a screened population: Results from the I-ELCAP. Berlin E1, Buckstein M2, Yip R3, Yankelevitz DF3, Rosenzweig K2, Henschke CI4; I-ELCAP Int J Radiat Oncol Biol Phys. 2019 Jan 21. pii: S0360-3016(19)30110-5. doi: 10.1016/j.ijrobp.2019.01.069. [Epub ahead of print]
This study examines the characteristics and outcomes of patients with clinical stage I NSCLC identified by CT screening treated with definitive radiotherapy versus surgical resection. Very few screened patients are treated with radiation. Despite worse baseline characteristics in the radiation group, there was no significant difference in lung cancer specific survival when compared with patients treated with surgery.

Differences in United States insurance payer policies and American Society for Radiation Oncology's (ASTRO) model policy on stereotactic body radiation therapy (SBRT). Roach MC1, Thomas TO2, Paravati AJ3, Mahajan A4. Int J Radiat Oncol Biol Phys. 2019 Jan 21. pii: S0360-3016(19)30040-9. doi:10.1016/j.ijrobp.2019.01.005. [Epub ahead of print]
PURPOSE: Insurance payers in the United States vary in what indications they consider SBRT "medically necessary." We compared changes in policies after the last update to ASTRO's SBRT model policy. **METHODS AND MATERIALS:** We identified 77 payers with SBRT policies in 2015 from a policy aggregator as well as 4 national benefits managers (NBMs). Of these, 65 payers and 3 NBMs had publicly available updates since 2015. For each of the indications in ASTRO's model policy, we calculated the proportion of payers that considered SBRT "medically necessary". We used Fischer's exact test to compare these proportions between 2015 and now, between policies updated in the past 12 months and those updated less often, and between national and regional payers currently. **RESULTS:** Payers consider SBRT as "medically necessary" most often for primary lung cancer (97%), reirradiation to the spine (91%), prostate cancer (68%), primary liver cancer (66%), and spinal metastases with radioresistant histologies (66%). Policies have become more aligned with ASTRO's model policy over time. National payers and NBMs cover indications in higher proportions than regional payers. **CONCLUSIONS:** Though there have been improvements over time, more work is needed to align payer policies with ASTRO's model SBRT policy, especially at the regional level.

SMALL CELL LUNG CANCER - SCLC

Retrospective study of the efficacy and toxicity of lobaplatin-etoposide chemotherapy in small cell lung cancer. Gu L1, Zhong D1, Yu T1, Tang P1, Meng F1, Qin Q1. Thorac Cancer. 2019 Jan 2. doi: 10.1111/1759-7714.12936. [Epub ahead of print]
BACKGROUND: A retrospective study was conducted to assess the efficacy and toxicity of lobaplatin-etoposide (EL) chemotherapy for small cell lung cancer (SCLC). **METHODS:** The clinical data of 50 patients treated in our department from May 2014 to March 2018 were obtained. Untreated patients with SCLC administered LBP intravenously (IV) at 30 mg/m2 on day 1 and etoposide IV at 100 mg/m2 on days 1, 2, and 3 were enrolled. The treatment was cycled every 21 days. **RESULTS:** The median overall and progression-free survival rates of the 50 patients were 11.67 (range: 7.30-16.04) and 6.8 (range: 5.25-8.35) months, respectively, with an overall response rate of 66% and a disease control rate of 90%. The most frequent drug-related adverse effects were leukopenia and neutropenia, and no grade 3/4 hepatotoxicity or nephrotoxicity was observed. **CONCLUSION:** These results indicate that LBP-containing chemotherapy is effective and tolerable for SCLC in terms of response and survival.

Stereotactic radiosurgery for brain metastases from newly diagnosed small cell lung cancer: practice patterns and outcomes. Jiang W1,2, Haque W1, Verma V3, Butler B1, Teh BS1. Acta Oncol. 2019 Jan 24:1-8. doi: 10.1080/0284186X.2018.1562207. [Epub ahead of print]

BACKGROUND: Up-front stereotactic radiosurgery (SRS) has been historically thought of as inadequate for brain metastases (BM) from newly diagnosed small cell lung cancer (SCLC). This study evaluates national practice patterns and clinical outcomes for BM from SCLC. **MATERIAL AND METHODS:** The National Cancer Database was queried (2004-2013) for patients with newly diagnosed metastatic SCLC receiving intracranial radiotherapy. Patients were grouped into three categories: upfront SRS, whole-brain radiotherapy (WBRT) alone, or WBRT with boost (SRS or fractionated radiotherapy). Statistics included temporal trend assessment by annual percent change (APC), logistic regression, exploratory Kaplan-Meier overall survival (OS) analysis without and with propensity matching, and Cox proportional hazards modeling. **RESULTS:** A total of 14,722 patients met selection criteria, of whom 487 (3.3%), 13,657 (92.8%), and 578 (3.9%) received upfront SRS, WBRT and WBRT with boost, respectively. Utilization of SRS showed a slight increasing trend from 2004 to 2013 (2.7-4.3%). In addition to socioeconomic factors, other variables associated with SRS use included diagnosis after 2010, treatment at academic centers, and residing in higher-educated regions. SRS was less often delivered to patients with node-positive disease (p < .05). On exploratory analysis, SRS cohort was observed to have a higher overall survival (OS) than WBRT-based groups (p < .001), namely in patients without extracranial metastases. **CONCLUSIONS:** Utilization of up-front SRS for SCLC BM has been increasing over time but is driven by socioeconomic disparities. Although there are likely numerous biases associated with the OS findings herein, further research is needed to validate this finding as well as the role of SRS on patients with brain metastases due to SCLC.

Surgical outcomes of early-stage small-cell lung cancer: single-center experience. Sayan M1, Satir Turk M1, Celik A1, Cuneyt Kurul I1, Irfan Tastepe A1. Asian Cardiovasc Thorac Ann. 2019 Jan 19:218492319826724. doi: 10.1177/0218492319826724. [Epub ahead of print]

BACKGROUND: Small-cell lung cancer is a highly aggressive and metastatic epithelial lung malignancy. A small percentage of these tumors can be detected at an early stage and may be appropriate for surgical treatment. We analyzed the data of patients with early-stage small-cell lung cancer who underwent lobectomy and mediastinal lymph node dissection. **METHODS:** Between January 2011 and December 2016, 26 patients with early-stage small-cell lung cancer underwent lobectomy and mediastinal lymph node dissection and were included the study. The mean age was 60.9 years and 18 (69.2%) were male. Patients with increased uptake of 18 F-fludeoxyglucose in mediastinal or distant organs on positron-emission tomography computed tomography, or lung resections other than lobectomy, were not included in the study. **RESULTS:** The most common tumor location was the right upper lobe. The diagnoses were achieved by intraoperative frozen section study in almost all patients (92.3%). Mean overall survival was 58.5 ± 6.7 months (range 45-71 months) and the 5-year survival rate was 53%. We found that a statistically significant correlation between lymph node metastasis in N1 or N2 stations and survival. There was also a significant relationship between N2 nodal metastasis and recurrence. **CONCLUSION:** As stated in the current guidelines, lung lobectomy and mediastinal lymph node resection should be considered in early-stage small-cell lung cancers. Survival outcomes of surgery for early-stage small-cell lung cancer are similar to the results in non-small-cell lung cancer.

A Randomized Non-Comparative Phase 2 Study of Anti-Programmed Cell Death-Ligand 1 Atezolizumab or Chemotherapy as Second-Line Therapy in Patients with Small Cell Lung Cancer: Results from the IFCT-1603 Trial. Pujol JL1, Greillier L2, Audigier-Valette C3, et al. J Thorac Oncol. 2019 Jan 18. pii: S1556-0864(19)30025-5. doi: 10.1016/j.jtho.2019.01.008. [Epub ahead of print]

INTRODUCTION: This randomized phase 2 trial aimed at evaluating the engineered programmed cell death-ligand 1 (PD-L1) antibody atezolizumab in small cell lung cancer progressing after first-line platinum-etoposide chemotherapy. **METHODS:** Patients were randomized 2:1 to atezolizumab (1200mg intravenously every 3 weeks) until progression or unacceptable toxicity, or conventional chemotherapy (up to six cycles of topotecan or re-induction of initial chemotherapy). Patients were not selected based on PD-L1 tissue expression. The primary endpoint was objective response rate at 6 weeks. A two-stage design with 2:1 randomization and O'Brien-Fleming stopping rules was employed. The null hypothesis was rejected if > 12/45 patients were responders. **RESULTS:** Overall, 73 patients were randomized (atezolizumab n = 49; chemotherapy n = 24). At 6 weeks, 1 of 43 eligible atezolizumab patients achieved an objective response (2.3%, 95% CI 0.0; 6.8), while 8 others had stable disease (20.9% disease control rate; CI 8.8 ; 33.1). Among eligible chemotherapy patients (n=20), 10% achieved an objective response (65% disease control rate). Median pProgression-free survival was 1.4 months (CI 1.2; 1.5) with atezolizumab and 4.3 months (CI: 1.5; 5.9) with chemotherapy. Overall survival did not significantly differ between groups: median OS: 9.5 months versus 8.7 months for the atezolizumab and the chemotherapy group, respectively; (adjusted HRatezolizumab = 0.84 CI: 0.45 ;1.58) ; p=0.60. Two atezolizumab patients (4.2%) experienced grade 3 fatigue, and two others grade 1 dysthyroidism. Among 53 evaluable specimens, only 1 (2%) had positive immunohistochemical PD-L1 staining (SP142 clone). **CONCLUSIONS:** Atezolizumab monotherapy in relapsed small cell lung cancer failed to demonstrate significant efficacy. No unexpected safety concerns were observed.

The role of immunotherapy in small cell lung cancer. Calles A1,2, Aguado G3, Sandoval C3, Álvarez R3,4. Clin Transl Oncol. 2019 Jan 12. doi: 10.1007/s12094-018-02011-9. [Epub ahead of print]
Despite decades of research, prognosis for SCLC patients remains poor, and treatment options limited. SCLC is an immunogenic tumor with high somatic mutation rates due to tobacco exposure resulting in potential neo-antigens, the presence of suppressed immune responses, and occurrence of paraneoplastic disorders. The use of T cell immune-checkpoint inhibitors (anti-PD1: nivolumab, pembrolizumab; anti-PD-L1: atezolizumab, durvalumab; anti-CTLA-4: ipilimumab, tremelimumab) have shown promising antitumor activity with the potential to prolong survival in SCLC patients. In fact, atezolizumab when combined with chemotherapy has achieved the milestone of being the first drug to improve survival in patients with newly diagnosed extensive-stage SCLC. Other immunotherapeutic approaches evaluated in clinical trials for SCLC include the use of cytokines, cancer vaccines, antiganglioside therapies, TLR9 inhibition, anti-Notch signaling, and anti-CD47. This review discusses the rationale and clinical evidence of immunotherapy in SCLC, the conflictive clinical results of novel immunotherapeutic agents and combinatorial therapies under evaluation in SCLC patients.

Advancements in Small-cell Lung Cancer: The Changing Landscape Following IMpower-133.
Pacheco J1, Bunn PA2. Clin Lung Cancer. 2019 Jan 2. pii: S1525-7304(18)30356-5. doi: 10.1016/j.cllc.2018.12.019. [Epub ahead of print]
The treatment landscape of small-cell lung cancer is rapidly evolving. Results of the first-line randomized trial comparing etoposide/carboplatin/placebo with etoposide/carboplatin/atezolizumab (IMpower-133) were recently published, showing a longer progression-free survival and overall survival for patients receiving atezolizumab. These results changed the standard first-line therapy for the first time in several decades. There are 4 additional ongoing randomized trials comparing chemotherapy alone with chemotherapy plus immune checkpoint inhibition as initial treatment. In addition to these major changes in first-line treatment, multiple second or later line options with new agents are likely to change therapeutic standards in these settings. In this article, we discuss the changing treatment landscape following IMpower-133, highlight new second/subsequent line approaches, and discuss the role of biomarkers in patient selection for these treatments.

[Phase II Study of Roniciclib in Combination with Cisplatin/Etoposide or Carboplatin/Etoposide as First-Line Therapy in Patients with Extensive-Disease Small-Cell Lung Cancer.](#) Reck M1, Horn L2, Novello S3, et al. J Thorac Oncol. 2019 Jan 21. pii: S1556-0864(19)30029-2. doi: 10.1016/j.jtho.2019.01.010. [Epub ahead of print]

INTRODUCTION: This Phase II study evaluated the efficacy and safety of the pan-cyclin-dependent kinase inhibitor roniciclib with platinum-based chemotherapy in patients with extensive-disease small-cell lung cancer. **METHODS:** In this randomized, double-blind study, unselected patients with previously untreated ED-SCLC received roniciclib 5 mg or placebo twice daily in a 3 days on/4 day off schedule in 21-day cycles, with concomitant cisplatin or carboplatin on day 1, and etoposide on days 1-3. The primary endpoint was progression-free survival. Other endpoints included overall survival (OS), objective response rate (ORR), and safety. **RESULTS:** 140 patients received treatment: 70 with roniciclib + chemo and 70 with placebo + chemo. Median PFS was 4.9 months (95% confidence interval [CI]: 4.2-5.5) with roniciclib + chemo and 5.5 months (95% CI: 4.6-5.6) with placebo + chemo (hazard ratio [HR] = 1.242; 95% CI: 0.820-1.881; p = 0.8653). Median OS was 9.7 months (95% CI: 7.9-11.1) with roniciclib + chemo and 10.3 months (95% CI: 8.7-11.9) with placebo + chemo (HR = 1.281; 95% CI: 0.776-1.912; p = 0.7858). The objective response rate was 60.6% with roniciclib + chemo and 74.6% with placebo + chemo. Common treatment-emergent adverse events (TEAEs) in both groups included nausea, vomiting, and fatigue. Serious TEAEs were more common with roniciclib + chemo (57.1%) than placebo + chemo (38.6%). **CONCLUSIONS:** Roniciclib combined with chemotherapy demonstrated an unfavorable risk-benefit profile in patients with ED-SCLC and the study was prematurely terminated.

PALLIATIVE AND SUPPORTIVE CARE

[Dyadic Yoga Program for Patients Undergoing Thoracic Radiotherapy and their Family Caregivers: Results of a Pilot Randomized Controlled Trial.](#) Milbury K1, Liao Z1, Shannon V1, et al. Psychooncology. 2019 Jan 18. doi: 10.1002/pon.4991. [Epub ahead of print]

OBJECTIVE: Thoracic radiotherapy (TRT) may result in toxicities that are associated with performance declines and poor quality of life (QOL) for patients and their family caregivers. The purpose of this randomized controlled trial was to establish feasibility and preliminary efficacy of a dyadic Yoga (DY) intervention as a supportive care strategy. **METHODS:** Patients with stage I-III non-small cell lung or esophageal cancer undergoing TRT and their caregivers (N=26 dyads) were randomized to a 15-session DY or a waitlist control (WLC) group. Prior to TRT and randomization, both groups completed measures of QOL (SF-36) and depressive symptoms (CES-D). Patients also completed the 6-minute walk test (6MWT). Dyads were reassessed on the last day of TRT and three months later. **RESULTS:** A priori feasibility criteria were met regarding consent (68%), adherence (80%) and retention (81%) rates. Controlling for relevant covariates, multilevel modeling analyses revealed significant clinical improvements for patients in the DY group compared to the WLC group for the 6MWT (means: DY=473m vs. WLC=397m, d=1.19) and SF-36 physical function (means: DY=38.77 vs. WLC=30.88; d=.66) and social function (means: DY=45.24 vs. WLC=39.09; d=.44) across the follow-up period. Caregivers in the DY group reported marginally clinically significant improvements in SF-36 vitality (means: DY=53.05 vs. WLC=48.84; d=.39) and role performance (means: DY=52.78 vs. WLC=48.59; d=.51) relative to those in the WLC group. **CONCLUSIONS:** This novel supportive care program appears to be feasible and beneficial for patients undergoing TRT and their caregivers. A larger efficacy trial with a more stringent control group is warranted.

[**Communication along Milestones in Lung Cancer Patients with Advanced Disease.**](#) Villalobos M, Siegle A, Hagelskamp L, Jung C, Thomas M. Oncol Res Treat. 2019 Jan 25;42(1-2). doi: 10.1159/000496407. [Epub ahead of print]
Patients with advanced lung cancer and their caregivers are confronted with a complex situation as their disease-related burden comprises physical, psychosocial, and spiritual needs. During the illness trajectory with limited prognosis, they are exposed to different multidisciplinary healthcare settings and providers that challenge the continuity and coordination of care. Additionally, decision-making between active cancer treatment and end-of-life care constitutes a continuous balancing act. Several studies have shown that early integration of palliative care and adequate advance care planning improve quality of life and satisfaction with care. For this strategy, the communication skills of healthcare providers and interprofessional collaboration should be strengthened. A longitudinally structured communication approach along pivotal milestones of the disease can empower patients by facilitating coping and prognostic awareness, and achieve early integration of palliative care and advance care planning. Good interprofessional collaboration and communication lead to better coordination and continuity of care.

[**The Effect of 20-Minute Mindful Breathing on the Rapid Reduction of Dyspnoea at Rest in Patients with Lung Diseases: A Randomized Controlled Trial.**](#) Tan SB1, Liam CK1, Pang YK1, et al. J Pain Symptom Manage. 2019 Jan 23. pii: S0885-3924(19)30042-9. doi:
CONTEXT: Dyspnoea is a common and distressing symptom in respiratory diseases. Despite advances in the treatment of various lung diseases, the treatment modalities for dyspnoea remain limited.
OBJECTIVES: This study aims to examine the effect of 20-minute mindful breathing on the rapid reduction of dyspnoea at rest in patients with lung cancer, chronic obstructive pulmonary disease (COPD) and asthma. **METHODS:** We conducted a parallel-group, non-blinded, randomized controlled trial of standard care plus 20-minute mindful breathing versus standard care alone for patients with moderate to severe dyspnoea due to lung disease named above at the respiratory unit of University Malaya Medical Centre in Malaysia, from 1st August 2017 to 31st March 2018. **RESULTS:** Sixty-three participants were randomly assigned to standard care plus a 20-minute mindful breathing session (n = 32) or standard care alone (n = 31), with no difference in their demographic and clinical characteristics. There was statistically significant reduction in dyspnoea in the mindful breathing group compared to the control group at minute 5 (U = 233.5, n1 = 32, n2 =31, mean rank1 = 23.28, mean rank2 = 37.72, z = -3.574, p < 0.001) and minute 20 (U = 232.0, n1 = 32, n2 =31, mean rank1 = 23.00, mean rank2 = 36.77, z = -3.285, p = 0.001).
CONCLUSION: Our results provide evidence that a single session of 20-minute mindful breathing is effective in reducing dyspnoea rapidly for patients with lung cancer, COPD and asthma.

[**Interprofessional Perspectives on Providing Spiritual Care for Patients With Lung Cancer in Outpatient Settings.**](#) Siler S1, Mamier I1, Winslow BW1, Ferrell BR2. Oncol Nurs Forum. 2019 Jan 13;46(1):49-58. doi: 10.1188/19.ONF.49-58.
PURPOSE: To explore palliative care and oncology clinicians' perspectives on current challenges and facilitating factors in meeting the spiritual needs of patients with lung cancer and family caregivers. This study was conducted in preparation for a community-based lung cancer palliative care intervention.
PARTICIPANTS & SETTING: 19 oncology and palliative care clinicians in three outpatient Kaiser Permanente sites in southern California. **METHODOLOGIC APPROACH:** This multisite qualitative study used focus group and key informant interviews. Data were analyzed using content analysis methodology, and a team approach was used to validate findings. **FINDINGS:** Clinicians described facilitating factors (interprofessional team support, assessment of spiritual needs, clinician-provided spiritual support, and provision of culturally respectful spiritual care) and challenges (related to providing culturally respectful spiritual care by respecting the patients' spiritual and cultural beliefs in an open way and in advocating for the patients' wishes) they encountered when addressing patient and

caregiver spiritual needs. **IMPLICATIONS FOR NURSING:** This study demonstrated the need to provide nurses with practical tools, education, and a supportive environment to address patients' and family caregivers' spiritual concerns.

[**Pilot Study of Self-care Breath Training Exercise for Reduction of Chronic Dyspnea.**](#) Deng G1, Feinstein MB, Benusis L, Tin AL, Stover DE. J Cardiopulm Rehabil Prev. 2019 Jan;39(1):56-59. doi: 10.1097/HCR.0000000000000368.

PURPOSE: Dyspnea related to chronic pulmonary disorders is difficult to manage. In this single-arm study, we evaluated feasibility and potential efficacy of a self-care breath training program to reduce dyspnea that persists despite standard treatments in patients with chronic lung disease. **METHODS:** Adult patients with a chronic pulmonary disorder and stable moderate dyspnea received one 30-min training on specific breathing techniques, followed by audio-guided at-home practice 15 min twice daily for 6 wk, supported with weekly telephone monitoring/coaching. The feasibility endpoints, Baseline and Transition Dyspnea Indexes, 6-min walk test, Hospital Anxiety and Depression Scale, and oxygen saturation at rest and exercise were evaluated at baseline and wk 6. **RESULTS:** Of the 23 patients enrolled over 2 yr, 19 completed the study. A majority (74%; 95% CI, 49%-91%) completed at least 75% of the home practice sessions. Significant objective improvements in physical performance, defined as distance walked, were observed after 6 wk of intervention. On average, patients walked significantly further in the 6-min walk test (59 ft; 95% CI, 18-99; P = .007). In addition, 53% reported clinically significant (20%, defined a priori) subjective improvement in the Transition Dyspnea Index, although the difference was not statistically significant (0.7; 95% CI, -0.8 to 2.3; P = .3). No significant differences were seen in the Hospital Anxiety and Depression Scale or oxygen saturation. **CONCLUSIONS:** A low-burden, low-cost, self-care breath training program improved distance walked by patients with chronic dyspnea after 6 wk of home practice. Promising data suggest that a randomized trial of this breath training program is warranted.

[**The Influence of Patient Race and Activation on Pain Management in Advanced Lung Cancer: a Randomized Field Experiment.**](#) Shields CG1,2,3, Griggs JJ4,5, Fiscella K6,7,8, et al. J Gen Intern Med. 2019 Jan 10. doi: 10.1007/s11606-018-4785-z. [Epub ahead of print]

BACKGROUND: Pain management racial disparities exist, yet it is unclear whether disparities exist in pain management in advanced cancer. **OBJECTIVE:** To examine the effect of race on physicians' pain assessment and treatment in advanced lung cancer and the moderating effect of patient activation. **DESIGN:** Randomized field experiment. Physicians consented to see two unannounced standardized patients (SPs) over 18 months. SPs portrayed 4 identical roles-a 62-year-old man with advanced lung cancer and uncontrolled pain-differing by race (black or white) and role (activated or typical). Activated SPs asked questions, interrupted when necessary, made requests, and expressed opinions. **PARTICIPANTS:** Ninety-six primary care physicians (PCPs) and oncologists from small cities, and suburban and rural areas of New York, Indiana, and Michigan. Physicians' mean age was 52 years (SD = 27.17), 59% male, and 64% white. **MAIN MEASURES:** Opioids prescribed (or not), total daily opioid doses (in oral morphine equivalents), guideline-concordant pain management, and pain assessment. **KEY RESULTS:** SPs completed 181 covertly audio-recorded visits that had complete data for the model covariates. Physicians detected SPs in 15% of visits. Physicians prescribed opioids in 71% of visits; 38% received guideline-concordant doses. Neither race nor activation was associated with total opioid dose or guideline-concordant pain management, and there were no interaction effects (p > 0.05). Activation, but not race, was associated with improved pain assessment (ß, 0.46, 95% CI 0.18, 0.74). In post hoc analyses, oncologists (but not PCPs) were less likely to prescribe opioids to black SPs (OR 0.24, 95% CI 0.07, 0.81). **CONCLUSIONS:** Neither race nor activation was associated with opioid prescribing; activation was associated with better pain assessment. In post hoc analyses, oncologists were less likely to

prescribe opioids to black male SPs than white male SPs; PCPs had no racial disparities. In general, physicians may be under-prescribing opioids for cancer pain.

COMPLEMENTARY & ALTERNATIVE THERAPY

Traditional Chinese medicine Ze-Qi-Tang formula inhibit growth of non-small-cell lung cancer cells through the p53 pathway. Xu Z1, Zhang F2, Zhu Y1, et al. J Ethnopharmacol. 2019 Jan 17. pii: S0378-8741(18)34126-6. doi: 10.1016/j.jep.2019.01.007. [Epub ahead of print]
ETHNOPHARMACOLOGICAL RELEVANCE: Ze-Qi-Tang (ZQT), a classic Chinese herbal formula, has been for over thousand years used for the treatment of several respiratory ailments like cough, asthma, hydrothorax and lung cancer. **AIM OF STUDY:** Cumulative literature on ZQT herbal formula reveals that its several constituent components are potent inducer of apoptosis in different cancer cells. However, the activity of ZQT against non-small-cell-lung cancer (NSCLC) has not been previously examined.The aim of the study is to investigate the molecular mechanism of ZQT on NSCLC cells.
MATERIALS AND METHODS: Cell growth were determined by CCK-8 and colony formation assay. Induction of cellular apoptosis or arrest of cell cycle were determined by flow cytometric analysis using annexin V/ propidium iodide, Hoechst 33342 or TUNEL staining method. In some assay p53 activity of NSCLC (A549 and H460) cells were blocked with pifithrin-a, prior to treatment with ZQT. The level of expression of cell cycle and apoptosis related marker proteins were estimated by western blot. The anticancer activity of ZQT in vivo were monitored in nude mice that were induced with tumor by subcutaneous inoculation of A549 cells and then treated by ZQT(100mg/kg,200mg/kg,400mg/kg) gavaging for 30 days. Mice' body weight and tumor volume were measured weekly. The survival carve was recorded. Apoptosis from mice' tissue was observed by TUNEL assay. Pathological histology of liver, kidney and heart were detected by H&E staining, and its functions were tested by ELISA.
RESULTS: Dose- and time-dependent inhibition of proliferation of NSCLC (A549 and H460) cells by ZQT therapy along with induction of cell cycle arrest at G0⁄G1 phase were observed. The arrest of cell cycle arrest and inhibition of cellular proliferation were associated with up regulation of p53 along with down regulation of Cyclin B1 and Cdk2 indicating a mitochondrial related induction of apoptosis with ZQT. A reversal of ZQT-induced apoptosis and G0⁄G1 arrest was observed with pifithrin-a pretreatment. ZQT was also found to suppress the progression of tumor growth in mouse xenograft models and prolong survival. In addition, no hepato- or nephro- or cardio-toxicity with ZQT treatment were detected in mice.
CONCLUSION: These findings suggest that the ZQT formula inhibits the growth of NSCLC cells and is a potential agent of complementary and alternative treatment for lung cancer.

MISCELLANEOUS WORKS

Evaluation of percentage-based radon testing requirements for federally-funded multi-family housing projects. Neri A1. J Occup Environ Hyg. 2019 Jan 8:1-8. doi: 10.1080/15459624.2019.1566735. [Epub ahead of print]
Radon is a leading cause of lung cancer. Recommendations for radon testing in multi-family housing focus on testing a percentage of all units. There is considerable variability among recommendations as well as their implementation. We used the hypergeometric distribution to determine the probability of identifying one or more units with radon at or above 4.0 pCi/L for two prevalences (1:15, the U.S. average) and 1:3 (for states with many homes with radon ≥4.0 pCi/L) using two approaches. First, the distribution was used to evaluate the probability of finding one or more units with radon at or above 4.0 pCi/L when: 1) testing 10% or 25% of a range of ground-floor units, or 2) testing a varying percentage of units in 10-, 20-, or 30- ground-floor unit buildings. Second, the method was used to determine the number of units to be tested to identify one or more units with radon at or above 4.0 pCi/L with 95%

probability given a range of total ground-floor units. Methods identified that that testing 10% or 25% of ground-floor units had low probability of identifying at least one unit with radon at or above 4.0 pCi/L, especially at low prevalence. At low prevalence (1:15), at least 10 units need to be tested in structures with 20 or fewer total units; at high prevalence (1:3), at least five units need to be tested in units with structures having 10 or fewer units to achieve 95% probability of identifying at least one unit with radon at or above 4.0 pCi/L. These findings indicate that recommendations for radon testing in multi-family housing may be improved by applying a well-established and more rigorous statistical approach than percentage-based testing to will more accurately characterize radon exposure to radon in multi-family housing units, which could improve lung cancer prevention efforts.

[Impact of Primary Care Access on Mortality of Lung Cancer Patients in an Underserved Community.](#) Su CT1,2, Chau V1, Halmos B3, et al. Am J Clin Oncol. 2019 Jan 16. doi: 10.1097/COC.0000000000000516. [Epub ahead of print]
BACKGROUND: Lack of access to primary care physicians (PCPs) may be an important contributor to mortality differences attributed to race/ethnicity. This study examined the effects of primary care access on mortality of lung cancer patients in an underserved community. **METHODS:** Medical records of all newly diagnosed patients with primary lung cancer from 2012 to 2016 at a National Cancer Institute (NCI)-designated center in Bronx, New York were reviewed. Demographic data, PCP status, and residence in primary care shortage areas (PCSAs) were collected. Survival data from time of first imaging to death or the end of follow-up on January 1, 2018 were recorded. Survival analysis was performed using Kaplan-Meier and Cox hazards modeling. **RESULTS:** Among 1062 patients, 874 (82%) were PCSA residents, 314 (30%) were Hispanic, and 445 (42%) were African American. PCSA residents were likely Hispanics (P<0.001), African Americans (P<0.001), of lower income (P<0.001), and had advanced disease at diagnosis (P=0.01). Patients without established PCPs had more comorbidities (P=0.04), more advanced disease (P<0.001), and less in-network cancer treatment (P<0.001). PCSA residence (P=0.03, hazard ratio [HR]=1.27) and no established PCP (P<0.001, HR=1.50) were associated with increased mortality. In multivariable modeling, lack of established PCP remained a predictor of increased mortality (P=0.02, HR=1.25). **DISCUSSION:** Among newly diagnosed lung cancer patients, lack of established PCP is associated with increased mortality. Hispanics and African Americans increasingly resided in PCSAs, suggesting race/ethnicity mortality differences may be mediated by primary care shortage. Patients without PCPs had worse health outcomes. Effective health policy efforts to reduce mortality in lung cancer patients must include approaches to improve primary care access.

[The Changing Face of Lung Cancer: Survivor Perspectives on Patient Engagement.](#) Fitch MI1. Asia Pac J Oncol Nurs. 2019 Jan-Mar;6(1):17-23. doi: 10.4103/apjon.apjon_43_18.
OBJECTIVE: Advances in the diagnosis and treatment of lung cancer have resulted in an increasing number of individuals living longer following their diagnosis. No longer is lung cancer the "death sentence" it once was. This initiative was designed to document the current experiences of lung cancer patients and explore the potential for patient engagement. **METHODS:** Three avenues of investigation were undertaken: a literature review regarding lung cancer and patient engagement, an environmental scan of lung organizations and cancer societies regarding their approaches to lung cancer patient and family engagement, and in-depth interviews with lung cancer survivors and family members about their experiences and perspectives about patient engagement. Information was collated and major themes identified. **RESULTS:** Evidence about the experience of lung cancer patients illustrates their needs are complex and dynamic. It also presents a clear picture of unmet physical, psychosocial, and spiritual needs. In particular, stigma is a significant issue for those diagnosed with lung cancer. Information, support, and communication play important roles in helping patients cope but access to resources remains challenging. Patients and family members expressed interest in becoming engaged in advocacy to improve care.

CONCLUSIONS: The changing face of lung cancer creates the potential for lung cancer survivors to become engaged not only in participating in their own care but also become more involved in peer support and advocacy than lung cancer patients have been able to do in the past.

Brain metastases. Achrol AS1, Rennert RC2, Anders C3, et al. Nat Rev Dis Primers. 2019 Jan 17;5(1):5. doi: 10.1038/s41572-018-0055-y.
An estimated 20% of all patients with cancer will develop brain metastases, with the majority of brain metastases occurring in those with lung, breast and colorectal cancers, melanoma or renal cell carcinoma. Brain metastases are thought to occur via seeding of circulating tumour cells into the brain microvasculature; within this unique microenvironment, tumour growth is promoted and the penetration of systemic medical therapies is limited. Development of brain metastases remains a substantial contributor to overall cancer mortality in patients with advanced-stage cancer because prognosis remains poor despite multimodal treatments and advances in systemic therapies, which include a combination of surgery, radiotherapy, chemotherapy, immunotherapy and targeted therapies. Thus, interest abounds in understanding the mechanisms that drive brain metastases so that they can be targeted with preventive therapeutic strategies and in understanding the molecular characteristics of brain metastases relative to the primary tumour so that they can inform targeted therapy selection. Increased molecular understanding of the disease will also drive continued development of novel immunotherapies and targeted therapies that have higher bioavailability beyond the blood-tumour barrier and drive advances in radiotherapies and minimally invasive surgical techniques. As these discoveries and innovations move from the realm of basic science to preclinical and clinical applications, future outcomes for patients with brain metastases are almost certain to improve.

The QuitIT Coping Skills Game for Promoting Tobacco Cessation Among Smokers Diagnosed With Cancer: Pilot Randomized Controlled Trial. Krebs P1, Burkhalter J2, Fiske J3, et al. JMIR Mhealth Uhealth. 2019 Jan 10;7(1):e10071. doi: 10.2196/10071.
BACKGROUND: Although smoking cessation apps have become popular, few have been tested in randomized clinical trials or undergone formative evaluation with target users. **OBJECTIVE:** We developed a cessation app targeting tobacco-dependent cancer patients. Game design and behavioral rehearsal principles were incorporated to help smokers identify, model, and practice coping strategies to avoid relapse to smoking. In this randomized pilot trial, we examined feasibility (recruitment and retention rates), acceptability (patient satisfaction), quitting self-confidence, and other cessation-related indices to guide the development of a larger trial. **METHODS:** We randomized 42 English-speaking cancer patients scheduled for surgical treatment to either the Standard Care (SC; telecounseling and cessation pharmacotherapies) or the experimental QuitIT study arm (SC and QuitIT game). Gameplay parameters were captured in-game; satisfaction with the game was assessed at 1-month follow-up. We report study screening, exclusion, and refusal reasons; compare refusal and attrition by key demographic and clinical variables; and report tobacco-related outcomes. **RESULTS:** Follow-up data were collected from 65% (13/20) patients in the QuitIT and 61% (11/18) in SC arms. Study enrollees were 71% (27/38) females, 92% (35/38) white people, and 95% (36/38) non-Hispanic people. Most had either lung (12/38, 32%) or gastrointestinal (9/38, 24%) cancer. Those dropping out were less likely than completers to have used a tablet (P<.01) and have played the game at all (P=.02) and more likely to be older (P=.05). Of 20 patients in the QuitIT arm, 40% (8/20) played the game (system data). There were no differences between those who played and did not play by demographic, clinical, technology use, and tobacco-related variables. Users completed an average of 2.5 (SD 4.0) episodes out of 10. A nonsignificant trend was found for increased confidence to quit in the QuitIT arm (d=0.25, 95% CI -0.56 to 1.06), and more participants were abstinent in the QuitIT group than in the SC arm (4/13, 30%, vs 2/11, 18%). Satisfaction with gameplay was largely positive, with most respondents enjoying use, relating to the characters, and

endorsing that gameplay helped them cope with actual smoking urges. **CONCLUSIONS:** Recruitment and retention difficulties suggest that the perihospitalization period may be a less than ideal time for delivering a smoking cessation app intervention. Framing of the app as a "game" may have decreased receptivity as participants may have been preoccupied with hospitalization demands and illness concerns. Less tablet experience and older age were associated with participant dropout. Although satisfaction with the gameplay was high, 60% (12/20) of QuitIT participants did not play the game. Paying more attention to patient engagement, changing the intervention delivery period, providing additional reward and support for use, and improving cessation app training may bolster feasibility for a larger trial.

[A global perspective on coal-fired power plants and burden of lung cancer.](#) Lin CK1, Lin RT2, Chen T3, Zigler C3, Wei Y4, Christiani DC4,5. Environ Health. 2019 Jan 28;18(1):9. doi: 10.1186/s12940-019-0448-8.
BACKGROUND: Exposure to ambient particulate matter generated from coal-fired power plants induces long-term health consequences. However, epidemiologic studies have not yet focused on attributing these health burdens specifically to energy consumption, impeding targeted intervention policies. We hypothesize that the generating capacity of coal-fired power plants may be associated with lung cancer incidence at the national level. **METHODS:** Age- and sex-adjusted lung cancer incidence from every country with electrical plants using coal as primary energy supply were followed from 2000 to 2016. We applied a Poisson regression longitudinal model, fitted using generalized estimating equations, to estimate the association between lung cancer incidence and per capita coal capacity, adjusting for various behavioral and demographic determinants and lag periods. **RESULTS:** The average coal capacity increased by 1.43 times from 16.01 gigawatts (GW) (2000~2004) to 22.82 GW (2010~2016). With 1 kW (KW) increase of coal capacity per person in a country, the relative risk of lung cancer increases by a factor of 59% (95% CI = 7.0%~ 135%) among males and 85% (95% CI = 22%~ 182%) among females. Based on the model, we estimate a total of 1.37 (range = 1.34 ~ 1.40) million standardized incident cases from lung cancer will be associated with coal-fired power plants in 2025. **CONCLUSIONS:** These analyses suggest an association between lung cancer incidence and increased reliance on coal for energy generation. Such data may be helpful in addressing a key policy question about the externality costs and estimates of the global disease burden from preventable lung cancer attributable to coal-fired power plants at the national level.

["A Tool, Not a Crutch": Patient Perspectives About IBM Watson for Oncology Trained by Memorial Sloan Kettering.](#) Hamilton JG1, Genoff Garzon M1, et al. J Oncol Pract. 2019 Jan 28:JOP1800417. doi: 10.1200/JOP.18.00417. [Epub ahead of print]
PURPOSE: IBM Watson for Oncology trained by Memorial Sloan Kettering (WFO) is a clinical decision support tool designed to assist physicians in choosing therapies for patients with cancer. Although substantial technical and clinical expertise has guided the development of WFO, patients' perspectives of this technology have not been examined. To facilitate the optimal delivery and implementation of this tool, we solicited patients' perceptions and preferences about WFO. **METHODS:** We conducted nine focus groups with 46 patients with breast, lung, or colorectal cancer with various treatment experiences: neoadjuvant/adjuvant chemotherapy, chemotherapy for metastatic disease, or systemic therapy through a clinical trial. In-depth qualitative and quantitative data were collected and analyzed to describe patients' attitudes and perspectives concerning WFO and how it may be used in clinical care. **RESULTS:** Analysis of the qualitative data identified three main themes: patient acceptance of WFO, physician competence and the physician-patient relationship, and practical and logistic aspects of WFO. Overall, participant feedback suggested high levels of patient interest, perceived value, and acceptance of WFO, as long as it was used as a supplementary tool to inform their physicians' decision making. Participants also described important concerns, including the need for strict processes to

guarantee the integrity and completeness of the data presented and the possibility of physician overreliance on WFO. **CONCLUSION:** Participants generally reacted favorably to the prospect of WFO being integrated into the cancer treatment decision-making process, but with caveats regarding the comprehensiveness and accuracy of the data powering the system and the potential for giving WFO excessive emphasis in the decision-making process. Addressing patients' perspectives will be critical to ensuring the smooth integration of WFO into cancer care.

[**Cardiovascular disease and survival in non-small cell lung cancer: a multicenter prospective assessment.**](#) Herrero Rivera D1, Nieto-Guerrero Gómez JM2, Cacicedo Fernández de Bobadilla J3, et al. Clin Transl Oncol. 2019 Jan 24. doi: 10.1007/s12094-019-02047-5. [Epub ahead of print]
PURPOSE: Chronic inflammation contributes to cancer development via multiple mechanisms. We hypothesized that cardiovascular diseases (CVD) are also an independent risk factor for survival in non-small cell lung cancer (NSCLC). **MATERIALS AND METHODS:** Prospective multicenter data from 345 consecutive NSCLC patients treated from January 2013 to January 2017 were assessed. Median follow-up for all patients was 13 months (range 3-60 months). There were 109 patients with baseline heart disease (HD 32%), 149 with arterial hypertension (43%), 85 with diabetes mellitus (25%), 129 with hyperlipidemia (37%) and 45 with venous thromboembolism events (VTE 13%). A total of 289 patients (84%) were treated with platinum-based chemotherapy (CT), 300 patients (87%) received thoracic radiation therapy (RT; median radiation dose: 60 Gy [range 12-70]); and 50 (15%) patients underwent surgery. **RESULTS:** Our cohort consisted of 305 men (88%) and 40 (12%) women, with a median age of 67 years (range 31-88 years). Seventy percent had a Karnofsky performance status (KPS) ≥ 80. Multivariate analyses showed a lower OS and higher risk of distant metastasis in patients with advanced stages ($p = 0.05$ and $p < 0.001$, respectively) and HD (HR 1.43, $p = 0.019$; and HR 1.49, $p = 0.025$, respectively). Additionally, patients with VTE had lower local control (HR 1.84, $p = 0.025$), disease-free survival (HR 1.64, $p = 0.020$) and distant metastasis-free survival (HR 1.73, $p = 0.025$).
CONCLUSIONS: HD and VTE are associated with a higher risk of mortality and distant metastasis in NSCLC patients. Chronic inflammation associated with CVDs could be an additional pathophysiologic factor in the development of distant metastasis.