



Caring Ambassadors Lung Cancer Program Literature Review, December 2019

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES	1-2
SCREENING, DIAGNOSIS AND STAGING	2-6
CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES	
NSCLC SURGERY	7-9
NSCLC SYSTEMIC THERAPY	9-17
NSCLC RADIOTHERAPY	17-19
SMALL CELL LUNG CANCER (SCLC)	19-22
PALLIATIVE AND SUPPORTIVE CARE	22-23
COMPLEMENTARY AND ALTERNATIVE THERAPY	23
MISCELLANEOUS WORKS	23-27

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[microRNAs Tune Oxidative Stress in Cancer Therapeutic Tolerance and Resistance.](#) Zhang WC1.

Int J Mol Sci. 2019 Dec 3;20(23). pii: E6094. doi: 10.3390/ijms20236094.

Relapsed disease following first-line therapy remains one of the central problems in cancer management, including chemotherapy, radiotherapy, growth factor receptor-based targeted therapy, and immune checkpoint-based immunotherapy. Cancer cells develop therapeutic resistance through both intrinsic and extrinsic mechanisms including cellular heterogeneity, drug tolerance, bypassing alternative signaling pathways, as well as the acquisition of new genetic mutations. Reactive oxygen species (ROSs) are byproducts originated from cellular oxidative metabolism. Recent discoveries have shown that a disabled antioxidant program leads to therapeutic resistance in several types of cancers. ROSs are finely tuned by dysregulated microRNAs, and vice versa. However, mechanisms of a crosstalk between ROSs and microRNAs in regulating therapeutic resistance are not clear. Here, we summarize how the microRNA-ROS network modulates cancer therapeutic tolerance and resistance and direct new vulnerable targets against drug tolerance and resistance for future applications.

[Influence of miR-199a on rats with non-small cell lung cancer via regulating the HIF-1 \$\alpha\$ /VEGF signaling pathway.](#) Wang LM1, Zhang LL, Wang LW, Zhu L, Ma XX. Eur Rev Med Pharmacol Sci.

2019 Dec;23(23):10363-10369. doi: 10.26355/eurrev_201912_19675.

OBJECTIVE: Micro-ribonucleic acids (miRNAs) are involved in the occurrence of various cancers, and the hypoxia-inducible factor 1- α (HIF-1 α) is the main regulator of cell proliferation induced by hypoxia. The relationships of miR-199a and HIF-1 α expressions with non-small cell lung cancer (NSCLC) remain unclear, so they were explored in this work. **MATERIALS AND METHODS:** On the basis of establishing the rat model of NSCLC, the messenger RNA (mRNA) expressions of miR-199a, HIF-1 α and the vascular endothelial growth factor (VEGF) were analyzed in NSCLC rats, and the correlations of miR-199a with the mRNAs of HIF-1 α and VEGF and cancer staging were investigated. To further study the role of miR-199a in NSCLC cell proliferation via the HIF-1 α /VEGF signaling pathway, NSCLC cells were treated with the signaling pathway inhibitor and transfected with miR-199a mimics, respectively. Also, the roles of the inhibitor PX-478 and miR-199a mimics in the expressions of miR-199a, HIF-1 α ,

and VEGF proteins, as well as their influences on cell proliferation ability were detected. **RESULTS:** In NSCLC rats, the expression of miR-199a was substantially decreased ($p < 0.01$), but the expressions of HIF-1 α and VEGF were notably raised ($p < 0.01$). MiR-199a was negatively correlated with the expression of VEGF. As cancer developed, the expression of miR-199a was gradually lowered, but the expressions of HIF-1 α and VEGF were gradually increased. Both HIF-1 α /VEGF signaling pathway inhibitor PX-478 and miR-199a mimics significantly reduced the expressions of HIF-1 α and VEGF proteins ($p < 0.01$) and suppressed the cell proliferation activity. **CONCLUSIONS:** MiR-199a prevents the proliferation of NSCLC cells via the targeted down-regulation of the HIF-1 α /VEGF signaling pathway.

Robot-assisted bronchoscopy for pulmonary lesion diagnosis: results from the initial multicenter experience. Chaddha U1, Kovacs SP2, Manley C3, Hogarth DK4, Cumbo-Nacheli G5, Bhavani SV4, Kumar R3, Shende M6, Egan JP 3rd5, Murgu S4. BMC Pulm Med. 2019 Dec 11;19(1):243. doi: 10.1186/s12890-019-1010-8.

BACKGROUND: The Robotic Endoscopic System (Auris Health, Inc., Redwood City, CA) has the potential to overcome several limitations of contemporary guided-bronchoscopic technologies for the diagnosis of lung lesions. Our objective is to report on the initial post-marketing feasibility, safety and diagnostic yield of this technology. **METHODS:** We retrospectively reviewed data on consecutive cases in which robot-assisted bronchoscopy was used to sample lung lesions at four centers in the US (academic and community) from June 15th, 2018 to December 15th, 2018. **RESULTS:** One hundred and sixty-seven lesions in 165 patients were included in the analysis, with an average follow-up of 185 ± 55 days. The average size of target lesions was 25.0 ± 15.0 mm. Seventy-one percent were located in the peripheral third of the lung. Pneumothorax and airway bleeding occurred in 3.6 and 2.4% cases, respectively. Navigation was successful in 88.6% of cases. Tissue samples were successfully obtained in 98.8%. The diagnostic yield estimates ranged from 69.1 to 77% assuming the cases of biopsy-proven inflammation without any follow-up information ($N = 13$) were non-diagnostic and diagnostic, respectively. The yield was 81.5, 71.7 and 26.9% for concentric, eccentric and absent r-EBUS views, respectively. Diagnostic yield was not affected by lesion size, density, lobar location or centrality. **CONCLUSIONS:** RAB implementation in community and academic centers is safe and feasible, with an initial diagnostic yield of 69.1-77% in patients with lung lesions that require diagnostic bronchoscopy. Comparative trials with the existing bronchoscopic technologies are needed to determine cost-effectiveness of this technology.

SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

Validation of the eighth edition clinical T categorization system for clinical stage IA resected lung adenocarcinomas: Prognostic implications of the ground-glass opacity component. Kim H1, Goo JM2, Kim YT3, Park CM4. J Thorac Oncol. 2019 Dec 23. pii: S1556-0864(19)33851-1. doi: 10.1016/j.jtho.2019.12.110. [Epub ahead of print]

INTRODUCTION: There is controversy regarding the clinical T category of lung adenocarcinomas that manifest as part-solid nodules (PSNs). We aimed to validate the clinical T category and to evaluate the independent prognostic role of the nodule type (i.e., part-solid vs. solid). **METHODS:** We retrospectively evaluated the prognostic value of clinico-radiological factors on the overall survival of patients with clinical stage IA lung adenocarcinomas that were resected between 2008 and 2014. Clinical T category, nodule type, and their interaction term were included in the multivariable Cox regression analysis with other variables. In addition, a mixture cure model analysis was performed to investigate the association between the covariates and long-term survival. **RESULTS:** A total of 744 patients (420 women; 362 PSNs; median age, 63 years) were included. The multivariable-adjusted HR of the nodule type was not significant (1.30; 95% CI: 0.80, 2.10; $P = 0.291$). However, the clinical T categories were significantly associated with overall survival (HR of cT1b, 2.33 [95% CI: 1.07, 5.06; $P = 0.033$]; HR of cT1c, 5.74 [95%

CI: 2.51, 13.12; P<0.001]). There were no interactions between the nodule type and the clinical T categories (all P>0.05). The multivariable mixture cure model revealed that solid nodules were associated with a decreased probability of long-term survival (OR, 0.40; 95% CI: 0.18, 0.92; P=0.030). Clinical T1c was also a negative predictor of long-term survival (OR, 0.26; 95% CI: 0.07, 0.94; P=0.040).

CONCLUSIONS: The clinical T categorization system is valid for PSNs and solid nodules. Nevertheless, PSNs are a prognostic factor associated with long-term survival.

Association of invitation to lung cancer screening and tobacco use outcomes in a VA demonstration project. Fu SS1,2, Melzer AC1,2,3, Fabbri AE3, Rice KL3, Clothier B1, Nelson DB1,2, Doro EA1, Partin MR1,2. *Prev Med Rep.* 2019 Nov 17;16:101023. doi: 10.1016/j.pmedr.2019.101023. eCollection 2019 Dec.

A potential unintended consequence of lung cancer screening (LCS) is an adverse effect on smoking behaviors. This has been difficult to assess in previous randomized clinical trials. Our goal was to determine whether cessation and relapse behaviors differ between Veterans directly invited (DI) to participate in LCS compared to usual care (UC). We conducted a longitudinal survey of tobacco use outcomes among Veterans (Minneapolis VA) from 2014 to 2015, randomized (2:1) to DI versus UC and stratified by baseline smoking status (current/former). Within the DI group, we explored differences between those who did and did not choose to undergo LCS. A total of 979 patients (n = 660 DI, n = 319 UC) returned the survey at a median of 484 days. Among current smokers (n = 488), smoking abstinence rates and cessation attempts did not differ between DI and UC groups. More baseline smokers in DI were non-daily smokers at follow-up compared to those in UC (25.3% vs 15.6%, OR 1.97 95%CI 1.15-3.36). A significant proportion of former smokers at baseline relapsed, with 17% overall indicating past 30-day smoking. This did not differ between arms. Of those invited to LCS, smoking outcomes did not significantly differ between those who chose to be screened (161/660) versus not. This randomized program evaluation of smoking behaviors in the context of invitation to LCS observed no adverse or beneficial effects on tobacco cessation or relapse among participants invited to LCS, or among those who completed screening. As LCS programs scale and spread nationally, effective cessation programs will be essential.

18F-FDG PET/CT in restaging and evaluation of response to therapy in lung cancer: state of art.

Castello A1, Rossi S2, Lopci E1. *Curr Radiopharm.* 2019 Dec 30. doi: 10.2174/1874471013666191230144821. [Epub ahead of print]

BACKGROUND: Metabolic information provided by 18F-FDG PET/CT are useful for initial staging, therapy planning, response evaluation, and at a lesser extend for the follow-up of non-small cell lung cancer (NSCLC). To date, there are no established clinical guidelines in treatment response and early detection of recurrence. **OBJECTIVE:** To provide an overview of 18F-FDG PET/CT in NSCLC and in particular to discuss its utility in treatment response evaluation and restaging of lung cancer. **METHODS:** A comprehensive search was used based on PubMed results. From all studies published in English, we selected those that explored the role of 18F-FDG PET/CT in treatment response scenario. **RESULTS:** Several studies have demonstrated that modifications in metabolic activity, expressed by changes in SUV both in the primary tumor as well as in regional lymph nodes, are associated with tumor response and survival. Beside SUV, other metabolic parameters (i.e. MTV, TLG, and percentage changes) are emerging to be helpful for predicting clinical outcomes. **CONCLUSION:** 18F-FDG parameters appear to be promising factors for evaluating treatment response and for detecting recurrences, although larger prospective trials are needed to confirm these evidences and to determine optimal cut-off values.

[TMPRSS4: A Novel Tumor Prognostic Indicator for the Stratification of Stage IA Tumors and a Liquid Biopsy Biomarker for NSCLC Patients.](#) Villalba M1,2,3, Exposito F1,2,3, Pajares MJ1,2,3, et al. *J Clin Med.* 2019 Dec 3;8(12). pii: E2134. doi: 10.3390/jcm8122134.

Relapse rates in surgically resected non-small-cell lung cancer (NSCLC) patients are between 30% and 45% within five years of diagnosis, which shows the clinical need to identify those patients at high risk of recurrence. The eighth TNM staging system recently refined the classification of NSCLC patients and their associated prognosis, but molecular biomarkers could improve the heterogeneous outcomes found within each stage. Here, using two independent cohorts (MDA and CIMA-CUN) and the eighth TNM classification, we show that TMPRSS4 protein expression is an independent prognostic factor in NSCLC, particularly for patients at stage I: relapse-free survival (RFS) HR, 2.42 (95% CI, 1.47-3.99), $p < 0.001$; overall survival (OS) HR, 1.99 (95% CI, 1.25-3.16), $p = 0.004$). In stage IA, high levels of this protein remained associated with worse prognosis ($p = 0.002$ for RFS and $p = 0.001$ for OS). As TMPRSS4 expression is epigenetically regulated, methylation status could be used in circulating tumor DNA from liquid biopsies to monitor patients. We developed a digital droplet PCR (ddPCR) method to quantify absolute copy numbers of methylated and unmethylated CpGs within the TMPRSS4 and SHOX2 (as control) promoters in plasma and bronchoalveolar lavage (BAL) samples. In case-control studies, we demonstrated that TMPRSS4 hypomethylation can be used as a diagnostic tool in early stages, with an AUROC of 0.72 ($p = 0.008$; 91% specificity and 52% sensitivity) for BAL and 0.73 ($p = 0.015$; 65% specificity and 90% sensitivity) for plasma, in early stages. In conclusion, TMPRSS4 protein expression can be used to stratify patients at high risk of relapse/death in very early stages NSCLC patients. Moreover, analysis of TMPRSS4 methylation status by ddPCR in blood and BAL is feasible and could serve as a non-invasive biomarker to monitor surgically resected patients.

[Liquid Biopsy in Non-Small Cell Lung Cancer: Highlights and Challenges.](#) Rijavec E1, Coco S2, Genova C2, Rossi G2,3, Longo L2, Grossi F1. *Cancers (Basel).* 2019 Dec 19;12(1). pii: E17. doi: 10.3390/cancers12010017.

Non-small cell lung cancer is one leading cause of death worldwide, and patients would greatly benefit from an early diagnosis. Since targeted and immunotherapies have emerged as novel approaches for more tailored treatments, repeated assessments of the tumor biology have become pivotal to drive clinical decisions. Currently, tumor tissue biopsy is the gold standard to investigate potentially actionable biomarkers, but this procedure is invasive and may prove inadequate to represent the whole malignancy. In this regard, liquid biopsy represents a minimally invasive and more comprehensive option for early detection and investigation of this tumor. Today, cell-free DNA is the only approved circulating marker to select patients for a targeted therapy. Conversely, the other tumor-derived markers (i.e., circulating tumor cells, miRNAs, exosomes, and tumor educated platelets) are still at a pre-clinical phase, although they show promising results for their application in screening programs or as prognostic/predictive biomarkers. The main challenges for their clinical translation are the lack of reliable cutoffs and, especially for miRNAs, the great variability among the studies. Moreover, no established tool has been approved for circulating tumor cells and exosome isolation. Finally, large prospective clinical trials are mandatory to provide evidence of their clinical utility.

[Multidisciplinary Team Based Management of Incidentally Detected Lung Nodules.](#) Verdial FC1, Madtes DK2, Cheng GS2, Pipavath S3, Kim R4, Hubbard JJ5, Zadworny M1, Wood DE1, Farjah F6. *Chest.* 2019 Dec 17. pii: S0012-3692(19)34401-0. doi: 10.1016/j.chest.2019.11.032. [Epub ahead of print]

BACKGROUND: Each year, over 1.5 million Americans are diagnosed with an incidentally-detected lung nodule. Practice guidelines attempt to balance the benefit of early detection of lung cancer with the risks of diagnostic testing, but adherence to guidelines is low. We sought to determine guideline-

adherence rates in the setting of a multidisciplinary nodule clinic and describe reasons for non-adherence as well as associated outcomes. **METHODS:** We performed a cohort study with 3 years of follow-up on patients ≥ 35 years of age with an incidentally-detected lung nodule evaluated in a multidisciplinary clinic that used the 2005 Fleischner Society Guidelines. **RESULTS:** Among 113 patients, 67% (95% confidence interval [CI] 58-76%) were recommended a guideline-concordant nodule evaluation whereas 7.1% (95% CI 3.1-13%) and 26% (95% CI 18-25) were recommended less or more intense evaluation, respectively. In contrast, 58% (95% CI 48-67%), 22% (95% CI 18-25%), and 23% (95% CI 16-32%) received a guideline-concordant, less intense, or more intense evaluation, respectively. The most common reason for recommending guideline-discordant care was concern for two different diagnoses that would each benefit from early detection and treatment. A majority of lung cancer diagnoses (88%) occurred in patients who received guideline-concordant care. There were no lung cancer cases in those who received less intense nodule care. **CONCLUSIONS:** A multidisciplinary nodule clinic may serve as a system-level intervention to promote guideline-concordant care, while also providing a multidisciplinary basis by which to deviate from guidelines in order to address the needs of a heterogeneous patient population.

[Integrated, Multidisciplinary Management of Pulmonary Nodules Can Streamline Care and Improve Adherence to Recommendations.](#)

Roberts TJ^{1,2}, Lennes IT^{1,3,2,4}, Hawari S¹, et al. Oncologist. 2019 Dec 26. doi: 10.1634/theoncologist.2019-0519. [Epub ahead of print]

Every year millions of pulmonary nodules are discovered incidentally and through lung cancer screening programs. Management of these nodules is often suboptimal, with low follow-up rates and poor provider understanding of management approaches. There is an emerging body of literature about how to optimize management of pulmonary nodules. The Pulmonary Nodule and Lung Cancer Screening Clinic (PNLCSC) at Massachusetts General Hospital was founded in 2012 to manage pulmonary nodules via a multidisciplinary approach with optimized support staff. Recommendations from clinic providers and treatment details were recorded for all patients seen at the PNLCS. Adherence to recommendations and outcomes were also tracked and reviewed. From October 2012 to September 2019, 1,136 patients were seen at the PNLCS, each for a mean of 1.8 appointments (range, 1-10). A total of 356 procedures were recommended by the clinic and 271 patients were referred for surgery and/or radiation. The majority of interventions (74%) were recommended at the initial PNLCS appointment. In total, 211 patients (19%) evaluated at the PNLCS had pathologically confirmed pulmonary malignancies or were treated empirically with radiation. Among patients followed by the clinic, the adherence rate to clinic recommendations was 95%. This study shows how a multidisciplinary approach to pulmonary nodule management can streamline care and optimize follow-up. The PNLCS provides a template that can be replicated in other health systems. It also provides an example of how multidisciplinary approaches can be applied to other complex conditions. **IMPLICATIONS FOR PRACTICE:** This work demonstrates how an integrated, multidisciplinary approach to management of pulmonary nodules can streamline patient care and improve adherence to provider recommendations. This approach has the potential to improve patient outcomes and reduce health care costs.

[Evaluating Lung Cancer Screening Across Diverse Healthcare Systems: A Process Model from the Lung PROSPR Consortium.](#)

Rendle KA¹, Burnett-Hartman AN², Neslund-Dudas C³, et al. Cancer Prev Res (Phila). 2019 Dec 23. pii: canprevres.0378.2019. doi: 10.1158/1940-6207.CAPR-19-0378. [Epub ahead of print]

Numerous organizations, including the United States Preventive Services Task Force, recommend annual lung cancer screening (LCS) with low-dose computed tomography (LDCT) for high-risk adults who meet specific criteria. Despite recommendations and national coverage for screening-eligible adults through the Centers for Medicare and Medicaid Services, LCS uptake in the United States remains low (<4%). In recognition of the need to improve and understand LCS across the population, as part of the larger

Population-based Research to Optimize the Screening Process (PROSPR) consortium, the National Cancer Institute funded the Lung PROSPR Research Consortium consisting of five diverse healthcare systems in Colorado, Hawaii, Michigan, Pennsylvania, and Wisconsin. Using various methods and data sources, the center aims to examine utilization and outcomes of LCS across diverse populations, and assess how variations in the implementation of LCS programs shape outcomes across the screening process. This commentary presents the PROSPR LCS process model, which outlines the interrelated steps needed to complete the screening process from risk assessment to treatment. In addition to guiding planned projects within the Lung PROSPR Research Consortium, this model provides insights on the complex steps needed to implement, evaluate, and improve LCS outcomes in community practice.

The Role of c-Met as a Biomarker and Player in Innate and Acquired Resistance in Non-Small-Cell Lung Cancer: Two New Mutations Warrant Further Studies.

Van Der Steen N1,2,3, Zwaenepoel K1,2, Mazzaschi G4, et al. *Molecules*. 2019 Dec 4;24(24). pii: E4443. doi: 10.3390/molecules24244443. The c-Met receptor is a therapeutically actionable target in non-small-cell lung cancer (NSCLC), with one approved drug and several agents in development. Most suitable biomarkers for patient selection include c-Met amplification and exon-14 skipping. Our retrospective study focused on the frequency of different c-Met aberrations (overexpression, amplification and mutations) in 153 primary, therapy-naïve resection samples and their paired metastases, from Biobank@UZA. Furthermore, we determined the correlation of c-Met expression with clinicopathological factors, Epidermal Growth Factor Receptor (EGFR)-status and TP53 mutations. Our results showed that c-Met expression levels in primary tumors were comparable to their respective metastases. Five different mutations were detected by deep sequencing: three (E168D, S203T, N375S) previously described and two never reported (I333T, G783E). I333T, a new mutation in the Sema(phorin) domain of c-Met, might influence the binding of antibodies targeting the HGF-binding domain, potentially causing innate resistance. E168D and S203T mutations showed a trend towards a correlation with high c-Met expression ($p = 0.058$). We found a significant correlation between c-MET expression, EGFR expression ($p = 0.010$) and EGFR mutations ($p = 0.013$), as well as a trend ($p = 0.057$) with regards to TP53 mutant activity. In conclusion this study demonstrated a strong correlation between EGFR mutations, TP53 and c-Met expression in therapy-naïve primary resection samples. Moreover, we found two new c-Met mutations that warrant further studies.

Effectiveness of Intraoperative Pulmonary Wedge Resection of Tumor Site Before Lobectomy for Early Lung Adenocarcinoma.

Yasukawa M1, Sawabata N2, Kawaguchi T2, Taniguchi S2. *Anticancer Res*. 2019 Dec;39(12):6829-6834. doi: 10.21873/anticancer.13899.

BACKGROUND/AIM: Circulating tumor cells (CTCs) are tumor cells shed from tumor sites and circulate in the peripheral blood. CTCs can be a surrogate biomarker of recurrence and prognosis. Because surgical manipulation could promote CTCs, it is important to reduce CTCs during surgery. This study aimed to evaluate the effectiveness of intraoperative wedge resection of the tumor site before lobectomy. **PATIENTS AND METHODS:** A total of 297 resected stage I lung adenocarcinoma patients were retrospectively reviewed. Patients were divided into two groups: Wedge and Non-Wedge. Recurrence-free survival (RFS) curves were plotted using the Kaplan-Meier method. Cox regression analyses were used to evaluate the hazard ratio (HR) with the endpoint RFS. **RESULTS:** The 5-year RFS rates were 92.9% and 85.5%, in Wedge and Non-Wedge groups, respectively ($p=0.006$). Wedge resection was an independent factor associated with RFS (HR=0.342, 95%CI=0.141-0.830, $p=0.018$). **CONCLUSION:** Wedge resection before lobectomy for lung adenocarcinoma patients can improve RFS rates.

NSCLC - SURGERY

[Survival disparities following surgery among patients with different histological types of non-small cell lung cancer.](#) Grosu HB1, Manzanera A2, Shivakumar S3, Sun S4, Noguras Gonzalez G5, Ost DE6. Lung Cancer. 2019 Dec 17;140:55-58. doi: 10.1016/j.lungcan.2019.12.007. [Epub ahead of print]

OBJECTIVES: Clinical decisions for NSCLC patients are often based on TNM stage, which does not account for different histological subtype. Whether histological subtype affects survival still remains unclear. The main objective of this study was to determine the extent to which the survival outcomes of patients with early-stage NSCLC differ by histological subtype. **MATERIAL AND METHODS:** Retrospective cohort study of SEER data base. Patients with stage IA and IB NSCLC that underwent surgery with lymph node dissection were included. The primary outcome was the time to death. Cox proportional hazards models were used to identify risk factors associated with overall survival (OS). The secondary outcome was the time to death from lung cancer. A Cox model and a Fine-Gray subdistribution hazards model in which death from causes other than lung cancer was considered a competing risk event were used to identify risk factors for death from lung cancer. **RESULTS:** Analysis of the SEER database identified 28,584 NSCLC patients, of whom 19,750 (69 %) had adenocarcinoma and 8834 (31 %) had squamous cell carcinoma. In the multivariate for OS, older age ($p < 0.001$), male gender ($p < 0.001$), pneumonectomy ($p < 0.001$), larger tumor size ($p < 0.001$), squamous cell carcinoma ($p < 0.001$) not being Hispanic or Asian were associated with increased risk of death. In the competing risk model, older age ($p < 0.001$), male gender ($p < 0.001$), pneumonectomy ($p < 0.001$), larger tumor size ($p < 0.001$), and squamous cell carcinoma ($p < 0.001$) were associated with an increased risk of death from lung cancer. **CONCLUSION:** This study suggests that among patients with stage I NSCLC, those with squamous histology have a higher risk of mortality than those with adenocarcinoma histology taking into account competing risks.

[Comparison of Double Sleeve Lobectomy by Uniportal Video-Assisted Thoracic Surgery \(VATS\) and Thoracotomy for NSCLC Treatment.](#) Wu L1, Wang H2, Cai H1, Fan J1, Jiang G1, He Y3, Jiang L1. Cancer Manag Res. 2019 Dec 2;11:10167-10174. doi: 10.2147/CMAR.S226459. eCollection 2019.

BACKGROUND: With the development of the surgical technique and experience of surgeons, uniportal VATS has been used in double sleeve lobectomy to treat non-small cell lung cancer (NSCLC). This retrospective study aims to evaluate the efficacy and safety of uniportal VATS in NSCLC treatment. **METHODS:** We reviewed 42 NSCLC patients who underwent double sleeve lobectomy in Shanghai Pulmonary Hospital from June 2015 to November 2017. 21 patients received double sleeve lobectomy through uniportal VATS and 21 through conventional thoracotomy with large incision. **RESULTS:** The characteristics of patients were similar between the two groups. The operation time was longer in the uniportal VATS group ($p=0.021$) and the drainage on postoperation day 1 was significantly less in the uniportal VATS group ($p=0.004$). Patients reported a lower postoperative pain level in the uniportal VATS group than in the thoracotomy group ($p=0.002$). No statistically significant difference showed in other aspects. **CONCLUSION:** Uniportal VATS double sleeve lobectomy for NSCLC treatment is safe and effective. Lower postoperative pain level was found in the uniportal VATS group. Its complication rate and postoperation survival were similar to the conventional thoracotomy approach with large incision. But a large randomized clinical trial is still necessary for further investigation.

[Digital pathology for intraoperative frozen section diagnosis of thoracic specimens: an evaluation of a system using remote sampling and whole slide imaging diagnosis.](#) Griffin J1, Kitsanta P2, Perunovic

B2, Suvarna SK2, Bury J2. J Clin Pathol. 2019 Dec 5. pii: jclinpath-2019-206236. doi: 10.1136/jclinpath-2019-206236. [Epub ahead of print]

BACKGROUND: Digital pathology is now used for primary diagnostic work as well as teaching, research and consultation. In our multisite institution service reorganisation led to histopathology being located in a separate hospital from some surgical specialities. We implemented remotely supervised specimen sampling and frozen section diagnosis using digital pathology. In this study we assessed the concordance of glass and digital slide diagnosis using this system. **METHODS:** We reviewed cases from the first 2 years of digital frozen section reporting at our institution. Cases with potential digital to glass slide discordance were reviewed by three experienced thoracic histopathologists. The reasons for discordance were determined and common themes identified. We also reviewed critical incidents relating to digital pathology during the study period. **RESULTS:** The study population comprised 211 cases. Frozen section to final diagnosis concordance between digital and glass slide diagnosis was found in 196 (92.6%) cases. The 15 potentially discordant cases were reviewed. Intraobserver concordance between glass and digital slide review ranged from 9/15 to 12/15 cases across the three pathologists. Glass slide review diagnosis showed better concordance with ground truth in two cases; digital slide review was more accurate in two cases. One relevant critical incident was identified during the study period. **DISCUSSION:** This is the largest study to examine digital pathology for thoracic frozen section diagnosis and shows that this is a safe and feasible alternative to glass slide diagnosis. Discordance between digital and glass slide diagnoses were unrelated to the processes of whole slide imaging and digital microscopy.

[Predicting Severe Postoperative Complication in Patients with Lung Cancer and Interstitial](#)

[Pneumonia](#). Ohsawa M1, Tsutani Y1, Fujiwara M1, Mimae T1, Miyata Y1, Okada M2. Ann Thorac Surg. 2019 Dec 27. pii: S0003-4975(19)31925-3. doi: 10.1016/j.athoracsur.2019.11.012. [Epub ahead of print]

BACKGROUND: Interstitial pneumonia (IP) is linked to lung cancer, and treatment can cause acute exacerbation. We aimed to identify predictors of severe postoperative complications in patients with lung cancer and IP. **METHODS:** Between April 2007 and April 2017, 199 patients were diagnosed with primary lung cancer and IP using high-resolution computed tomography. Multivariable logistic regression analyses were performed to identify independent predictors of severe complications (Clavien-Dindo grade IIIa or higher). **RESULTS:** Multivariable analyses revealed that severe complications were independently predicted by the percent diffusing capacity of the lungs for carbon monoxide (%DLCO; odds ratio [OR]: 0.88, 95% confidence interval [CI]: 0.82-0.95; $P < 0.0001$) and surgical procedures (lobectomy; OR: 4.49, 95% CI: 1.86-23.32; $P = 0.0454$). Severe complications occurred in 39.2% of patients with low-%DLCO (<40%) and in 4.2% of those with high-%DLCO (>40%). The rates of severe complications were 11.5% for patients who underwent lobectomy and 9.7% for those who underwent sublobar resection. In patients with low-%DLCO, the rates of severe complications were 85.7% for those undergoing lobectomy and 23.8% for those undergoing sublobar resection ($P = 0.0085$). Overall survival (OS) was significantly different between patients with low-%DLCO (5-year OS: 33.5%) and those with high-%DLCO (5-year OS: 65.3%; $P = 0.0011$). In patients with low-%DLCO, there was a significant difference in OS between patients who underwent lobectomy (5-year OS: 0%) and those who underwent sublobar resection (5-year OS: 49.5%; $P = 0.029$). **CONCLUSIONS:** Severe postoperative complications were predicted by %DLCO and surgery type. Sublobar resection might be a better option for patients with low-%DLCO values (<40%).

[Impact on Health-Related Quality of Life of Video-Assisted Thoracoscopic Surgery for Lung](#)

[Cancer](#). Avery KNL1, Blazeby JM1,2, Chalmers KA1, et al. Ann Surg Oncol. 2019 Dec 1. doi: 10.1245/s10434-019-08090-4. [Epub ahead of print]

BACKGROUND: Video-assisted thoracoscopic surgery (VATS) approaches are increasingly used in lung cancer surgery, but little is known about their impact on patients' health-related quality of life (HRQL). This prospective study measured recovery and HRQL in the year after VATS for non-small cell lung cancer (NSCLC) and explored the feasibility of HRQL data collection in patients undergoing VATS or open lung resection. **PATIENTS AND METHODS:** Consecutive patients referred for surgical assessment (VATS or open surgery) for proven/suspected NSCLC completed HRQL and fatigue assessments before and 1, 3, 6 and 12 months post-surgery. Mean HRQL scores were calculated for patients who underwent VATS (segmental, wedge or lobectomy resection). Paired t-tests compared mean HRQL between baseline and expected worst (1 month), early (3 months) and longer-term (12 months) recovery time points. **RESULTS:** A total of 92 patients received VATS, and 18 open surgery. Questionnaire response rates were high (pre-surgery 96-100%; follow-up 67-85%). Pre-surgery, VATS patients reported mostly high (good) functional health scores [(European Organisation for Research and Treatment of Cancer) EORTC function scores > 80] and low (mild) symptom scores (EORTC symptom scores < 20). One-month post-surgery, patients reported clinically and statistically significant deterioration in overall health and physical, role and social function (19-36 points), and increased fatigue, pain, dyspnoea, appetite loss and constipation [EORTC 12-26; multidimensional fatigue inventory (MFI-20) 3-5]. HRQL had not fully recovered 12 months post-surgery, with reduced physical, role and social function (10-14) and persistent fatigue and dyspnoea (EORTC 12-22; MFI-20 2.7-3.2). **CONCLUSIONS:** Lung resection has a considerable detrimental impact on patients' HRQL that is not fully resolved 12 months post-surgery, despite a VATS approach.

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

[Association Between Body Mass Index and Overall Survival With Immune Checkpoint Inhibitor Therapy for Advanced Non-Small Cell Lung Cancer.](#) Kichenadasse G1,2, Miners JO1, Mangoni AA1, Rowland A1, Hopkins AM1, Sorich MJ1. *JAMA Oncol.* 2019 Dec 26. doi: 10.1001/jamaoncol.2019.5241. [Epub ahead of print]

IMPORTANCE: High body mass index (BMI) is independently associated with overall survival benefit from immune checkpoint inhibitor therapy in patients with melanoma, yet whether BMI is associated with outcomes in patients with advanced non-small cell lung cancer treated with atezolizumab remains unknown. **OBJECTIVE:** To examine whether BMI is associated with survival outcomes and adverse events in patients with non-small cell lung cancer (NSCLC) treated with atezolizumab. **DESIGN, SETTING, AND PARTICIPANTS:** A pooled analysis of individual patient-level data from 4 international, multicenter clinical trials was performed. Two were single-arm phase 2 trials (BIRCH [data cutoff of May 28, 2015] and FIR [data cutoff of January 7, 2015]), and 2 were 2-arm randomized clinical trials (POPLAR [phase 2; data cutoff of May 8, 2015] and OAK [phase 3; data cutoff of July 7, 2016]). Patients with advanced NSCLC previously untreated or treated with at least 1 line of systemic therapy, with measurable disease and good organ function and without contraindications for chemotherapy or immune checkpoint inhibitor therapy, were included in these trials. Data analyses were performed from February 28, 2019, to September 30, 2019. **INTERVENTIONS:** The control group was treated with docetaxel once every 3 weeks until disease progression or unacceptable toxic effects occurred in POPLAR and OAK. The experimental group was treated with atezolizumab once every 3 weeks until disease progression or unacceptable toxic effects occurred in all available trials. **MAIN OUTCOMES AND MEASURES:** Association between BMI and overall survival (OS), progression-free survival (PFS), and treatment-related adverse events. Intention-to-treat analysis was conducted. **RESULTS:** Adequate data were available for 2110 patients from a total pool of 2261 across 4 trials. Of those 2110, 1434 patients (median age, 64 years [range, 57-70 years]; 890 men [62%]) received atezolizumab and 676 patients (median age, 63 years [range, 57-69 years]; 419 men [62%]) received docetaxel. There was a

linear association between increasing BMI and OS in patients treated with atezolizumab. Obesity (BMI ≥ 30 [calculated as weight in kilograms divided by height in meters squared]) was associated with significantly improved OS in patients treated with atezolizumab, but not in those who received docetaxel after adjusting for confounding variables. The association between BMI and OS/PFS was the strongest in the high PD-L1 expression subgroup. Overall survival for patients with the highest category of PD-L1 expression ($\geq 50\%$ of tumor cells or $\geq 10\%$ of tumor-infiltrating immune cells; $n = 436$) had hazard ratios of 0.36 (95% CI, 0.21-0.62) for the group with obesity and 0.69 (95% CI, 0.48-0.98) for the group with overweight. Patients with the highest category of PD-L1 expression had PFS hazard ratios of 0.68 (95% CI, 0.49-0.94) for the group with obesity and 0.72 (95% CI, 0.56-0.92) for the group with overweight. Treatment-related adverse events were not associated with BMI. **CONCLUSIONS AND RELEVANCE:** High BMI appears to be independently associated with improved survival with atezolizumab in patients with NSCLC, raising the possibility that baseline BMI should be considered as a stratification factor in future immune checkpoint inhibitor therapy trials.

[Long-Term Results of NRG Oncology RTOG 0617: Standard- Versus High-Dose Chemoradiotherapy With or Without Cetuximab for Unresectable Stage III Non-Small-Cell Lung Cancer.](#) Bradley JD1, Hu C2,3, Komaki RR4, et al. J Clin Oncol. 2019 Dec 16;JCO1901162. doi: 10.1200/JCO.19.01162. [Epub ahead of print]

PURPOSE: RTOG 0617 compared standard-dose (SD; 60 Gy) versus high-dose (HD; 74 Gy) radiation with concurrent chemotherapy and determined the efficacy of cetuximab for stage III non-small-cell lung cancer (NSCLC). **METHODS:** The study used a 2×2 factorial design with radiation dose as 1 factor and cetuximab as the other, with a primary end point of overall survival (OS). **RESULTS:** Median follow-up was 5.1 years. There were 3 grade 5 adverse events (AEs) in the SD arm and 9 in the HD arm. Treatment-related grade ≥ 3 dysphagia and esophagitis occurred in 3.2% and 5.0% of patients in the SD arm v 12.1% and 17.4% in the HD arm, respectively ($P = .0005$ and $< .0001$). There was no difference in pulmonary toxicity, with grade ≥ 3 AEs in 20.6% and 19.3%. Median OS was 28.7 v 20.3 months ($P = .0072$) in the SD and HD arms, respectively, 5-year OS and progression-free survival (PFS) rates were 32.1% and 23% and 18.3% and 13% ($P = .055$), respectively. Factors associated with improved OS on multivariable analysis were standard radiation dose, tumor location, institution accrual volume, esophagitis/dysphagia, planning target volume and heart V5. The use of cetuximab conferred no survival benefit at the expense of increased toxicity. The prior signal of benefit in patients with higher H scores was no longer apparent. The progression rate within 1 month of treatment completion in the SD arm was 4.6%. For comparison purposes, the resultant 2-year OS and PFS rates allowing for that dropout rate were 59.6% and 30.7%, respectively, in the SD arms. **CONCLUSION:** A 60-Gy radiation dose with concurrent chemotherapy should remain the standard of care, with the OS rate being among the highest reported in the literature for stage III NSCLC. Cetuximab had no effect on OS. The 2-year OS rates in the control arm are similar to the PACIFIC trial.

[Comparison between 18F-FDG-PET- and CT-based criteria in non-small cell lung cancer \(NSCLC\) patients treated with Nivolumab.](#)

Rossi G1, Bauckneht M2, Genova C1, et al. J Nucl Med. 2019 Dec 5. pii: jnumed.119.233056. doi: 10.2967/jnumed.119.233056. [Epub ahead of print]

Due to their peculiar mechanism of action, the evaluation of radiological response to immune checkpoint inhibitors (ICI) presents many challenges in solid tumors. We aimed to compare the evaluation of first response to Nivolumab by means of CT-based criteria with respect to fluorodeoxyglucose positron emission tomography (FDG-PET) response criteria in non-small-cell lung cancer (NSCLC) patients. **Methods:** 72 patients with advanced NSCLC were recruited in a mono-institutional ancillary trial within the expanded access program (EAP; NCT02475382) for Nivolumab. Patients underwent CT scan and

FDG-PET at baseline and after 4 cycles (first evaluation). In case of progressive disease (PD), an additional evaluation was performed after two further cycles in order to confirm progression. We evaluated the response to treatment with CT scan by means of response evaluation criteria in solid tumors (RECIST) 1.1 and Immuno-related Response Criteria (IrRC) and with FDG-PET by means of PERCIST and immunotherapy-modified-PERCIST (imPERCIST) criteria. The concordance between CT- and PET-based criteria and the capability of each method to predict overall survival (OS) were evaluated. Results: 48/72 patients were evaluable for first response assessment with both PET- and CT-based criteria. We observed low concordance between CT- and PET-based criteria (Kappa value of 0.346 and 0.355 and Kappa value of 0.128 and 0.198 between PERCIST and imPERCIST versus RECIST and IrRC respectively). Looking at OS, IrRC were more reliable to distinguish responders from non-responders. However thanks to the prognostic value of partial metabolic response assessed by both PERCIST and Immuno-PERCIST, PET-based response maintained prognostic significant in patients classified as progressive disease on the basis of IrRC. Conclusion: Even though the present study did not support the routine use of FDG-PET in the general population of NSCLC patients treated with ICI, it suggests the added prognostic value of the metabolic response assessment, potentially improving the therapeutic decision-making.

[Anlotinib Combined with S-1 in the Third-Line Treatment of Stage IV Non-Small Cell Lung Cancer: Study Protocol for Phase II Clinical Trial.](#) Yang X1,2, Xiang M1, Geng L1,2, Wen Y1,2, Du X1. Asian Pac J Cancer Prev. 2019 Dec 1;20(12):3849-3853. doi: 10.31557/APJCP.2019.20.12.3849.

BACKGROUND: A proportion of patients with stage IV non-small-cell lung cancer (NSCLC) is predicted to receive third-line treatment. However, currently no standard third-line treatment for NSCLC is available. Anlotinib is an oral, multi-targeted tyrosine kinase (TK) receptor inhibitor, which was approved as a third-line treatment for stage IV NSCLC in China on May 9, 2018. Nevertheless, The objective response rate of patients treated with anlotinib was merely 9.2% and the overall survival was only 3 months compared with the patients treated with placebo. Previous studies have shown that cancer treatment with a combination of chemotherapy with TK receptor inhibitors is effective and safe well tolerated. Therefore, the combination of anlotinib with other chemotherapeutic agents may be an effective treatment strategy for patients with stage IV NSCLC. Oral S-1 is a third-generation fluorouracil derivative; it showed good efficacy and caused relatively low toxicity in patients with NSCLC.

METHODS: The purpose of this trial is to evaluate the efficacy and safety of anlotinib combined with S-1 as the third-line treatment for patients with stage IV NSCLC. This is a prospective, phase II clinical trial. We will enroll 29 patients with stage IV NSCLC treated with anlotinib plus S-1. Tumors will be assessed using computed tomography prior to treatment, after two, four, and six cycles of treatment, and during follow-up every 3 months until disease progression or death. The primary endpoint is the objective response rate (ORR). The secondary endpoints are progression-free survival, duration of response, proportion of disease control, and safety. **DISCUSSION:** The expected outcome of this study is that anlotinib combined with S-1 has tolerable toxicity and better ORR than anlotinib monotherapy. The results may indicate additional treatment options for patients with stage IV NSCLC.

[Emerging insights of tumor heterogeneity and drug resistance mechanisms in lung cancer targeted therapy.](#) Lim ZF1,2,3, Ma PC4. J Hematol Oncol. 2019 Dec 9;12(1):134. doi: 10.1186/s13045-019-0818-2.

The biggest hurdle to targeted cancer therapy is the inevitable emergence of drug resistance. Tumor cells employ different mechanisms to resist the targeting agent. Most commonly in EGFR-mutant non-small cell lung cancer, secondary resistance mutations on the target kinase domain emerge to diminish the binding affinity of first- and second-generation inhibitors. Other alternative resistance mechanisms include activating complementary bypass pathways and phenotypic transformation. Sequential

monotherapies promise to temporarily address the problem of acquired drug resistance, but evidently are limited by the tumor cells' ability to adapt and evolve new resistance mechanisms to persist in the drug environment. Recent studies have nominated a model of drug resistance and tumor progression under targeted therapy as a result of a small subpopulation of cells being able to endure the drug (minimal residual disease cells) and eventually develop further mutations that allow them to regrow and become the dominant population in the therapy-resistant tumor. This subpopulation of cells appears to have developed through a subclonal event, resulting in driver mutations different from the driver mutation that is tumor-initiating in the most common ancestor. As such, an understanding of intratumoral heterogeneity—the driving force behind minimal residual disease—is vital for the identification of resistance drivers that results from branching evolution. Currently available methods allow for a more comprehensive and holistic analysis of tumor heterogeneity in that issues associated with spatial and temporal heterogeneity can now be properly addressed. This review provides some background regarding intratumoral heterogeneity and how it leads to incomplete molecular response to targeted therapies, and proposes the use of single-cell methods, sequential liquid biopsy, and multiregion sequencing to discover the link between intratumoral heterogeneity and early adaptive drug resistance. In summary, minimal residual disease as a result of intratumoral heterogeneity is the earliest form of acquired drug resistance. Emerging technologies such as liquid biopsy and single-cell methods allow for studying targetable drivers of minimal residual disease and contribute to preemptive combinatorial targeting of both drivers of the tumor and its minimal residual disease cells.

[Patient-reported outcomes from FLAURA: Osimertinib versus erlotinib or gefitinib in patients with EGFR-mutated advanced non-small-cell lung cancer.](#)

Leighl NB1, Karaseva N2, Nakagawa K3, Cho BC4, Gray JE5, Hovey T6, Walding A7, Rydén A8, Novello S9. *Eur J Cancer*. 2019 Dec 12;125:49-57. doi: 10.1016/j.ejca.2019.11.006. [Epub ahead of print]

BACKGROUND: In the FLAURA trial, osimertinib demonstrated superior progression-free survival and a favorable toxicity profile to erlotinib or gefitinib as initial therapy in patients with EGFR-mutated advanced non-small-cell lung cancer. Patient-reported outcomes from FLAURA are discussed here.

METHODS: Patients (N = 556) completed the EORTC QLQ-LC13 weekly for 6 weeks, then every 3 weeks, and the QLQ-C30 every 6 weeks. Prespecified key symptoms were cough, dyspnea, chest pain, appetite loss, and fatigue. Score changes from baseline to randomized treatment discontinuation were assessed using a mixed-effects model. A ≥ 10 -point change was considered clinically relevant. Odds of improvement and time to deterioration were investigated. QLQ-C30 functioning scores were assessed post hoc. **RESULTS:** Questionnaire completion rates were $>70\%$ at most time points. Baseline mean scores were similar in the osimertinib and erlotinib/gefitinib arms. Scores improved in both arms, but none reached clinical relevance at 5% significance level. A statistically significant difference favoring osimertinib for chest pain was not clinically relevant (-6.84 vs -3.88 ; $p = 0.021$). Odds of improvement and time to deterioration were similar between treatments. In post hoc analyses, improvements favored osimertinib for emotional functioning (8.79 vs 4.91 ; $p = 0.004$) and social functioning (7.66 vs 1.74 ; $p < 0.001$). Cognitive functioning remained stable with osimertinib but deteriorated with erlotinib/gefitinib (0.03 vs -3.91 ; $p = 0.005$). **CONCLUSIONS:** Key symptoms improved from baseline in both treatment arms in FLAURA. Key symptom improvements that were both statistically significant and clinically relevant were not observed in favor of either treatment arm.

[Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials.](#) Drilon A1, Siena S2, Dziadziuszko R3, et al. *Lancet Oncol*. 2019 Dec 11. pii: S1470-2045(19)30690-4. doi: 10.1016/S1470-2045(19)30690-4. [Epub ahead of print]

BACKGROUND: Recurrent gene fusions, such as ROS1 fusions, are oncogenic drivers of various cancers, including non-small-cell lung cancer (NSCLC). Up to 36% of patients with ROS1 fusion-positive

NSCLC have brain metastases at the diagnosis of advanced disease. Entrectinib is a ROS1 inhibitor that has been designed to effectively penetrate and remain in the CNS. We explored the use of entrectinib in patients with locally advanced or metastatic ROS1 fusion-positive NSCLC. **METHODS:** We did an integrated analysis of three ongoing phase 1 or 2 trials of entrectinib (ALKA-372-001, STARTRK-1, and STARTRK-2). The efficacy-evaluable population included adult patients (aged ≥ 18 years) with locally advanced or metastatic ROS1 fusion-positive NSCLC who received entrectinib at a dose of at least 600 mg orally once per day, with at least 12 months' follow-up. All patients had an Eastern Cooperative Oncology Group performance status of 0-2, and previous cancer treatment (except for ROS1 inhibitors) was allowed. The primary endpoints were the proportion of patients with an objective response (complete or partial response according to Response Evaluation Criteria in Solid Tumors version 1.1) and duration of response, and were evaluated by blinded independent central review. The safety-evaluable population for the safety analysis included all patients with ROS1 fusion-positive NSCLC in the three trials who received at least one dose of entrectinib (irrespective of dose or duration of follow-up). These ongoing studies are registered with ClinicalTrials.gov, NCT02097810 (STARTRK-1) and NCT02568267 (STARTRK-2), and EudraCT, 2012-000148-88 (ALKA-372-001). **FINDINGS:** Patients were enrolled in ALKA-372-001 from Oct 26, 2012, to March 27, 2018; in STARTRK-1 from Aug 7, 2014, to May 10, 2018; and in STARTRK-2 from Nov 19, 2015 (enrolment is ongoing). At the data cutoff date for this analysis (May 31, 2018), 41 (77%; 95% CI 64-88) of 53 patients in the efficacy-evaluable population had an objective response. Median follow-up was 15.5 months (IQR 13.4-20.2). Median duration of response was 24.6 months (95% CI 11.4-34.8). In the safety-evaluable population, 79 (59%) of 134 patients had grade 1 or 2 treatment-related adverse events. 46 (34%) of 134 patients had grade 3 or 4 treatment-related adverse events, with the most common being weight increase (ten [8%]) and neutropenia (five [4%]). 15 (11%) patients had serious treatment-related adverse events, the most common of which were nervous system disorders (four [3%]) and cardiac disorders (three [2%]). No treatment-related deaths occurred. **INTERPRETATION:** Entrectinib is active with durable disease control in patients with ROS1 fusion-positive NSCLC, and is well tolerated with a manageable safety profile, making it amenable to long-term dosing in these patients. These data highlight the need to routinely test for ROS1 fusions to broaden therapeutic options for patients with ROS1 fusion-positive NSCLC. **FUNDING:** Ignyta/F Hoffmann-La Roche.

[Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials.](#) Doebele RC1, Drilon A2, Paz-Ares L3, et al. *Lancet Oncol.* 2019 Dec 11. pii: S1470-2045(19)30691-6. doi: 10.1016/S1470-2045(19)30691-6. [Epub ahead of print]

BACKGROUND: Entrectinib is a potent inhibitor of tropomyosin receptor kinase (TRK) A, B, and C, which has been shown to have anti-tumour activity against NTRK gene fusion-positive solid tumours, including CNS activity due to its ability to penetrate the blood-brain barrier. We present an integrated efficacy and safety analysis of patients with metastatic or locally advanced solid tumours harbouring oncogenic NTRK1, NTRK2, and NTRK3 gene fusions treated in three ongoing, early-phase trials. **METHODS:** An integrated database comprised the pivotal datasets of three, ongoing phase 1 or 2 clinical trials (ALKA-372-001, STARTRK-1, and STARTRK-2), which enrolled patients aged 18 years or older with metastatic or locally advanced NTRK fusion-positive solid tumours who received entrectinib orally at a dose of at least 600 mg once per day in a capsule. All patients had an Eastern Cooperative Oncology Group performance status of 0-2 and could have received previous anti-cancer therapy (except previous TRK inhibitors). The primary endpoints, the proportion of patients with an objective response and median duration of response, were evaluated by blinded independent central review in the efficacy-evaluable population (ie, patients with NTRK fusion-positive solid tumours who were TRK inhibitor-naive and had received at least one dose of entrectinib). Overall safety evaluable population included patients from STARTRK-1, STARTRK-2, ALKA-372-001, and STARTRK-NG (NCT02650401; treating young adult

and paediatric patients [aged ≤ 21 years]), who received at least one dose of entrectinib, regardless of tumour type or gene rearrangement. NTRK fusion-positive safety evaluable population comprised all patients who have received at least one dose of entrectinib regardless of dose or follow-up. These ongoing studies are registered with ClinicalTrials.gov, NCT02097810 (STARTRK-1) and NCT02568267 (STARTRK-2), and EudraCT, 2012-000148-88 (ALKA-372-001). **FINDINGS:** Patients were enrolled in ALKA-372-001 from Oct 26, 2012, to March 27, 2018; in STARTRK-1 from Aug 7, 2014, to May 10, 2018; and in STARTRK-2 from Nov 19, 2015 (enrolment is ongoing). At the data cutoff date for this analysis (May 31, 2018) the efficacy-evaluable population comprised 54 adults with advanced or metastatic NTRK fusion-positive solid tumours comprising ten different tumour types and 19 different histologies. Median follow-up was 12.9 months (IQR 8.77-18.76). 31 (57%; 95% CI 43.2-70.8) of 54 patients had an objective response, of which four (7%) were complete responses and 27 (50%) partial responses. Median duration of response was 10 months (95% CI 7.1 to not estimable). The most common grade 3 or 4 treatment-related adverse events in both safety populations were increased weight (seven [10%] of 68 patients in the NTRK fusion-positive safety population and in 18 [5%] of 355 patients in the overall safety-evaluable population) and anaemia (8 [12%] and 16 [5%]). The most common serious treatment-related adverse events were nervous system disorders (three [4%] of 68 patients and ten [3%] of 355 patients). No treatment-related deaths occurred. **INTERPRETATION:** Entrectinib induced durable and clinically meaningful responses in patients with NTRK fusion-positive solid tumours, and was well tolerated with a manageable safety profile. These results show that entrectinib is a safe and active treatment option for patients with NTRK fusion-positive solid tumours. These data highlight the need to routinely test for NTRK fusions to broaden the therapeutic options available for patients with NTRK fusion-positive solid tumours. **FUNDING:** Ignyta/F Hoffmann-La Roche.

[Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of patients with metastatic non-squamous non-small cell lung cancer, including patients with EGFR mutations.](#)

Reck M1, Shankar G2, Lee A2, Coleman S2, McClelland M2, Papadimitrakopoulou VA3, Socinski MA4, Sandler A2. *Expert Rev Respir Med.* 2019 Dec 12:1-12. doi: 10.1080/17476348.2020.1701439. [Epub ahead of print]

INTRODUCTION: Cancer immunotherapy has revolutionized the treatment of patients with advanced or metastatic non-small cell lung cancer (NSCLC). However, specific patient groups (e.g. patients with activating epidermal growth factor receptor [EGFR] mutations) do not appear to derive benefit from immune checkpoint inhibitor (ICI) monotherapy. Combining ICIs, such as atezolizumab, with chemotherapy and/or targeted therapies may help to address this unmet need. **AREAS COVERED:** Atezolizumab is an anti-programmed death-ligand 1 therapy for several tumor types. We review its clinical efficacy and safety in the treatment of advanced or metastatic NSCLC, with a specific focus on the combination of atezolizumab with bevacizumab, carboplatin, and paclitaxel (ABCP). Data from IMpower150 show that the ABCP regimen provided clinical benefit to patients with non-squamous NSCLC, including those with EGFR mutations. **EXPERT OPINION:** Combining ICIs with chemotherapy has proven to be superior to chemotherapy alone. However, tumor resistance to ICIs will likely increase as these drugs enter earlier lines of therapy, underscoring a need for effective treatments when immunotherapy fails. Data suggest that the ABCP regimen may circumvent ICI resistance mechanisms. Continued investigation into the regimen's mechanisms, improved patient profiling/selection, and treatment personalization will drive further development/discoveries.

[Osimertinib for Patients With Non-Small-Cell Lung Cancer Harboring Uncommon EGFR Mutations: A Multicenter, Open-Label, Phase II Trial \(KCSG-LU15-09\).](#) Cho JH1, Lim SH2, An HJ3, et al. *J Clin Oncol.* 2019 Dec 11:JCO1900931. doi: 10.1200/JCO.19.00931. [Epub ahead of print]

PURPOSE: Approximately 10% of patients with epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) harbor uncommon mutations. Here, we report the efficacy and safety of osimertinib in patients with NSCLC harboring uncommon EGFR mutations. **PATIENT AND METHODS:** This was a multicenter, single-arm, open-label, phase II study in Korea. Patients with histologically confirmed metastatic or recurrent NSCLC harboring EGFR mutations other than the exon 19 deletion, L858R and T790M mutations, and exon 20 insertion were eligible for the study. The primary end point of objective response rate was assessed every 6 weeks by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Secondary end points were progression-free survival, overall survival, duration of response, and safety. **RESULTS:** Between March 2016 and October 2017, 37 patients were enrolled. All were evaluable except one patient who withdrew consent after starting treatment. Median age was 60 years, and 22 (61%) were male. Among patients, 61% received osimertinib as first-line therapy. The mutations identified were G719X (n = 19; 53%), followed by L861Q (n = 9; 25%), S768I (n = 8; 22%), and others (n = 4; 11%). Objective response rate was 50% (18 of 36 patients; 95% CI, 33% to 67%). Median progression-free survival was 8.2 months (95% CI, 5.9 to 10.5 months), and median overall survival was not reached. Median duration of response was 11.2 months (95% CI, 7.7 to 14.7 months). Adverse events of any grade were rash (n = 11; 31%), pruritus (n = 9; 25%), decreased appetite (n = 9; 25%), diarrhea (n = 8; 22%), and dyspnea (n = 8; 22%), but all adverse events were manageable. **CONCLUSION:** Osimertinib demonstrated favorable activity with manageable toxicity in patients with NSCLC harboring uncommon EGFR mutations.

[Osimertinib for patients with leptomeningeal metastases associated with epidermal growth factor receptor T790M positive advanced NSCLC: the AURA LM analysis.](#) Ahn MJ1, Chiu CH2, Cheng Y3, et al. J Thorac Oncol. 2019 Dec 27. pii: S1556-0864(19)33854-7. doi: 10.1016/j.jtho.2019.12.113. [Epub ahead of print]

BACKGROUND: Osimertinib has shown promising activity in patients with leptomeningeal metastases (LM) from epidermal growth factor receptor (EGFR) positive NSCLC at 160 mg once daily (qd) (BLOOM; NCT02228369). We report LM activity with osimertinib 80 mg qd in a retrospective analysis of studies across the AURA program (AURA extension, AURA2, AURA17 and AURA3). **METHODS:** Patients with EGFR T790M-positive advanced NSCLC and progression on prior EGFR-TKI received osimertinib 80 mg qd. Patients with central nervous system (CNS) metastases (including LM) were eligible if lesions were neurologically asymptomatic and stable. Patients with evidence of LM at study entry were retrospectively included for analysis; brain scans were assessed for radiologic LM response by neuroradiological blinded independent central review as per modified Response Assessment in Neuro-Oncology LM criteria. LM objective response rate (ORR), duration of response (DoR), progression-free survival (PFS) and overall survival (OS) were assessed. A longitudinal analysis was performed to investigate the relationship between baseline non-CNS tumor size changes and LM responses at each visit for AURA LM and BLOOM patients. **RESULTS:** In 22 patients included for analysis, LM ORR was 55% (95% confidence interval [CI]: 32-76). Median LM DoR was not reached (95% CI: 2.8-not calculable [NC]). Median LM PFS and OS were 11.1 months (95% CI: 4.6-NC) and 18.8 months (95% CI: 6.3-NC), respectively. The longitudinal analysis showed similar non-CNS and LM responses between AURA LM and BLOOM patients. **CONCLUSION:** Patients with EGFR T790M-positive NSCLC and radiologically-detected LM derived clinical benefit from osimertinib 80 mg qd.

[Phase II study of bevacizumab, cisplatin, and pemetrexed in advanced non-squamous non-small cell lung cancer \(NS-NSCLC\) with EGFR wild-type.](#) Murakami S1, Saito H1, Kondo T1, Oshita F2, Yamada K1. J Exp Ther Oncol. 2019 Dec;13(2):131-138.

BACKGROUND: Continuation maintenance therapy with pemetrexed (PEM) and bevacizumab (BEV) following induction therapy with cisplatin (CDDP), PEM, and BEV is beneficial in advanced non-

squamous non-small-cell lung cancer (NS-NSCLC), but the survival benefit of addition of BEV to CDDP/PEM as induction therapy is still unclear. The aim of this phase II study was to evaluate the feasibility and safety of a CDDP/PEM/BEV regimen in Japanese patients with EGFR wild-type NS-NSCLC. **PATIENTS AND METHODS:** This study included 25 patients who receive intravenous CDDP, PEM, and BEV (15 mg/kg) from August 2010 to February 2013. The primary endpoint of this study was the response rate (RR) and the secondary endpoint was progression free survival (PFS), overall survival (OS), and safety. **RESULTS:** The median cycles of induction chemotherapy were four (range 1-6). RR was 64%. Most patients (64%) transitioned to maintenance therapy. The median PFS was 9.7 months. Median OS was 21.6 months. Haematological adverse events reaching grade 3 to 4 were neutropenia (8%) without febrile neutropenia, thrombocytopenia (4%), and anemia (4%). BEV-related non-haematological toxicities of grade 3/4 were hypertension (16%), thrombosis (4%), and gastrointestinal perforation (4%). Each adverse events was controllable, and there were no treatment-related deaths. **CONCLUSIONS:** CDDP/PEM/BEV regimen is effective and tolerable in patients with EGFR wild-type advanced NS-NSCLC, but should be paid attention to some BEV-related toxicities.

Randomized Phase III Study of Continuation Maintenance Bevacizumab With or Without Pemetrexed in Advanced Nonsquamous Non-Small-Cell Lung Cancer: COMPASS (WJOG5610L).

Seto T1, Azuma K2, Yamanaka T3, et al. J Clin Oncol. 2019 Dec 27;JCO1901494. doi: 10.1200/JCO.19.01494. [Epub ahead of print]

PURPOSE: Patients with non-small-cell lung cancer (NSCLC) have been shown to benefit from maintenance therapy. COMPASS evaluated the efficacy and safety of bevacizumab with or without pemetrexed as continuation maintenance therapy after carboplatin, pemetrexed, and bevacizumab induction therapy. **PATIENTS AND METHODS:** Patients with untreated advanced nonsquamous NSCLC without confirmed EGFR 19 deletion or L858R mutation received first-line therapy with carboplatin area under the curve 6, pemetrexed 500 mg/m², and bevacizumab 15 mg/kg once every 3 weeks for 4 cycles. Patients without disease progression during the induction therapy were randomly assigned 1:1 for maintenance therapy with pemetrexed 500 mg/m² plus bevacizumab 15 mg/kg or bevacizumab 15 mg/kg once every 3 weeks until disease progression or unacceptable toxicity. The primary end point was overall survival (OS) after random assignment. **RESULTS:** Between September 2010 and September 2015, 907 patients received induction therapy. Of those, 599 were randomly assigned: 298 received pemetrexed plus bevacizumab, and 301 received bevacizumab. The median OS was 23.3 v 19.6 months (hazard ratio [HR], 0.87; 95% CI, 0.73 to 1.05; 1-sided stratified log-rank P = .069). In the wild-type EGFR subset, the OS HR was 0.82 (95% CI, 0.68 to 0.99; 1-sided unstratified log-rank P = .020). The median progression-free survival (PFS) was 5.7 v 4.0 months (HR, 0.67; 95% CI, 0.57 to 0.79; 2-sided log-rank P < .001). The safety data were consistent with previous reports of treatment regimens. **CONCLUSION:** In terms of the primary end point of OS, no statistically significant benefit was observed; however, PFS in the total patient population and OS in patients with wild-type EGFR was prolonged with the addition of pemetrexed to bevacizumab maintenance therapy.

Predictive factors for progression-free survival in non-small cell lung cancer patients receiving nivolumab based on performance status.

Adachi Y1, Tamiya A1, Taniguchi Y1, Enomoto T1, Azuma K1, Kouno S1, Inagaki Y1, Saijo N1, Okishio K2, Atagi S2. Cancer Med. 2019 Dec 27. doi: 10.1002/cam4.2807. [Epub ahead of print]

BACKGROUND: Nivolumab has promising efficacy for the treatment of non-small cell lung cancer (NSCLC). Various predictive factors for nivolumab response in those with NSCLC have been reported, including performance status (PS). The objective of this retrospective study was to determine the predictive factors for nivolumab response in those with NSCLC with good PS and those with poor PS.

METHODS: We retrospectively collected pretreatment clinical data of 296 consecutive patients with SCLC treated with nivolumab. We investigated the relationship between progression-free survival (PFS) and patient characteristics and analyzed predictive factors associated with good PS (PS 0-1) or poor PS (PS 2-4). **RESULTS:** The median age of patients was 70 years; 206 patients were male, and 224 were classified as having good PS (PS 0-1). The median PFS was 3.0 months, 3.7 months, and 1.2 months for all patients, patients with good PS, and patients with poor PS respectively. Multivariate analysis showed that never smoking (hazard ratio [HR], 1.77; 95% confidence interval [CI], 1.15-2.75), high C-reactive protein (CRP) (HR, 1.39; 95% CI, 1.00-1.93), liver metastasis (HR, 1.95; 95% CI, 1.24-3.07), pleural effusion (HR, 1.45; 95% CI, 1.06-2.00), and steroid use (HR, 2.85; 95% CI, 1.65-4.94) were associated with significantly shorter PFS in patients with good PS. A high advanced lung cancer inflammation index (ALI) was significantly associated with longer PFS in patients with poor PS (HR, 0.24; 95% CI, 0.08-0.79). **CONCLUSIONS:** In patients with NSCLC treated with nivolumab, the factors found to be predictive of shorter PFS in patients with good PS were never smoking, high CRP, liver metastasis, pleural effusion, and steroid administration, whereas high ALI was predictive of longer PFS in patients with poor PS.

NSCLC - RADIOTHERAPY

[High dose radiation therapy based on normal tissue constraints with concurrent chemotherapy achieves promising survival of patients with unresectable stage III non-small cell lung cancer.](#) Zhao Q1, Liu M2, Wang Z1, et al. *Radiother Oncol.* 2019 Dec 20;145:7-12. doi: 10.1016/j.radonc.2019.11.024. [Epub ahead of print]

BACKGROUND AND PURPOSE: We aimed to investigate the potential of individual isotoxic dose escalation based on normal tissue constraints (NTC), hypothesizing that high dose radiation therapy would be superior to standard-dose in concurrent chemoradiotherapy for unresectable stage III non-small cell lung cancer (NSCLC). **MATERIALS AND METHODS:** Individually prescribed radiation doses were calculated based on NTC. Patients with total tumour radiation doses ≥ 66 Gy were assigned to the high dose (HD, ≥ 66 Gy) group, and all other patients were assigned to the standard-dose (SD, < 66 Gy) group. Each patient was retrospectively assigned an Eighth edition of American Joint Committee on Cancer disease stage based on the imaging data of initial diagnosis to avoid over- and under-staging. Intensity modulated radiation therapy plans were optimized to minimize the volumes of organs at risk exposed to radiation. The primary endpoint was overall survival. **RESULTS:** From March 2006 to September 2012, 140 patients were enrolled and assigned to two groups: 71 patients into the HD group and 69 patients into the SD group. The median survival time (MST) was significantly higher in the HD group (33.5 months) than in the SD group (21 months), ($p < 0.0001$). Overall 5-year survival rates were significantly higher in the HD group than in the SD group (37.8% vs 16.7%). Median progression-free survival was 19 months in the HD group and 11 months in the SD group ($p < 0.0001$). No difference in severe (grade 3-5) toxic effects was noted between the two groups. **CONCLUSIONS:** The significant positive association observed between prescribed dose and survival suggests that individualized isotoxic dose-escalated radiation based on NTC might improve survival in this cohort of stage III NSCLC Chinese patients.

[Assessment of precision irradiation in early non-small cell lung cancer and interstitial lung disease \(ASPIRE-ILD\): study protocol for a phase II trial.](#) Palma DA1, Chen H2, Bahig H3, et al. *BMC Cancer.* 2019 Dec 11;19(1):1206. doi: 10.1186/s12885-019-6392-8.

BACKGROUND: Stereotactic ablative radiotherapy (SABR) has become an established treatment option for medically-inoperable early-stage (Stage I-IIA) non-small cell lung cancer (ES-NSCLC). SABR is able to obtain high rates of local control with low rates of symptomatic toxicity in this patient population.

However, in a subset of patients with fibrotic interstitial lung disease (ILD), elevated rates of SABR-related toxicity and mortality have been described. The Assessment of Precision Irradiation in Early Non-Small Cell Lung Cancer and Interstitial Lung Disease (ASPIRE-ILD) study will conduct a thorough prospective evaluation of the clinical outcomes, toxicity, changes in diagnostic test parameters and patient-related outcomes following SABR for ES-NSCLC for patients with fibrotic ILD. **METHODS:** ASPIRE-ILD is a single-arm Phase II prospective study. The accrual target is 39 adult patients with T1-2N0M0 non-small cell lung cancer with co-existing ILD who are not candidates for surgical excision. Pathological confirmation of diagnosis is strongly recommended but not strictly required. Enrolled patients will be stratified by ILD-related mortality risk. The starting SABR dose will be 50 Gy in 5 fractions every other day (biologically effective dose: 100 Gy10 or 217 Gy3), but the radiation dose can be de-escalated up to two times to 50 Gy in 10 fractions daily (75 Gy10 or 133 Gy3) and 45 Gy in 15 fractions daily (58 Gy10 or 90 Gy3). Dose de-escalation will occur if 2 or more of the first 7 patients in a cohort experiences grade 5 toxicity within 6 months of treatment. Similarly, dose de-escalation can also occur if 2 or more of the first 7 patients with a specific subtype of ILD experiences grade 5 toxicity within 6 months of treatment. The primary endpoint is overall survival. Secondary endpoints include toxicity (CTC-AE 4.0), progression-free survival, local control, patient-reported outcomes (cough severity and quality of life), rates of ILD exacerbation and changes in pulmonary function tests/high-resolution computed tomography findings post-SABR. **DISCUSSION:** ASPIRE-ILD will be the first prospective study specifically designed to comprehensively evaluate the effectiveness and safety of SABR for ES-NSCLC in patients with co-existing ILD.

[Radiomics of 18F-FDG PET/CT images predicts clinical benefit of advanced NSCLC patients to checkpoint blockade immunotherapy.](#) Mu W1, Tunali I1, Gray JE2, Qi J1, Schabath MB2,3, Gillies RJ4. *Eur J Nucl Med Mol Imaging*. 2019 Dec 5. doi: 10.1007/s00259-019-04625-9. [Epub ahead of print] **INTRODUCTION:** Immunotherapy has improved outcomes for patients with non-small cell lung cancer (NSCLC), yet durable clinical benefit (DCB) is experienced in only a fraction of patients. Here, we test the hypothesis that radiomics features from baseline pretreatment 18F-FDG PET/CT scans can predict clinical outcomes of NSCLC patients treated with checkpoint blockade immunotherapy. **METHODS:** This study included 194 patients with histologically confirmed stage IIIB-IV NSCLC with pretreatment PET/CT images. Radiomics features were extracted from PET, CT, and PET+CT fusion images based on minimum Kullback-Leibler divergence (KLD) criteria. The radiomics features from 99 retrospective patients were used to train a multiparametric radiomics signature (mpRS) to predict DCB using an improved least absolute shrinkage and selection operator (LASSO) method, which was subsequently validated in both retrospective (N = 47) and prospective test cohorts (N = 48). Using these cohorts, the mpRS was also used to predict progression-free survival (PFS) and overall survival (OS) by training nomogram models using multivariable Cox regression analyses with additional clinical characteristics incorporated. **RESULTS:** The mpRS could predict patients who will receive DCB, with areas under receiver operating characteristic curves (AUCs) of 0.86 (95%CI 0.79-0.94), 0.83 (95%CI 0.71-0.94), and 0.81 (95%CI 0.68-0.92) in the training, retrospective test, and prospective test cohorts, respectively. In the same three cohorts, respectively, nomogram models achieved C-indices of 0.74 (95%CI 0.68-0.80), 0.74 (95%CI 0.66-0.82), and 0.77 (95%CI 0.69-0.84) to predict PFS and C-indices of 0.83 (95%CI 0.77-0.88), 0.83 (95%CI 0.71-0.94), and 0.80 (95%CI 0.69-0.91) to predict OS. **CONCLUSION:** PET/CT-based signature can be used prior to initiation of immunotherapy to identify NSCLC patients most likely to benefit from immunotherapy. As such, these data may be leveraged to improve more precise and individualized decision support in the treatment of patients with advanced NSCLC.

["Dose of the day" based on cone beam computed tomography and deformable image registration for lung cancer radiotherapy.](#) Yuan Z1,2, Rong Y1, Benedict SH1, Daly ME1, Qiu J3, Yamamoto T1. J Appl Clin Med Phys. 2019 Dec 9. doi: 10.1002/acm2.12793. [Epub ahead of print]

PURPOSE: Adaptive radiotherapy (ART) has potential to reduce toxicity and facilitate safe dose escalation. Dose calculations with the planning CT deformed to cone beam CT (CBCT) have shown promise for estimating the "dose of the day". The purpose of this study is to investigate the "dose of the day" calculation accuracy based on CBCT and deformable image registration (DIR) for lung cancer radiotherapy. **METHODS:** A total of 12 lung cancer patients were identified, for which daily CBCT imaging was performed for treatment positioning. A re-planning CT (rCT) was acquired after 20 Gy for all patients. A virtual CT (vCT) was created by deforming initial planning CT (pCT) to the simulated CBCT that was generated from deforming CBCT to rCT acquired on the same day. Treatment beams from the initial plan were copied to the vCT and rCT for dose calculation. Dosimetric agreement between vCT-based and rCT-based accumulated doses was evaluated using the Bland-Altman analysis.

RESULTS: Mean differences in dose-volume metrics between vCT and rCT were smaller than 1.5%, and most discrepancies fell within the range of $\pm 5\%$ for the target volume, lung, esophagus, and heart. For spinal cord Dmax, a large mean difference of -5.55% was observed, which was largely attributed to very limited CBCT image quality (e.g., truncation artifacts). **CONCLUSION:** This study demonstrated a reasonable agreement in dose-volume metrics between dose accumulation based on vCT and rCT, with the exception for cases with poor CBCT image quality. These findings suggest potential utility of vCT for providing a reasonable estimate of the "dose of the day", and thus facilitating the process of ART for lung cancer.

SMALL CELL LUNG CANCER - SCLC

[Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic Small-Cell Lung Cancer: Results From the KEYNOTE-028 and KEYNOTE-158 Studies.](#) Chung HC1, Piha-Paul SA2, Lopez-Martin J3, Schellens JHM4, et al. J Thorac Oncol. 2019 Dec 20. pii: S1556-0864(19)33850-X. doi: 10.1016/j.jtho.2019.12.109. [Epub ahead of print]

INTRODUCTION: Pembrolizumab has shown clinical benefit in patients with previously treated recurrent/metastatic small-cell lung cancer (SCLC) in the phase 1b multicohort study KEYNOTE-028 (NCT02054806) and the phase 2 multicohort study KEYNOTE-158 (NCT02628067). We present a pooled analysis of patients from KEYNOTE-028 and KEYNOTE-158 who had received ≥ 2 lines of previous therapy for SCLC. **METHODS:** Eligible patients were ≥ 18 years, had histologically/cytologically confirmed incurable recurrent/metastatic SCLC, an Eastern Cooperative Oncology Group performance status of ≤ 1 , and had received ≥ 2 lines of previous therapy. Patients in KEYNOTE-028 were required to have a programmed death ligand 1 (PD-L1)-positive tumor. Patients received pembrolizumab 10 mg/kg every 2 weeks (KEYNOTE-028) or 200 mg every 3 weeks (KEYNOTE-158) for up to 2 years. The primary endpoint was objective response rate (ORR) per RECIST version 1.1; presented here per independent review. **RESULTS:** Eighty-three patients who had received ≥ 2 lines of previous therapy (KEYNOTE-028, n=19; KEYNOTE-158, n=64) were included. Median follow-up duration was 7.7 months (range, 0.5–48.7). ORR was 19.3% (95% CI, 11.4–29.4); 2 patients had a complete response (1 with a PD-L1-positive tumor) and 14 had a partial response (13 with PD-L1-positive tumors). Median duration of response was not reached (range, 4.1–35.8+ months); 61% of responders had responses lasting ≥ 18 months. Fifty-one patients (61.4%) experienced any-grade treatment-related adverse events; 8 (9.6%) patients had grade ≥ 3 events. **CONCLUSION:** Pembrolizumab demonstrated durable antitumor activity in subset of patients with recurrent/metastatic SCLC who had ≥ 2 previous lines of therapy, regardless of PD-L1 expression. Pembrolizumab was well tolerated.

Clinical outcome for small cell lung cancer patients with bone metastases at the time of diagnosis.

Gong L1, Xu L1, Yuan Z1, Wang Z1, Zhao L1, Wang P1. J Bone Oncol. 2019 Nov 2;19:100265. doi: 10.1016/j.jbo.2019.100265. eCollection 2019 Dec.

OBJECTIVES: The characteristics and prognostic factors of small-cell lung cancer (SCLC) patients with bone metastases at first diagnosis have scarcely been reported. This study aimed to analyze the prognostic factors of these patients and to develop a scoring system for survival to provide evidence for clinical treatment decisions. **MATERIALS AND METHODS:** The records of 102 SCLC patients with bone metastasis at the time of diagnosis who were seen in our hospital between May 2010 and May 2015 were retrospectively reviewed. The log-rank test and multivariate Cox regression analysis were used to evaluate potential clinical predictors of survival. A scoring system was developed based on the hazard ratios of significant independent prognostic factors. **RESULT:** The most common site of bone metastases was the spine (64.7%), and 26 patients (25.6%) had a single bone metastasis. The median survival was 10.4 months, and the 2-year survival rate was 10.3%. Age, number of bone metastases, and occurrence of extraosseous distant metastases were significant independent prognostic factors for overall survival. Based on their scores, patients were divided into three groups. The median survival times of the three groups were 6.4 months, 8.5 months and 12.4 months, and the 2-year survival rates were 0%, 2.9%, and 19.3% ($p=0.000$). Twenty-six patients (25.5%) developed skeletal-related events (SREs), and the most common SREs were radiation to the bone (22.5%) and spinal cord compression (11.8%). **CONCLUSION:** This study includes preliminary clinical data of SCLC patients with bone metastases at the time of diagnosis, and more studies are needed.

The prognostic role of PET/CT in small-cell lung cancer. Budak E1, Yanarates A2, Akgün A3. Rev

Esp Med Nucl Imagen Mol. 2019 Dec 18. pii: S2253-654X(19)30129-5. doi: 10.1016/j.remnm.2019.09.003. [Epub ahead of print]

OBJECTIVE: The aim in the present study is to determine the prognostic value of metabolic parameters related to the primary tumors detected in pretreatment Fluorine-18 2-fluoro-2-Deoxy-D-glucose (18F FDG) positron emission tomography/computerized tomography (PET/CT) scans of patients diagnosed with small-cell lung cancer (SCLC). **MATERIAL AND METHODS:** Enrolled in this retrospective study were 63 patients with a histopathologically confirmed diagnosis of SCLC who underwent an 18F FDG PET/CT scan at baseline. Disease stage, age at diagnosis, gender, albumin level and maximum standardized uptake value (SUVmax), SUVmean, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) values related to the primary tumor at the baseline PET scan were recorded, and the relationship of these factors with progression-free survival (PFS) and overall survival (OS) was evaluated. **RESULTS:** The study included a total of 63 patients (10 female, 53 male, mean age of 64.8 and age range of 43-82 years), 22 of which had limited disease (LD) and 41 had extensive disease (ED). The OS and PFS were significantly higher in patients with LD than in patients with ED (15 ± 2.9 vs. 10 ± 0.9 months, $p = 0.002$ for OS; 10 ± 0.7 vs 6 ± 0.6 months, $p = 0.014$ for PFS). However, no statistically significant relationship was identified between gender, albumin level, age and SUVmax, SUVmean, MTV, TLG values related to the primary tumor and PFS or OS. **CONCLUSION:** The present study found that pretreatment PET parameters were of not predictive value for PFS and OS in patients with SCLC.

The prognostic role of circulating CD8+ T cell proliferation in patients with untreated extensive stage small cell lung cancer. An N1, Wang H2, Jia W3, Jing W3, Liu C3, Zhu H4, Yu J5,6. J Transl

Med. 2019 Dec 3;17(1):402. doi: 10.1186/s12967-019-02160-7.

BACKGROUND: Immunosuppression caused by tumorigenesis may promote tumor progress and invasion. Here, we investigated whether the characteristics of circulating T lymphocyte subtypes in patients with extensive small cell lung cancer (ED-SCLC) can be used as an alternative marker of tumor

progression. **METHODS:** This study included 36 newly diagnosed ED-SCLC patients before treatment and the patients were followed up. 22 age and sex-matched healthy volunteers were selected as control. The percentages and proliferation potential of T lymphocyte subpopulations from peripheral blood were measured. **RESULTS:** CD4+ CD25+ Foxp3+ regulatory T cells (Tregs) were elevated in ED-SCLC patients compared with healthy controls ($p = 0.0083$). In contrast, the percentages of CD3+ and CD3+CD4+ T cells were significantly lower in SCLC patients ($p < 0.001$; $p = 0.0014$). The proliferation (%divided) of CD8+ T cells of SCLC patients was suppressed compared with healthy controls ($p = 0.0058$), but not of CD4+ T cells ($p = 0.1611$). Multivariate analyses showed that the %divided of CD8+ T cells is an independent predictor for PFS (HR: 4.342, 95% CI 1.324-14.245; $p = 0.015$). The percentages of peripheral Tregs and the degree of chemotherapy or radiotherapy induced lymphopenia negatively correlated with the proliferation of CD8+ T cells ($p = 0.0225$, $r = -0.379$; $p = 0.0003$, $r = -0.464$). **CONCLUSION:** The present study indicates that SCLC patients have impaired immunity in peripheral blood, and the proliferation potential of circulating CD8+ T cells is a significant predictor for PFS.

[Recent progress in mapping the emerging landscape of the small-cell lung cancer genome.](#)

Kim KB1, Dunn CT2, Park KS3. *Exp Mol Med.* 2019 Dec 12;51(12):157. doi: 10.1038/s12276-019-0349-5.

Small-cell lung cancer (SCLC) remains the deadliest of all the lung cancer types. Its high mortality is largely attributed to the invariable development of resistance to standard chemo/radiotherapies, which have remained unchanged for the past 30 years, underscoring the need for new therapeutic approaches. The discovery of molecular targets for chemoprevention and treatment has been hampered by the poor understanding of SCLC progression. In recent years, comprehensive omics-based analyses have led to the discovery of recurrent alterations in patient tumors, and functional studies using genetically engineered mouse models and patient-derived tumor models have provided information about the alterations critical for SCLC pathogenesis. Defining the somatic alterations scattered throughout the SCLC genome will help to understand the underlying mechanism of this devastating disease and pave the way for the discovery of therapeutic vulnerabilities associated with the genomic alterations.

[Different distant metastasis patterns based on tumor size could be found in extensive-stage small cell lung cancer patients: a large, population-based SEER study.](#) Li J#1, Liu F#1, Yu H2, Zhao C3, Li Z4, Wang H5. *PeerJ.* 2019 Dec 3;7:e8163. doi: 10.7717/peerj.8163. eCollection 2019.

BACKGROUND: Small-cell lung cancer (SCLC) is a malignant cancer with the ability to metastasize quickly. The relationship between tumor size and the distant metastasis patterns of Extensive-Stage Small Cell Lung Cancer (ES-SCLC) has not been reported. **OBJECTIVES:** The aim of this study was to determine the different distant metastasis patterns as they related to tumor size in ES-SCLC.

PATIENTS AND METHODS: We used Surveillance, Epidemiology, and End Results (SEER) population-based data collected from 2010 through 2013 to identify 11058 ES-SCLC patients with definite evidence of distant metastases. Multivariate logistic regression analysis was used to demonstrate the association between tumor size and distant metastasis patterns including bone, liver, brain, and lung metastases. Age, race, sex, and N stage were also selected in the logistic regression model.

RESULTS: Subtle differences in metastasis patterns were found among patients based on different tumor sizes. Patients with tumors 3-7 cm have a higher risk of bone metastasis compared with those that have tumors ≤ 3 cm (OR 1.165, 95% CI [1.055-1.287], $P = 0.003$) and patients with tumors ≥ 7 cm have a higher risk of lung metastasis (OR 1.183, 95% CI [1.039-1.347], $P = 0.011$). In addition, patients with tumors ≥ 7 cm had a lower risk of brain metastasis and liver metastasis than patients with tumors ≤ 3 cm (OR 0.799, 95% CI [0.709-0.901], $P < 0.001$; OR 0.747, 95% CI [0.672-0.830], $P < 0.001$). Interestingly, there was no correlation between a larger tumor and a higher risk of metastasis. However, the tumor metastasis

pattern did have some correlation with age, gender, race and N-status. **CONCLUSION:** The pattern of distant metastasis of ES-SCLC is related to the tumor size and the tumor size is indicative of the metastatic site. Larger tumor sizes did not correlate with a higher risk of distant metastasis, but the size is related to the pattern of distant metastasis. The study of different distant metastasis patterns based on tumor size and other clinical features (e.g., age, race, sex, and N stage) in ES-SCLC is clinically valuable.

[The role of postoperative thoracic radiotherapy and prophylactic cranial irradiation in early stage small cell lung cancer: Patient selection among ESTRO experts.](#) Putora PM1, De Ruyscher D2, Glatzer M3, et al. *Radiother Oncol.* 2019 Dec 27;145:45-48. doi: 10.1016/j.radonc.2019.11.022. [Epub ahead of print]

BACKGROUND: The role of prophylactic cranial irradiation (PCI) and thoracic radiotherapy (TRT) is unclear in resected small cell lung cancer (SCLC). **METHODS:** Thirteen European radiotherapy experts on SCLC were asked to describe their strategies on PCI and TRT for patients with resected SCLC. The treatment strategies were converted into decision trees and analyzed for consensus and discrepancies. **RESULTS:** For patients with resected SCLC and positive lymph nodes most experts recommend prophylactic cranial irradiation and thoracic radiotherapy. For elderly patients with resected node negative SCLC, most experts do not recommend thoracic radiotherapy or prophylactic cranial irradiation. **CONCLUSION:** PCI and TRT are considered in patients with resected SCLC and these treatments should be discussed with the patient in the context of shared decision-making.

PALLIATIVE AND SUPPORTIVE CARE

[Deterioration in Muscle Mass and Physical Function Differs According to Weight Loss History in Cancer Cachexia.](#) Stene GB1,2,3, Balstad TR2,3, Leer ASM1,2, et al. *Cancers (Basel).* 2019 Dec 3;11(12). pii: E1925. doi: 10.3390/cancers11121925.

BACKGROUND: Muscle mass and physical function (PF) are common co-primary endpoints in cancer cachexia trials, but there is a lack of data on how these outcomes interact over time. The aim of this secondary analysis of data from a trial investigating multimodal intervention for cancer cachexia (ClinicalTrials.gov: NCT01419145) is to explore whether changes in muscle mass and PF are associated with weight loss and cachexia status at baseline. **METHODS:** Secondary analysis was conducted using data from a phase II randomized controlled trial including 46 patients with stage III-IV non-small cell lung cancer (n = 26) or inoperable pancreatic cancer (n = 20) due to commence chemotherapy. Cachexia status at baseline was classified according to international consensus. Muscle mass (assessed using computed tomography (CT)) and PF outcomes, i.e., Karnofsky performance status (KPS), self-reported PF (self-PF), handgrip strength (HGS), 6-minute walk test (6MWT), and physical activity (PA), were measured at baseline and after six weeks. **RESULTS:** When compared according to cachexia status at baseline, patients with no/pre-cachexia had a mean loss of muscle mass (-5.3 cm², p = 0.020) but no statistically significant change in PF outcomes. Patients with cachexia also lost muscle mass but to a lesser extent (-2.8 cm², p = 0.146), but demonstrated a statistically significant decline in PF; KPS (-3.8 points, p = 0.030), self-PF (-8.8 points, p = 0.027), and HGS (-2.7 kg, p = 0.026). **CONCLUSIONS:** Weight loss history and cachexia status at baseline are of importance if one aims to detect changes in PF outcomes in cancer cachexia trials. To improve the use of co-primary endpoints that include PF in future trials, outcomes that have the potential to detect change relative to weight loss should be investigated further.

[Decision-making factors for best supportive care alone and prognostic factors after best supportive care in non-small cell lung cancer patients.](#) Kitazawa H1, Takeda Y2, Naka G2, Sugiyama H2. *Sci Rep.* 2019 Dec 27;9(1):19872. doi: 10.1038/s41598-019-56431-w.

Among patients with non-small cell lung cancer (NSCLC), best supportive care (BSC) is well-known to improve patient's quality of life and prolong survival. This study aimed to clarify (1) the decision-making factors of BSC alone and (2) the prognostic factors after selection of no further anticancer therapies. We retrospectively reviewed the clinical data of patients with NSCLC between November 2004 and February 2014, who received BSC as only therapy and BSC after completion of anticancer therapies. One hundred eighteen patients received BSC alone. Among 860 patients treated with anticancer therapies, 236 were selected as control group, 160 of whom received BSC after anticancer therapy. The significant reasons for receiving BSC alone were: comorbidities of dementia, poor Eastern Cooperative Oncology Group performance status (ECOG-PS), patients' wishes, pulmonary comorbidities, wild type epidermal growth factor receptor (EGFR), relevant social background and psychiatric comorbidities. Poor prognostic factors at the start of BSC were poor ECOG-PS, presence of disseminated intravascular coagulation (DIC), and history of anticancer therapy. NSCLC patients with comorbidities, wild type EGFR, and relevant social background factors tended to receive BSC alone. Post-cancer therapy NSCLC patients and those with DIC and declining ECOG-PS have a shorter survival period from the start of BSC.

COMPLEMENTARY & ALTERNATIVE THERAPY

[Auricular acupressure for cancer-related fatigue during lung cancer chemotherapy: a randomised trial.](#) Lin L#1,2, Zhang Y#3, Qian HY1, Xu JL1, Xie CY2, Dong B2, Tian L4,2. *BMJ Support Palliat Care.* 2019 Dec 13. pii: bmjspcare-2019-001937. doi: 10.1136/bmjspcare-2019-001937. [Epub ahead of print]

PURPOSE: To evaluate the effect of auricular acupressure (AA) on cancer-related fatigue (CRF), sleep disturbance and anxiety in lung cancer patients undergoing chemotherapy. **MATERIALS AND METHODS:** Patients were recruited from the respiratory department of a general hospital and were randomised into three groups. A 9-week course of AA using Semen Vaccariae (SV) (Group A)/AA using magnetic beads (Group B)/routine care (Group C) was implemented. CRF scores were used as the primary outcome while the sleep and anxiety scores were the secondary outcomes. Analysis of variance and least significant difference t-test were used to determine the intergroup differences and paired-sample t-test was used for the intragroup comparison. **RESULTS:** 100 lung cancer patients undergoing chemotherapy were included. Compared with Group C, AA could significantly alleviate CRF (F:24.63, $p<0.01$), especially for physical and affective fatigue and Group A was more effective for managing physical fatigue than Group B in per-protocol (PP) (-1.75 (-2.69 to -0.82), $p<0.01$)/Intention to Treat analysis (ITT) (-1.41 (-2.39 to -0.41), $p=0.01$) analysis. However, AA had no effect on cognitive fatigue. Compared with Group C, only Group A produced significant improvements in sleep quality in PP analysis (-1.17 (-2.23 to -0.10), $p=0.03$) while it yielded negative results in ITT analysis (-0.82 (-1.74 to 0.10), $p=0.08$). Compared with Group C, AA could significantly reduce anxiety in PP analysis (F:9.35, $p<0.01$) while there was no statistical difference between Group B and Group C (-0.95 (-2.81 to 0.90), $p=0.31$), Group A and Group B (-1.26 (-3.12 to 0.59), $p=0.18$) in ITT analysis. **CONCLUSION:** AA can alleviate CRF of lung cancer patients undergoing chemotherapy, especially for physical and affective fatigue. AA using SV is more effective for physical fatigue while AA using magnetic beads works better for anxiety. However, AA cannot improve the sleep quality.

MISCELLANEOUS WORKS

[NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 1.2020.](#) Ettinger DS1, Wood DE2, Aggarwal C3, et al. *J Natl Compr Canc Netw.* 2019 Dec;17(12):1464-1472. doi: 10.6004/jnccn.2019.0059.

The NCCN Guidelines for Non-Small Cell Lung Cancer (NSCLC) address all aspects of management for NSCLC. These NCCN Guidelines Insights focus on recent updates in immunotherapy. For the 2020 update, all of the systemic therapy regimens have been categorized using a new preference stratification system; certain regimens are now recommended as "preferred interventions," whereas others are categorized as either "other recommended interventions" or "useful under certain circumstances."

[From clinical specimens to human cancer preclinical models-a journey the NCI-cell line database-25 years later.](#) Mulshine JL1, Ujhazy P2, Antman M3, et al. J Cell Biochem. 2019 Dec 5. doi: 10.1002/jcb.29564. [Epub ahead of print]

The intramural the National Cancer Institute (NCI) and more recently the University of Texas Southwestern Medical Center with many different collaborators comprised a complex, multi-disciplinary team that collaborated to generated large, comprehensively annotated, cell-line related research resources which includes associated clinical, and molecular characterization data. This material has been shared in an anonymized fashion to accelerate progress in overcoming lung cancer, the leading cause of cancer death across the world. However, this cell line collection also includes a range of other cancers derived from patient-donated specimens that have been remarkably valuable for other types of cancer and disease research. A comprehensive analysis conducted by the NCI Center for Research Strategy of the 278 cell lines reported in the original Journal of Cellular Biochemistry Supplement, documents that these cell lines and related products have since been used in more than 14 000 grants, and 33 207 published scientific reports. This has resulted in over 1.2 million citations using at least one cell line. Many publications involve the use of more than one cell line, to understand the value of the resource collectively rather than individually; this method has resulted in 2.9 million citations. In addition, these cell lines have been linked to 422 clinical trials and cited by 4700 patents through publications. For lung cancer alone, the cell lines have been used in the research cited in the development of over 70 National Comprehensive Cancer Network clinical guidelines. Finally, it must be underscored again, that patient altruism enabled the availability of this invaluable research resource.

[A way forward for cancer prevention therapy: personalized risk assessment.](#) Zhang Z1, Bien J2, Mori M3,4, Jindal S5, Bergan R1. Oncotarget. 2019 Dec 3;10(64):6898-6912. doi: 10.18632/oncotarget.27365. eCollection 2019 Dec 3.

Cancer is characterized by genetic and molecular aberrations whose number and complexity increase dramatically as cells progress along the spectrum of carcinogenesis. The pharmacologic application of agents in the context of a lower burden of dysregulated cellular processes constitutes an efficient strategy to enhance therapeutic efficacy, and underlies the rationale for using cancer prevention agents in high-risk populations. A longstanding barrier to implementing this strategy is that the risk in the general population is low for any given cancer, many people would have to be treated in order to benefit a few. Therefore, identifying and treating high-risk individuals will improve the risk: benefit ratio. Currently, risk is defined by considering a relatively low number of factors. A strategy that considers multiple factors has the ability to define a much-higher-risk cohort than the general population. This article will review the rationale for evaluating multiple risk factors so as to identify individuals at highest risk. It will use breast and lung cancer as examples, will describe currently available risk assessment tools, and will discuss ongoing efforts to expand the impact of this approach. The high potential of this strategy to provide a way forward for developing cancer prevention therapy will be highlighted.

[E-cigarette flavored pods induce inflammation, epithelial barrier dysfunction, and DNA damage in lung epithelial cells and monocytes.](#) Muthumalage T1, Lamb T1, Friedman MR2, Rahman I3. Sci Rep. 2019 Dec 13;9(1):19035. doi: 10.1038/s41598-019-51643-6.

E-cigarette flavored pods are increasing in use among young adults. Although marketed as a safer alternative to conventional cigarettes, the health effects of e-cigarette flavored pods are unknown. We hypothesized that e-cigarette flavored pods would cause oxidative stress, barrier dysfunction, and an inflammatory response in monocytes and lung epithelial cells. JUUL pod flavors (Fruit Medley, Virginia Tobacco, Cool Mint, Crème Brulee, Cool Cucumber, Mango, and Classic Menthol) and similar pod flavors (Just Mango-Strawberry Coconut and Caffé Latte) were tested. These pod flavors generated significant amounts of acellular ROS and induced significant mitochondrial superoxide production in bronchial epithelial cells (16-HBE). Lung epithelial cells (16-HBE, BEAS-2B) and monocytes (U937) exposed to various pod aerosols resulted in increased inflammatory mediators, such as IL-8 or PGE2. JUUL pod flavors, Crème Brulee and Cool Cucumber, caused epithelial barrier dysfunction in 16-HBE cells. Moreover, tested flavors also showed DNA damage upon exposure in monocytes. We determined the chemical constituents present in various flavors. Our data suggest that these constituents in flavored pods induce oxidative stress, inflammation, epithelial barrier dysfunction, and DNA damage in lung cells. These data provide insights into the regulation of e-cigarette flavored pods, as well as constituents in these flavors.

[Lung Cancer Surveillance After Definitive Curative-Intent Therapy: ASCO Guideline.](#)

Schneider BJ1, Ismaila N2, Aerts J3, et al. *J Clin Oncol.* 2019 Dec 12;JCO1902748. doi: 10.1200/JCO.19.02748. [Epub ahead of print]

PURPOSE: To provide evidence-based recommendations to practicing clinicians on radiographic imaging and biomarker surveillance strategies after definitive curative-intent therapy in patients with stage I-III non-small-cell lung cancer (NSCLC) and SCLC. **METHODS:** ASCO convened an Expert Panel of medical oncology, thoracic surgery, radiation oncology, pulmonary, radiology, primary care, and advocacy experts to conduct a literature search, which included systematic reviews, meta-analyses, randomized controlled trials, and prospective and retrospective comparative observational studies published from 2000 through 2019. Outcomes of interest included survival, disease-free or recurrence-free survival, and quality of life. Expert Panel members used available evidence and informal consensus to develop evidence-based guideline recommendations. **RESULTS:** The literature search identified 14 relevant studies to inform the evidence base for this guideline. **RECOMMENDATIONS:** Patients should undergo surveillance imaging for recurrence every 6 months for 2 years and then annually for detection of new primary lung cancers. Chest computed tomography imaging is the optimal imaging modality for surveillance. Fluorodeoxyglucose positron emission tomography/computed tomography imaging should not be used as a surveillance tool. Surveillance imaging may not be offered to patients who are clinically unsuitable for or unwilling to accept further treatment. Age should not preclude surveillance imaging. Circulating biomarkers should not be used as a surveillance strategy for detection of recurrence. Brain magnetic resonance imaging should not be used for routine surveillance in stage I-III NSCLC but may be used every 3 months for the first year and every 6 months for the second year in patients with stage I-III small-cell lung cancer who have undergone curative-intent treatment.

[Survival, Chemotherapy Treatments, and Health Care Utilization Among Patients with Advanced Small Cell Lung Cancer: An Observational Study.](#)

He J1, Shao C2, Hui SL3, Zhang Z3,4, Baker J3, Dexter PR3, Kachroo S2, Jin F2. *Adv Ther.* 2019 Dec 11. doi: 10.1007/s12325-019-01161-8. [Epub ahead of print]

INTRODUCTION: Most cases of small cell lung cancer (SCLC) are diagnosed at an advanced stage. The objective of this study was to investigate patient characteristics, survival, chemotherapy treatments, and health care use after a diagnosis of advanced SCLC in subjects enrolled in a health system network. **METHODS:** This was a retrospective cohort study of patients aged ≥ 18 years who either were diagnosed with stage III/IV SCLC or who progressed to advanced SCLC during the study period (2005-2015).

Patients identified from the Indiana State Cancer Registry and the Indiana Network for Patient Care were followed from their advanced diagnosis index date until the earliest date of the last visit, death, or the end of the study period. Patient characteristics, survival, chemotherapy regimens, associated health care visits, and durations of treatment were reported. Time-to-event analyses were performed using the Kaplan-Meier method. **RESULTS:** A total of 498 patients with advanced SCLC were identified, of whom 429 were newly diagnosed with advanced disease and 69 progressed to advanced disease during the study period. Median survival from the index diagnosis date was 13.2 months. First-line (1L) chemotherapy was received by 464 (93.2%) patients, most commonly carboplatin/etoposide, received by 213 (45.9%) patients, followed by cisplatin/etoposide (20.7%). Ninety-five (20.5%) patients progressed to second-line (2L) chemotherapy, where topotecan monotherapy (20.0%) was the most common regimen, followed by carboplatin/etoposide (14.7%). Median survival was 10.1 months from 1L initiation and 7.7 months from 2L initiation. **CONCLUSION:** Patients in a regional health system network diagnosed with advanced SCLC were treated with chemotherapy regimens similar to those in earlier reports based on SEER-Medicare data. Survival of patients with advanced SCLC was poor, illustrating the lack of progress over several decades in the treatment of this lethal disease and highlighting the need for improved treatments.

Whole Exome Sequencing of Highly Aggregated Lung Cancer Families Reveals Linked Loci for Increased Cancer Risk on Chromosomes 12q, 7p and 4q.

Musolf AM1, Moiz BA1, Sun H1,3 et al. Cancer Epidemiol Biomarkers Prev. 2019 Dec 11. pii: cebp.0887.2019. doi: 10.1158/1055-9965.EPI-19-0887. [Epub ahead of print]

BACKGROUND: Lung cancer kills more people than any other cancer in the United States. In addition to environmental factors, lung cancer has genetic risk factors as well, though the genetic etiology is still not well understood. We have performed whole exome sequencing on 262 individuals from 28 extended families with a family history of lung cancer. **METHODS:** Parametric genetic linkage analysis was performed on these samples using two distinct analyses - the lung cancer only (LCO) analysis, where only lung cancer patients were coded as affected, and the all aggregated cancers (AAC) analysis, where other cancers seen in the pedigree were coded as affected. **RESULTS:** The AAC analysis yielded a genome-wide significant result at rs61943670 in POLR3B at 12q23.3. POLR3B has been implicated somatically in lung cancer but this germline finding is novel. is a significant eQTL in lung tissue. Interesting genome-wide suggestive haplotypes were also found within individual families, particularly near SSPO at 7p36.1 in one family and a large linked haplotype spanning 4q21.3-28.3 in a different family. The 4q haplotype contains potential causal rare variants in DSPP at 4q22.1 and PTPN13 at 4q21.3. **CONCLUSIONS:** Regions on 12q, 7p, and 4q are linked to increased cancer risk in highly aggregated lung cancer families, 12q across families and 7p and 4q within a single family. POLR3B, SSPO, DSPP, and PTPN13 are currently the best candidate genes. **IMPACT:** Functional work on these genes is planned for future studies and if confirmed would lead to potential biomarkers for risk in cancer.

Racial Disparities in Resection of Early Stage Non-Small Cell Lung Cancer: Variability Among Surgeons.

Ezer N1,2, Mhango G2, Bagiella E3, Goodman E2, Flores R4, Wisnivesky JP2,5. Med Care. 2019 Dec 30. doi: 10.1097/MLR.0000000000001280. [Epub ahead of print]

BACKGROUND: Racial disparities in resection of non-small cell lung cancer (NSCLC) are well documented. Patient-level and system-level factors only partially explain these findings. Although physician-related factors have been suggested as mediators, empirical evidence for their contribution is limited. **OBJECTIVE:** To determine if racial disparities in receipt of thoracic surgery persisted after patients had a surgical consultation and whether there was a physician contribution to disparities in care. **METHODS:** The authors identified 19,624 patients with stage I-II NSCLC above 65 years of age from the Surveillance-Epidemiology and End-Results-Medicare database. They studied black and white patients evaluated by a surgeon within 6 months of diagnosis. They assessed for racial differences in

resection rates among surgeons using hierarchical linear modeling. Our main outcome was receipt of NSCLC resection. A random intercept was included to test for variability in resection rates across surgeons. Interaction between patient race and the random surgeon intercept was used to evaluate for heterogeneity between surgeons in resection rates for black versus white patients. **RESULTS:** After surgical consultation, black patients were less likely to undergo resection (adjusted odds ratio, 0.57; 95% confidence interval, 0.47-0.69). Resection rates varied significantly between surgeons ($P < 0.001$). A significant interaction between the surgeon intercept and race ($P < 0.05$) showed variability beyond chance across surgeons in resection rates of black versus white patients. When the model included thoracic surgery specialization the physician contribution to disparities in care was decreased. **CONCLUSIONS:** Racial disparities in resection of NSCLC exist even among patients who had access to a surgeon. Heterogeneity between surgeons in resection rates between black and white patients suggests a physician's contribution to observed racial disparities. Specialization in thoracic surgery attenuated this contribution.