



## Caring Ambassadors Lung Cancer Program Literature Review, March 2019

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### **BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES**

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[The PI3K inhibitor buparlisib suppresses osteoclast formation and tumour cell growth in bone metastasis of lung cancer, as evidenced by multimodality molecular imaging.](#) Wang S1, Niu X2, Bao X3, et al. *Oncol Rep.* 2019 May;41(5):2636-2646. doi: 10.3892/or.2019.7080. Epub 2019 Mar 20.

Non-small cell lung cancer (NSCLC) metastasis commonly occurs in bone, which often results in pathological fractures. Sustained phosphoinositide-3-kinase (PI3K) signalling promotes the growth of PI3K-dependent NSCLC and elevates osteoclastogenic potential. The present study investigated the effects of a PI3K inhibitor on NSCLC growth in bone and osteoclast formation, and aimed to determine whether it could control symptoms associated with bone metastasis. A bone metastasis xenograft model was established by implanting NCI-H460-luc2 lung cancer cells, which contain a phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit  $\alpha$  mutation, into the right tibiae of mice. After 1 week, the tumours were challenged with a PI3K inhibitor (buparlisib) or blank control for 3 weeks. Tumour growth and burden were longitudinally assessed in vivo via reporter gene bioluminescence imaging (BLI), small animal positron emission tomography/computed tomography (CT) [18F-fluorodeoxyglucose (18F-FDG)] and single-photon emission computed tomography/CT [99mTc-methylene diphosphonate (99mTc-MDP)] imaging. Tibia sections of intraosseous NCI-H460 tumours were analysed by immunohistochemistry (IHC), western blotting and flow cytometry. Dynamic weight bearing (DWB) tests were further performed to examine the improvement of symptoms associated with bone metastasis during the entire study. Administration of buparlisib significantly inhibited the progression of bone metastasis of NSCLC, as evidenced by significantly reduced uptake of 18F-FDG, 99mTc-MDP and BLI signals in the treated lesions. In addition, buparlisib appeared to inhibit the expression of tartrate-resistant acid phosphatase and receptor activator of nuclear factor- $\kappa$ B ligand, as determined by IHC. Buparlisib also resulted in increased cell apoptosis, as determined by a higher percentage of Annexin V staining and increased caspase 3 expression. Furthermore, buparlisib significantly increased weight-bearing capacity, as revealed by DWB tests. The PI3K inhibitor, buparlisib, suppressed osteoclast formation in vivo, and exhibited antitumour activity, thus leading to increased weight-bearing ability in mice with bone metastasis of lung cancer. Therefore, targeting the PI3K pathway may be a potential therapeutic strategy that prevents the structural skeletal damage associated with bone metastasis of lung cancer.

### [MicroRNA-148b regulates tumor growth of non-small cell lung cancer through targeting](#)

[MAPK/JNK pathway](#). Lu L1,2, Liu Q1,2, Wang P1,2, et al. BMC Cancer. 2019 Mar 8;19(1):209. doi: 10.1186/s12885-019-5400-3.

**BACKGROUND:** MicroRNA-148b (miR-148b) has been detected in various types of tumors, and is generally viewed as a tumor suppressor. Our previous study found the decreased expression of miR-148b in human non small cell lung cancer (NSCLC) specimens and cell lines. However, the underlying mechanisms of miR-148b in regulating tumor progression remain unclear. **METHODS:** Firstly animal experiments were performed to verify whether miR-148b could inhibit the tumor growth. Then, the underlying mechanisms were studied by transfecting recombinant plasmids containing a miR-148b mimic or a negative control (NC) mimic (shRNA control) into NSCLC cell lines PC14/B and A549 cells. Tumor cells transfected with unpackaged lentiviral vectors was used as blank control. Cell proliferation capabilities were measured by using CCK-8 kit and colony formation assay. Cell cycle arrest was compared to clarify the mechanism underlying the tumor cell proliferation. Annexin V-FITC Apoptosis Detection kit was applied to investigate the effect of miR-148b on cell apoptosis. Furthermore, western blot analysis were performed to study the targeting pathway. **RESULTS:** We found that over-expression of miR148b could significantly inhibit tumor growth, while knocking down miR148b could obviously promote tumor growth. Further experiment showed that miR-148b inhibited tumor cell proliferation. Besides, over-expression of miR148b decreased the G2/M phase population of the cell cycle by preventing NSCLC cells from entering the mitotic phase and enhanced tumor cell apoptosis. Further western blot analysis indicated that miR148b could inhibit mitogen-activated protein kinase/Jun N-terminal kinase (MAPK/JNK) signaling by decreasing the expression of phosphorylated (p) JNK. **CONCLUSIONS:** These results demonstrate that miR-148b could inhibit the tumor growth and act as tumor suppressor by inhibiting the proliferation and inducing apoptosis of NSCLC cells by blocking the MAPK/JNK pathway.

### [Dysregulated Redox Regulation Contributes to Nuclear EGFR Localization and Pathogenicity in Lung Cancer](#). Little AC1,2, Hristova M1, van Lith L1, et al. Sci Rep. 2019 Mar 19;9(1):4844. doi: 10.1038/s41598-019-41395-8.

Lung cancers are frequently characterized by inappropriate activation of epidermal growth factor receptor (EGFR)-dependent signaling and epigenetic silencing of the NADPH oxidase (NOX) enzyme DUOX1, both potentially contributing to worse prognosis. Based on previous findings linking DUOX1 with redox-dependent EGFR activation, the present studies were designed to evaluate whether DUOX1 silencing in lung cancers may be responsible for altered EGFR regulation. In contrast to normal epithelial cells, EGF stimulation of lung cancer cell lines that lack DUOX1 promotes EGF-induced EGFR internalization and nuclear localization, associated with induction of EGFR-regulated genes and related tumorigenic outcomes. Each of these outcomes could be reversed by overexpression of DUOX1 or enhanced by shRNA-dependent DUOX1 silencing. EGF-induced nuclear EGFR localization in DUOX1-deficient lung cancer cells was associated with altered dynamics of cysteine oxidation of EGFR, and an overall reduction of EGFR cysteines. These various outcomes could also be attenuated by silencing of glutathione S-transferase P1 (GSTP1), a mediator of metabolic alterations and drug resistance in various cancers, and a regulator of cysteine oxidation. Collectively, our findings indicate DUOX1 deficiency in lung cancers promotes dysregulated EGFR signaling and enhanced GSTP1-mediated turnover of EGFR cysteine oxidation, which result in enhanced nuclear EGFR localization and tumorigenic properties.

**[Is Calcification in the Regional Lymph Nodes a Benign Feature in Patients with Lung Cancer?](#)**

Nakanishi K1, Nakagawa K2, Asakura K1, Yoshida Y1, Watanabe H3, Watanabe S11. World J Surg. 2019 Mar 7. doi: 10.1007/s00268-019-04937-9. [Epub ahead of print]

**BACKGROUND:** Calcified lymph nodes (LNs) on computed tomography (CT) in patients with lung cancer are generally considered to be a benign feature. However, few studies have evaluated the pathological status of such calcified LNs. We investigated the clinicopathological findings of patients with calcified LNs on preoperative CT who underwent operation for lung cancer and assessed the frequency of metastasis to calcified LNs as well as the risk factors associated with such metastases.

**METHODS:** This was a retrospective study of 72 consecutive patients with calcified LNs detected on preoperative CT who underwent pulmonary resection for primary lung cancer between 2011 and 2013. A total of 354 LN stations including 101 LN stations with calcified LNs were evaluated. **RESULTS:** The frequency of metastasis to calcified LNs was 19.4% (14 of 72 patients) on a per-person basis and 18.8% (19 of 101 stations) on a per-nodal station basis. When the size of calcification was major (>5 mm), the frequency of metastasis to such calcified LNs was significantly lower than when it was minor ( $\leq 5$  mm) on a per-nodal station basis (11.1% vs 27.7%,  $P = 0.043$ ). Furthermore, when the size of calcification was major and the status of LN stations with calcified LNs was single, there was no metastasis to such LN stations (0 of 26 stations). **CONCLUSIONS:** The frequency of metastasis to calcified LNs was about 20% on both a per-person and a per-nodal station basis. Although calcified LNs as well as non-calcified LNs should be dissected during operation, dissection of a single LN station with calcification, particularly major calcification, can be omitted.

**[Liquid Biopsy Assay for Lung Carcinoma Using Centrifuged Supernatants from Fine Needle Aspiration Specimens.](#)**

Hannigan B1, Ye W1, Mehrotra M2, et al. Ann Oncol. 2019 Mar 18. pii: mdz102. doi: 10.1093/annonc/mdz102. [Epub ahead of print]

**INTRODUCTION:** Tumor mutation profiling is standard-of-care in lung carcinoma patients. However, comprehensive molecular profiling of small specimens, including core needle biopsy (CNB) and fine needle aspiration (FNA) specimens, may often be inadequate due to limited tissue. Centrifuged FNA supernatants, which are typically discarded, have emerged recently as a novel liquid-based biopsy for molecular testing. In this study, we evaluate the use of lung carcinoma FNA supernatants for detecting clinically relevant mutations. **METHODS:** Supernatants from lung carcinoma FNA samples ( $n = 150$ ) were evaluated. Samples were further analyzed using next-generation sequencing (NGS) and ultrasensitive droplet digital PCR (ddPCR). Mutation profiles in a subset of samples were compared to results derived from paired tissue samples from the same patient ( $n = 67$ ) and available plasma liquid biopsy assay ( $n = 45$ ). **RESULTS:** All 150 samples yielded adequate DNA and NGS was performed successfully on 104 (90%) of 116 selected samples. Somatic mutations were detected in 82% of the samples and in 50% of these patients a clinically relevant mutation was identified that would qualify them for targeted therapy or a clinical trial. There was high overall concordance between the mutation profiles of supernatants and the corresponding tissue samples, with 100% concordance with concurrent FNA and 96% with concurrent CNB samples. Comparison of actionable driver mutations detected in supernatant versus plasma samples showed 84% concordance. **CONCLUSIONS:** FNA supernatants can provide a valuable specimen source for genotyping lung carcinoma especially in patients with insufficient tumor tissue, thereby reducing multigene mutation profiling failure rates, improving turnaround times, and avoiding repeat biopsies.

### [Liquid Biopsies in Lung Cancer: Four Emerging Technologies and Potential Clinical Applications.](#)

Chudasama D1,2, Katopodis P3,4, Stone N5, et al. *Cancers (Basel)*. 2019 Mar 7;11(3). pii: E331. doi: 10.3390/cancers11030331.

**BACKGROUND:** Liquid biopsies offer a promising alternative to tissue samples, providing non-invasive diagnostic approaches or serial monitoring of disease evolution. However, certain challenges remain, and the full potential of liquid biopsies has yet to be reached. Here we report several methodological approaches to interrogate liquid biopsies using circulating tumour cell (CTC) enumeration and characterisation, transcriptomics, Raman spectroscopy, and copy number instability (CNI) scores using blood samples of lung cancer (LC) patients. **METHODS:** We choose LC; since it still is the most common cause of cancer-related mortality worldwide, and therefore there is a need for development of new non-invasive diagnostic/prognostic technologies. Changes in gene expression were assessed using RNA-seq, and in CTCs using ImageStream, an imaging flow-cytometer. CNI scores, from paired tissue/ctDNA were also explored. Raman spectroscopy was used to provide chemical fingerprints of plasma samples. **RESULTS:** CTCs were detected in all LC patients (n = 10). We observed a significant increase in CTC levels in LC patients (n = 10) compared to controls (n = 21). A similar CNI was noted in the tissue and plasma of 2 patients, where higher CNI scores corresponded with poorer outcome. Significant changes in Raman spectra (carotenoid concentrations) were noted in LC patients (n = 20) compared to controls (n = 10). RNA-seq revealed differential expression of 21 genes between LC cases and controls in both LC tissue and blood samples. **CONCLUSIONS:** Liquid biopsies can potentially provide a more comprehensive picture of the disease compared to a single tissue biopsy. CTC enumeration is feasible and sensitive for LC patients. Molecular profiling of CTCs is also possible from total blood. CNI scores and Raman spectra require further investigation. Further work is being undertaken to explore these methods of detection in a larger LC cohort.

### [Next-Generation Sequencing for Genotyping of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration Samples in Lung Cancer.](#)

Xie F1, Zheng X2, Mao X1, Zhao R3, Ye J4, Zhang Y1, Sun J5. *Ann Thorac Surg*. 2019 Mar 15. pii: S0003-4975(19)30347-9. doi: 10.1016/j.athoracsur.2019.02.010. [Epub ahead of print]

**BACKGROUND:** Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) can obtain a small amount of specimen. This study aims to evaluate the feasibility and robustness of using EBUS-TBNA samples to perform capture-based targeted next-generation sequencing (NGS).

**METHODS:** Tissue samples from patients with advanced non-small cell lung cancer (NSCLC) were collected via EBUS-TBNA and formalin-fixed paraffin-embedded. Three representative genes, EGFR, ALK and ROS1, were examined by amplification refractory mutation system polymerase chain reaction (ARMS-PCR), immunohistochemistry and quantitative reverse transcription PCR (RT-qPCR). The remaining samples were processed with NGS assay with a 56 gene panel. Classic driver mutations detected by NGS were verified by conventional methods. **RESULTS:** Of the 85 patients diagnosed with advanced NSCLC, 77 successfully performed all assays. Forty-one mutations in EGFR, ALK and ROS1 were detected in both conventional methods and NGS, representing a 100% concordance. In the contrast, four EGFR mutations detected by NGS were not covered in the targeted regions of ARMS-PCR, leading to a negative call in these patients. Altogether, NGS detected 12 additional variants including 6 KRAS mutations, 1 BRAF mutation, 1 RET fusion, 1 MET amplification concurrent with EGFR L858R, 1 KRAS amplification together with EGFR 19del and 1 ERBB2 amplification. The mean number of needle passes per lymph node was 5.2 in samples successfully applied all assays. **CONCLUSIONS:** NGS assay can be successfully conducted with limited tissue samples obtained from EBUS-TBNA. Compared to conventional methods, NGS assay provides more comprehensive information on genetic alterations in tumor, which greatly assists therapeutic decision-making for advanced lung cancer.



### **Liquid biopsy in newly diagnosed patients with locoregional (I-IIIa) non-small cell lung cancer.**

Chen K1, Kang G1, Zhao H1, Zhang K1, Zhang J1, Yang F1, Wang J1. *Expert Rev Mol Diagn.* 2019 Mar 24;1-9. doi: 10.1080/14737159.2019.1599717. [Epub ahead of print]

Liquid biopsy is a promising method for the management of lung cancer, but previous studies focused mainly on patients with advanced-stage disease. As the methodology has progressed for the detection of circulating tumor DNA (ctDNA) and its aberrant methylation, researchers are gradually investigating the utility of liquid biopsy in early-stage patients. As a result, liquid biopsy has shown its potential for the application in patients with early- and locally advanced-stage non-small cell lung cancer (NSCLC). Areas covered: This review summarizes the utility of liquid biopsy in NSCLC and provide an outlook for future development. We focus on the role of ctDNA and its aberrant methylation in patients with stage IA to stage IIIA NSCLC, in the field of early detection and screening, perioperative management, and postoperative surveillance. Expert opinion: Liquid biopsy has shown the potential for clinical application of early-stage patients but has not been routinely applied yet. The utilization of liquid biopsy will be promoted by improved detection methods and data from well-designed clinical trials. With the development of precision medicine, liquid biopsy will likely play an increasingly important clinical role.

### **Utilization of Archived Plasma to Detect Epidermal Growth Factor Receptor Mutation in Non-Small Cell Lung Cancer Patients.**

Oh AC1, Lee JK1,2, Kim JY2, Jin HO2, Jung JW1, Chang YH1, Hong YJ1. *Biopreserv Biobank.* 2019 Mar 19. doi: 10.1089/bio.2018.0126. [Epub ahead of print]

Precision medicine has received increased attention as an effective approach for the treatment of cancer patients. Because of challenges associated with the availability of archived tissue, liquid biopsies are often performed to detect cancer-specific mutations. One of the major advantages of the liquid biopsy is that the treatment can be monitored longitudinally, even after the tumor tissue is no longer available. In a clinical setting, one component of precision medicine is the detection of cancer-specific mutations using archived samples. In this study, we evaluated the epidermal growth factor receptor (EGFR) mutation status of samples of lung cancer patients stored before introduction of the plasma EGFR test at our institution. The aim of this study was to validate the utility of archived plasma samples for detection of the EGFR mutation in nonsmall cell lung cancer (NSCLC) patients. The Cobas® EGFR Mutation Test v2 was the first liquid biopsy test approved as a companion diagnostic test for patients with NSCLC treated with tyrosine kinase inhibitors. We tested for the EGFR mutation in 116 plasma samples archived in the biobank, and the results were compared with those obtained in the tissue or cytology EGFR mutation test. The EGFR mutation-positive rate from archived plasma was lower than that determined from tissue or cytology at 19.0% and 53.4%, respectively, and the concordance rate between the two tests was 58.6%. Of interest, five (4.3%) samples showed the T790M mutation in the plasma test, whereas this mutation was only detected in two (1.7%) tissue/cytology samples. Five (4.3%) samples were additionally positive in the plasma test. Overall, these results indicate that archived plasma samples can serve as an alternative source for the plasma EGFR mutation test when tissue samples are not available, and can improve precision medicine and long-term follow-up in a noninvasive manner.

### **The value of 18F-FDG PET/CT in the diagnosis of different size of solitary pulmonary nodules.**

Tang K1,2, Wang L3, Lin J2, Zheng X2, Wu Y1. *Medicine (Baltimore).* 2019 Mar;98(11):e14813. doi: 10.1097/MD.00000000000014813.

This study aimed to evaluate the diagnostic value of F-fluorodeoxyglucose (F-FDG) positron emission tomography/computed tomography (PET/CT) for solitary pulmonary nodules (SPNs) with different diameters. One hundred eighty two consecutive patients with SPN who underwent F-FDG PET/CT examination were retrospectively studied. Patients were categorized into 3 groups according to the diameter of nodules: Group A with the diameter of greater than or equal to 6mm and less than or equal to

10mm; Group B with diameter greater than 10mm and less than or equal to 20 mm; Group C with diameter greater than 20mm and less than or equal to 30mm. The efficiency of PET/CT, PET and CT in the diagnosis of benign and malignant SPNs and different subgroup of SPNs was calculated. Receiver operating characteristic curves (ROCs) were drawn and area under the curves (AUCs) were compared between different groups. The age, diameter, mean standardized uptake value (SUV<sub>mean</sub>) and maximum standardized uptake value (SUV<sub>max</sub>) of benign and malignant nodules were significantly different ( $P < .05$ ). For overall SPNs, the sensitivity, specificity, accuracy, PPV, and NPV of PET/CT were 98.35%, 77.05%, 91.21%, 89.47%, and 95.92%, respectively. The AUC of PET/CT was significantly larger than that of SUV<sub>mean</sub>, SUV<sub>max</sub>, and CT ( $P < .05$ ). For different size of SPNs, the AUC of PET/CT in group A was higher than that in group B and group C, but there was no significant difference with CT ( $P > .05$ ). In group B, the accuracy of PET/CT in the diagnosis of SPN was significantly higher than that of CT ( $P < .05$ ). F-FDG PET/CT demonstrated excellent performance in identifying different size of SPNs, especially for those with diameter between 11 and 20mm, the diagnostic value of F-FDG PET/CT is significantly higher than other methods.

[Barriers to Lung Cancer Screening With Low-Dose Computed Tomography.](#) Lei F1, Lee E1. *Oncol Nurs Forum.* 2019 Mar 1;46(2):E60-E71. doi: 10.1188/19.ONF.E60-E71.

**PROBLEM IDENTIFICATION:** Despite lung cancer screening guidelines and insurance coverage changes, rates of lung cancer screening with low-dose computed tomography remain suboptimal among the eligible population in the United States. **LITERATURE SEARCH:** Electronic literature databases, including PubMed, CINAHL®, PsycINFO, and Google Scholar, were searched. **DATA EVALUATION:** After applying filter information and inclusion and exclusion criteria, 10 articles were reviewed. Methodological rigor was evaluated. **SYNTHESIS:** Based on the social-ecological approach, barriers to lung cancer screening at the individual level, including sociodemographic characteristics, financial cost, lack of knowledge, inaccurate beliefs about lung cancer screening, distrust of the medical system, stigma around smoking and lung cancer, negative attitudes about outcomes of lung cancer screening, and inconvenience of receiving lung cancer screening, were identified. Barriers at the health-system level included lack of information from primary care providers. **IMPLICATIONS FOR PRACTICE:** Overcoming barriers to lung cancer screening at individual and health-system levels is essential to increase lung cancer screening uptake rates.

[Early detection of lung cancer in a population at high risk due to occupation and smoking.](#)

Welch LS1, Dement JM2, Cranford K3, Shorter J3, Quinn PS1, Madtes DK4,5, Ringen K1. *Occup Environ Med.* 2019 Mar;76(3):137-142. doi: 10.1136/oemed-2018-105431. Epub 2018 Nov 10.

**OBJECTIVE:** The US National Comprehensive Cancer Network (NCCN) recommends two pathways for eligibility for Early Lung Cancer Detection (ELCD) programmes. Option 2 includes individuals with occupational exposures to lung carcinogens, in combination with a lesser requirement on smoking. Our objective was to determine if this algorithm resulted in a similar prevalence of lung cancer as has been found using smoking risk alone, and if so to present an approach for lung cancer screening in high-risk worker populations. **METHODS:** We enrolled 1260 former workers meeting NCCN criteria, with modifications to account for occupational exposures in an ELCD programme. **RESULTS:** At baseline, 1.6% had a lung cancer diagnosed, a rate similar to the National Lung Cancer Screening Trial (NLST). Among NLST participants, 59% were current smokers at the time of baseline scan or had quit smoking fewer than 15 years prior to baseline; all had a minimum of 30 pack-years of smoking. Among our population, only 24.5% were current smokers and 40.1% of our participants had smoked fewer than 30 pack-years; only 43.5% would meet entry criteria for the NLST. The most likely explanation for the high prevalence of screen-detected lung cancers in the face of a reduced risk from smoking is the addition of occupational risk factors for lung cancer. **CONCLUSION:** Occupational exposures to lung carcinogens

should be incorporated into criteria used for ELCD programmes, using the algorithm developed by NCCN or with an individualised risk assessment; current risk assessment tools can be modified to incorporate occupational risk.

**Occurrence of Discussion about Lung Cancer Screening Between Patients and Healthcare Providers in the USA, 2017.** Soneji S1, Yang J2, Tanner NT3,4, Silvestri GA3. J Cancer Educ. 2019 Mar 9. doi: 10.1007/s13187-019-01510-9. [Epub ahead of print]

Computed tomography lung cancer screening reduces lung cancer mortality. However, screening is underutilized. This study assesses the extent to which providers discuss lung cancer screening with their patients, as a lack of discussion and counseling may serve as a potential cause of low utilization rates. Data from 1667 adults aged 55-80 years sampled in the 2017 Health Information National Trends Survey was utilized. A weighted multivariable logistic regression model was fit with past-year discussion about lung cancer screening with a provider as the outcome. The adjusted odds of discussion were higher for current cigarette smokers compared to non-cigarette smokers (adjusted odds ratio = 3.91; 95% confidence interval [CI], 1.75 to 8.74). Despite higher odds, the absolute prevalence was low with only 18% (95% CI, 11.8 to 24.2%) of current adult smokers reporting a past-year discussion. Knowledge of screening from trusted sources of medical information, such as doctors, can increase screening rates and may ultimately reduce lung cancer mortality.

**Lung Cancer Screening and Epigenetics in African Americans: The Role of the Socioecological Framework.** Watson KS1, Hulbert A1,2, Henderson V1, Chukwudozie IB1, Aponte-Soto L1, Lerner L1, Martinez E1, Kim S3, Winn RA1,2,4. Front Oncol. 2019 Mar 12;9:87. doi: 10.3389/fonc.2019.00087. eCollection 2019.

Lung cancer is the leading cause of cancer morbidity and mortality in the U.S. and racial/ethnic minorities carry the greatest burden of lung cancer disparities with African Americans (AAs) impacted disproportionately. Inequities in lung cancer health disparities are often associated with multiple bio-behavioral and socio-cultural factors among racial/ethnic minorities. Epigenetic research has advanced the understanding of the intersectionality between biological and socio-cultural factors in lung cancer disparities among AAs. However, gaps exist in the engagement of diverse populations in epigenetic lung cancer research, which poses a challenge in ensuring the generalizability and implementation of epigenetic research in populations that carry an unequal cancer burden. Grounding epigenetic lung cancer research within a socio-ecological framework may prove promising in implementing a multi-level approach to community engagement, screening, navigation, and research participation among AAs. The University of Illinois Cancer Center (UI Cancer Center) is employing an evidence-based (EB) model of community/patient engagement utilizing the socio-ecological model (SEM) to develop a culturally sensitive epigenetic lung cancer research program that addresses multiple factors that impact lung cancer outcomes in AAs. By implementing epigenetic research within a group of Federally Qualified Health Centers (FQHCs) guided by the SEM, the UI Cancer Center is proposing a new pathway in mitigating lung cancer disparities in underserved communities. At the individual level, the framework examines tobacco use among patients at FQHCs (the organizational level) and also tailors epigenetic research to explore innovative biomarkers in high risk populations. Interpersonal interventions use Patient Navigators to support navigation to EB tobacco cessation resources and lung cancer screening. Community level support within the SEM is developed by ongoing partnerships with local and national partners such as the American Lung Association (ALA) and the American Cancer Society (ACS). Lastly, at the policy level, the UI Cancer Center acknowledges the role of policy implications in lung cancer screening and advocates for policies and screening recommendations that examine the current guidelines from the United States Preventive Services Task Force (USPTF).

[Racial disparities in eligibility for low-dose computed tomography lung cancer screening among older adults with a history of smoking.](#) Li CC1, Matthews AK2, Rywant MM3, Hallgren E4, Shah RC5. *Cancer Causes Control.* 2019 Mar;30(3):235-240. doi: 10.1007/s10552-018-1092-2. Epub 2018 Oct 30.

**PURPOSE:** Lung cancer early detection screening has been demonstrated to decrease lung cancer mortality among high-risk smokers. This study aimed to examine whether current screening guidelines may disproportionately exclude African American smokers who are at higher overall risk for lung cancer.

**METHODS:** Data from the 2014 Health and Retirement Study were analyzed. Older African Americans and Whites with a history of smoking were included in the analyses (n = 7,348). Eligibility criteria established by the U.S. Preventive Services Task Force (USPSTF) for LDCT lung cancer screening were used. Multivariate logistic regression analyses were conducted to examine racial differences in eligibility for LDCT lung cancer screening. **RESULTS:** Overall, 21.1% of current and 10.5% of former smokers met USPSTF's eligibility criteria for LDCT screening. In multivariate logistic regression analyses, African American smokers were less likely to be eligible for LDCT lung cancer screening compared to Whites (odds ratio = 0.5; p < 0.001). **CONCLUSION:** African American smokers were less likely to meet established lung cancer screening eligibility criteria compared to Whites. Current lung cancer screening criteria may not adequately capture African Americans at risk and may widen the health disparities in African Americans. Further longitudinal studies are needed to evaluate the efficacy of current lung cancer screening guideline.

## CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

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### NSCLC - SURGERY

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[Role of preoperative blood markers as prognostic factors for lung cancer surgery.](#) Hamid UI1, Al-Saudi R1, Paul I1, Graham A1. *Asian Cardiovasc Thorac Ann.* 2019 May;27(4):288-293. doi: 10.1177/0218492319834812. Epub 2019 Mar 4.

**OBJECTIVE:** This study was undertaken to assess the potential value of preoperative blood components as prognostic markers of outcome after lung cancer resection, and hence their potential to aid in the selection of patients for curative surgery. **METHODS:** This was a single-center study on 313 patients who underwent surgery for non-small-cell lung cancer from 2006 to 2008. Data were analyzed retrospectively from a prospectively maintained thoracic database. Preoperative blood results including plasma fibrinogen levels, serum C-reactive protein, hemoglobin concentration, and platelet count were included in the analysis. **RESULTS:** The mean age was 75 years, and 40% of the patients were females. The most common resection was lobectomy in 68% of patients, followed by pneumonectomy, wedge resection, and segmentectomy in 18%, 10%, and 1.6%, respectively. Patients with abnormal C-reactive protein, fibrinogen, and hemoglobin levels had a worse overall survival. Large tumor size and nodal metastasis on clinical staging was also associated with poor survival. However, on Cox regression analysis, plasma fibrinogen and nodal metastasis were the only independent predictors of survival after lung resection. **CONCLUSIONS:** Among the different blood markers, elevated preoperative plasma fibrinogen was an independent marker of reduced survival in patients with resected non-small-cell lung cancer, and its value in selecting patients who may benefit from surgery needs further investigation.

[A National Analysis of Short-term Outcomes and Long-term Survival Following Thoracoscopic Versus Open Lobectomy for Clinical Stage II Non-Small-Cell Lung Cancer.](#) Yang CJ1, Kumar A2, Deng JZ1, Raman V2, Lui NS1, D'Amico TA2, Berry MF1,3. *Ann Surg.* 2019 Mar 26. doi: 10.1097/SLA.0000000000003231. [Epub ahead of print]



**MINI:** In this national analysis, thoracoscopic lobectomy was associated with shorter hospital stay and no significant difference in long-term survival when compared to open lobectomy for cT1-2N1M0 non-small-cell lung cancer (NSCLC). These results suggest that thoracoscopic techniques are feasible in the treatment of stage II (cN1) NSCLC. **OBJECTIVE:** To compare outcomes after open versus thoracoscopic (VATS) lobectomy for clinical stage II (cN1) non-small-cell lung cancer (NSCLC). **BACKGROUND:** There have been no published studies evaluating the impact of a VATS approach to lobectomy for N1 NSCLC on short-term outcomes and survival. **METHODS:** Outcomes of patients with clinical T1-2, N1, M0 NSCLC who underwent lobectomy without induction therapy in the National Cancer Data Base (2010-2012) were evaluated using multivariable Cox proportional hazards modeling and propensity score-matched analysis. **RESULTS:** Median follow-up of 1559 lobectomies (1204 open and 355 VATS) was 43.2 months. The VATS approach was associated with a shorter median hospitalization (5 vs 6 d,  $P < 0.001$ ) than the open approach. There were no significant differences between the VATS and open approach with regard to nodal upstaging (12.0% vs 10.5%,  $P = 0.41$ ), 30-day mortality (2.3% vs 3.1%,  $P = 0.31$ ), and overall survival (5-yr survival: 48.6% vs 48.7%,  $P = 0.76$ ; multivariable-adjusted HR for VATS approach: 1.08, 95% CI: 0.90-1.30,  $P = 0.39$ ). A propensity score-matched analysis of 334 open and 334 VATS patients who were well matched by 14 common prognostic covariates, including tumor size, and comorbidities, continued to show no significant differences in nodal upstaging, 30-day mortality, and 5-year survival between the VATS and open groups. **CONCLUSION:** In this national analysis, VATS lobectomy was used in the minority of N1 NSCLC cases but was associated with shorter hospitalization and similar nodal upstaging rates, 30-day mortality, and long-term survival when compared to open lobectomy. These findings suggest thoracoscopic techniques are feasible for the treatment of stage II (cN1) NSCLC.

[\*\*Uptake of Video-Assisted Thoracoscopic Lung Resections Within the Veterans Affairs for Known or Suspected Lung Cancer.\*\*](#) Maiga AW1,2, Deppen SA1,2, Denton J1,2, Matheny ME1,2, Gillaspie EA2, Nesbitt JC1,2, Grogan EL1,2. JAMA Surg. 2019 Mar 13. doi: 10.1001/jamasurg.2019.0035. [Epub ahead of print]

**IMPORTANCE:** Minimally invasive lobectomy for early-stage lung cancer has become more prevalent. Video-assisted thoracoscopic surgery has lower rates of morbidity, better long-term survival, and equivalent oncologic outcomes compared with thoracotomy. However, little has been published on the use and outcomes of video-assisted thoracoscopic surgery within Veterans Affairs. There is a public assumption that the Veterans Affairs is slow to adopt new procedures and technologies. **OBJECTIVE:** To determine the uptake of video-assisted thoracoscopic surgery within the Veterans Affairs for patients with known or suspected lung cancer. **DESIGN, SETTING, AND PARTICIPANTS:** In this retrospective cohort study of national Veterans Affairs Corporate Data Warehouse data from January 2002 to December 2015, a total of 11 004 veterans underwent lung resection for known or suspected lung cancer. Data were analyzed from March to November 2018. **EXPOSURES:** Open or video-assisted thoracoscopic lobectomy or wedge resection. **MAIN OUTCOMES AND MEASURES:** Patient demographic characteristics and procedure and diagnosis International Classification of Diseases, Ninth Revision codes were abstracted from Corporate Data Warehouse data. **RESULTS:** Of the 11 004 included veterans, 10 587 (96.2%) were male, and the median (interquartile range) age was 66.0 (61.0-72.0) years. Of 11 004 included procedures, 8526 (77.5%) were lobectomies and 2478 (22.5%) were wedge resections. The proportion of video-assisted thoracoscopic lung resections increased steadily from 15.6% in 2002 to 50.6% in 2015. Video-assisted thoracoscopic surgery use by Veterans Integrated Service Networks ranged from 0% to 81.7%, and higher Veterans Integrated Service Network volume was correlated with higher video-assisted thoracoscopic surgery use (Pearson  $r = 0.35$ ; 95% CI, 0.15-0.52;  $P < .001$ ). Video-assisted thoracoscopic surgery use and rate of uptake varied widely across Veteran Affairs regions ( $P < .001$  by Wilcoxon signed rank test). **CONCLUSIONS AND RELEVANCE:**

Paralleling academic hospitals, most lung resections are now performed in the Veterans Affairs using video-assisted thoracoscopic surgery. More research is needed to identify reasons behind the heterogeneous uptake of video-assisted thoracoscopic surgery across Veterans Affairs regions.

[Choice of surgical procedure - lobectomy, segmentectomy, or wedge resection - for patients with stage T1-2N0M0 small cell lung cancer: A population-based study.](#) Liu Y1, Shan L2, Shen J3, et al/ Thorac Cancer. 2019 Apr;10(4):593-600. doi: 10.1111/1759-7714.12943. Epub 2019 Mar 10.

**BACKGROUND:** To date, few studies have evaluated the impact of lobectomy versus sublobar resection for early small cell lung cancer (SCLC). We investigated the survival rates of patients with pathological stage T1-2N0M0 SCLC who underwent lobectomy or sublobar resection. **METHODS:** We identified 548 SCLC patients in the Surveillance, Epidemiology, and End Results database who underwent lobectomy or sublobar resection. Propensity score matching (PSM) and Cox regression analysis were used to adjust for baseline characteristics. **RESULTS:** The three-year overall survival (OS) of patients treated with lobectomy (n = 376, 60%) was significantly higher than those treated with sublobar resection (n = 172, 38%). PSM and Cox multivariable analysis further confirmed this result (hazard ratio [HR] 0.543, 95% confidence interval [CI] 0.421-0.680; P < 0.001). The three-year OS of patients treated with segmentectomy (n = 24, 54%) and wedge resection (n = 148, 36%) was not significantly different (HR 0.639, 95% CI 0.393-1.039; P = 0.071). Based on PSM analysis, segmentectomy conferred a superior survival advantage to patients relative to wedge resection (HR 0.466, 95% CI 0.221-0.979; P = 0.040). **CONCLUSION:** Lobectomy correlated with superior survival. For patients in which lobectomy is unsuitable, prognosis following segmentectomy appears to be better than after wedge resection.

[EGFR mutations are significantly associated with visceral pleural invasion development in non-small-cell lung cancer patients.](#) Shi J1, Yang Y1, Zhao Y1, Zhu J1, Song X1, Jiang G1. Cancer Manag Res. 2019 Mar 1;11:1945-1957. doi: 10.2147/CMAR.S195747. eCollection 2019.

**OBJECTIVES:** A retrospective study was performed to investigate the association between EGFR mutations and visceral pleural invasion (VPI), and evaluate the prognostic value of EGFR in resected non-small-cell lung cancer (NSCLC) patients with VPI. **MATERIALS AND METHODS:** Clinico-pathological characteristics and follow-up information were collected from 508 consecutive patients with surgically resected stage I-III NSCLC, and EGFR mutations were detected based on real-time PCR technology. Significant results (P<0.05) from univariate logistic regression analysis were involved as covariates to adjust confounding factors in the analysis of independent factors. **RESULTS:** VPI and EGFR mutations were detected in 229 (45.1%) and 243 (47.8%) cases in NSCLC, respectively. There was a significant association between EGFR mutations and VPI development. Both 19-del (adjusted OR =2.13, 95% CI =1.13-3.99, P=0.019) and L858R (adjusted OR =2.89, 95% CI =1.59-5.29, P=0.001) could significantly increase the risk of VPI development compared with EGFR wild-type. Higher frequency of L858R (adjusted OR =2.63, 95% CI =1.42-4.88, P=0.002) was detected in VPI patients compared with non-VPI patients. 19-del (adjusted HR =0.31, 95% CI =0.12-0.80, P=0.015) was an independent prognostic factor for a better disease-free survival (DFS) in non-VPI patients. No significant association was shown between EGFR mutations and DFS in VPI patients. **CONCLUSION:** EGFR mutations were significantly associated with VPI development in NSCLC, but no significant association was observed between EGFR mutations and DFS in the patients with VPI. 19-del was a favorable prognostic factor for DFS in non-VPI patients.

[Induction chemoradiation is associated with improved survival in chest wall invasion lung cancer.](#)

Muñoz-Largacha JA1, Rao SR2, Brinckerhoff LH3, Daly BD1, Fernando HC4, Litle VR1, Suzuki K1. Tumori. 2019 Mar 25;300891619839283. doi: 10.1177/0300891619839283. [Epub ahead of print]

**OBJECTIVE:** To determine if induction chemotherapy with concurrent high-dose radiation followed by resection is associated with improved survival in patients with nonsuperior sulcus lung cancer with chest wall invasion. **METHODS:** We performed a retrospective review of clinical T3 (chest wall invasion) N0/N1 patients with non-small cell lung cancer who underwent surgical resection between January 1, 1992, and January 31, 2017. Exclusion criteria included superior sulcus tumors and resection performed for palliation/recurrence. Patients undergoing induction chemoradiation followed by surgical resection were compared to those undergoing resection first or those receiving induction radiation followed by resection. Overall survival was calculated using the Kaplan-Meier method. **RESULTS:** Thirty-four patients were included in the analysis, with 5-year overall survival (OS) of 30%. By clinical stage, 31 (91%) were IIB (T3N0) and 3 (9%) were IIIA (T3N1). Sixteen patients (47%) received induction chemoradiation before surgery. Of the remaining 18 patients, 5 (15%) received induction radiation followed by surgery, and 13 (38%) underwent surgery as the first treatment. Three patients belonging to the group not receiving induction chemoradiation died within 30 days after surgery and were excluded from survival analysis. In the remaining 31 patients, induction chemoradiation was associated with improved 5-year OS (53% for induction chemoradiation vs 7% for others;  $P < 0.01$ ). Disease recurrence was evident in 9 cases, 2 (12.5%) in the induction chemoradiation group and 7 (46.6%) in the others (median disease-free time 103.0 months for induction chemoradiation group vs 8.0 months for others;  $P < 0.01$ ). **CONCLUSION:** In patients with nonsuperior sulcus lung cancer with chest wall invasion, induction chemoradiation therapy followed by resection is associated with improved OS.

[Updated Efficacy and Safety Data and Impact of the EML4-ALK Fusion Variant on the Efficacy of Alectinib in Untreated ALK-positive Advanced Non-small-cell Lung Cancer in the Global Phase III ALEX Study.](#)

Camidge DR1, Dziadziuszko R2, Peters S3, et al. J Thorac Oncol. 2019 Mar 19. pii: S1556-0864(19)30210-2. doi: 10.1016/j.jtho.2019.03.007. [Epub ahead of print]

**INTRODUCTION:** At the prior data cut-off (February 9, 2017) the ALEX trial showed superior investigator-assessed progression-free survival (PFS) for alectinib versus crizotinib in untreated, anaplastic lymphoma kinase (ALK)-positive, advanced non-small-cell lung cancer (ALK+ NSCLC) (hazard ratio [HR], 0.47, 95% confidence interval [CI], 0.34-0.65;  $p < 0.001$ ). Median PFS in the alectinib arm was not reached versus 11.1 months with crizotinib. Retrospective analyses suggests that the echinoderm microtubule-associated protein like 4-ALK (EML4-ALK) variant may influence ALK inhibitor treatment benefit. We present updated analyses, including exploratory subgroup analysis by EML4-ALK variant, after an additional 10 months' follow-up (cut-off: December 1, 2017). **METHODS:** Patients were randomized to receive twice-daily alectinib 600 mg or crizotinib 250 mg until disease progression, toxicity, death, or withdrawal. PFS was determined by investigators. Baseline plasma and tissue biomarker samples were analyzed using hybrid-capture, next-generation sequencing to determine EML4-ALK variant. **RESULTS:** Baseline characteristics were balanced. Investigator-assessed PFS was prolonged with alectinib; stratified HR, 0.43 (95% CI, 0.32-0.58), median 34.8 months versus crizotinib 10.9 months. EML4-ALK fusions were detectable in 129 patients (plasma) and 124 (tissue); variants 1, 2 and 3/ab did not impact PFS, objective response rate or duration of response. Investigator-assessed PFS was longer for alectinib versus crizotinib across EML4-ALK variants 1, 2 and 3a/b in plasma and tissue. Despite longer treatment duration (alectinib 27.0 months versus crizotinib 10.8 months), safety of alectinib compared favorably with crizotinib. **CONCLUSION:** Alectinib continues to demonstrate

superior investigator-assessed PFS versus crizotinib in untreated ALK+ NSCLC, irrespective of EML4-ALK variant.

**Phase II Trial of Cabozantinib Plus Erlotinib in Patients With Advanced Epidermal Growth Factor Receptor (EGFR)-Mutant Non-small Cell Lung Cancer With Progressive Disease on Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy: A California Cancer Consortium Phase II Trial (NCI 9303).**

Reckamp KL1, Frankel PH1, Ruel N1, et al. *Front Oncol.* 2019 Mar 11;9:132. doi: 10.3389/fonc.2019.00132. eCollection 2019.

**INTRODUCTION:** Mesenchymal epidermal transition and vascular endothelial growth factor pathways are important in mediating non-small cell lung cancer (NSCLC) tumorigenesis and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) resistance. We hypothesized that treatment with cabozantinib plus erlotinib in EGFR mutation-positive NSCLC following progression on EGFR TKI therapy may allow tumors to overcome this resistance or restore sensitivity to therapy regardless of T790M status. **METHODS:** Patients with advanced NSCLC, known EGFR mutation and progressive disease on an EGFR TKI immediately prior to enrollment without intervening therapy were enrolled. Patients received erlotinib 150 mg and cabozantinib 40 mg daily. The primary endpoint was evaluation of efficacy by objective response rate. Secondary endpoints included assessment of progression free survival (PFS), overall survival, change in tumor growth rate, safety and toxicity, and the evaluation of specific EGFR mutations and MET amplification in pre-treatment tissue and plasma. **RESULTS:** Thirty-seven patients were enrolled at 4 centers. Four patients had partial response (10.8%) and 21 had stable disease (59.5%). A greater than 30% increase in tumor doubling time was observed in 79% of assessable patients (27/34). Median PFS was 3.6 months for all patients. Diarrhea (32%) was the most common grade 3 adverse event; 3 patients had asymptomatic grade 4 elevation of amylase and lipase. **CONCLUSIONS:** Combination erlotinib and cabozantinib demonstrates activity in a highly pretreated population of patients with EGFR mutation and progression on EGFR TKI. Further elucidation of beneficial patient subsets is warranted. Clinical Trial Registration: [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), identifier: NCT01866410.

**Clinical Management of Adverse Events Associated with Lorlatinib.** Bauer TM1, Felip E2, Solomon BJ3, Thurm H4, Peltz G5, Chioda MD6, Shaw AT7. *Oncologist.* 2019 Mar 19. pii: theoncologist.2018-0380. doi: 10.1634/theoncologist.2018-0380. [Epub ahead of print]

Lorlatinib is a novel, highly potent, brain-penetrant, third-generation ALK/ROS1 tyrosine kinase inhibitor (TKI), which has broad-spectrum potency against most known resistance mutations that can develop during treatment with crizotinib and second-generation ALK TKIs. The safety profile of lorlatinib was established based on 295 patients who had received the recommended dose of lorlatinib 100 mg once daily. Adverse events associated with lorlatinib are primarily mild to moderate in severity, with hypercholesterolemia (82.4%), hypertriglyceridemia (60.7%), edema (51.2%), peripheral neuropathy (43.7%), and central nervous system effects (39.7%) among the most frequently reported. These can be effectively managed with dose modification and/or standard supportive medical therapy, as indicated by a low incidence of permanent discontinuations due to adverse reactions. Most patients (81.0%) received at least one lipid-lowering agent. Prescription of supportive therapy should also consider the potential for drug-drug interactions with lorlatinib via engagement of specific CYP450 enzymes. This article summarizes the clinical experience from lorlatinib phase I investigators and was generated from discussion and review of the clinical study protocol and database to provide an expert consensus opinion on the management of the key adverse reactions reported with lorlatinib, including hyperlipidemia, central nervous system effects, weight increase, edema, peripheral neuropathy, and gastrointestinal effects. Overall, lorlatinib 100 mg once daily has a unique safety profile to be considered when prescribed, based on the recent U.S. Food and Drug Administration approval, for the treatment of patients with ALK-positive metastatic non-small cell lung cancer previously treated with a second-generation ALK TKI.



**IMPLICATIONS FOR PRACTICE:** Despite the advancement of second-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs), the emergence of resistance and progression of central nervous system metastases remain clinically significant problems in ALK-positive non-small cell lung cancer. Lorlatinib is a potent, brain-penetrant, third-generation, macrocyclic ALK/ROS1 TKI, with broad-spectrum potency against most known resistance mutations that can develop during treatment with existing first- and second-generation ALK TKIs. This article provides recommendations for the clinical management of key adverse reactions reported with lorlatinib.

[Newer-Generation EGFR Inhibitors in Lung Cancer: How Are They Best Used?](#) Le T1, Gerber DE2,3,4. *Cancers (Basel)*. 2019 Mar 15;11(3). pii: E366. doi: 10.3390/cancers11030366.

The FLAURA trial established osimertinib, a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), as a viable first-line therapy in non-small cell lung cancer (NSCLC) with sensitizing EGFR mutations, namely exon 19 deletion and L858R. In this phase 3 randomized, controlled, double-blind trial of treatment-naïve patients with EGFR mutant NSCLC, osimertinib was compared to standard-of-care EGFR TKIs (i.e., erlotinib or gefitinib) in the first-line setting. Osimertinib demonstrated improvement in median progression-free survival (18.9 months vs. 10.2 months; hazard ratio 0.46; 95% CI, 0.37 to 0.57;  $p < 0.001$ ) and a more favorable toxicity profile due to its lower affinity for wild-type EGFR. Furthermore, similar to later-generation anaplastic lymphoma kinase (ALK) inhibitors, osimertinib has improved efficacy against brain metastases. Despite this impressive effect, the optimal sequencing of osimertinib, whether in the first line or as subsequent therapy after the failure of earlier-generation EGFR TKIs, is not clear. Because up-front use of later-generation TKIs may result in the inability to use earlier-generation TKIs, this treatment paradigm must be evaluated carefully. For EGFR mutant NSCLC, considerations include the incidence of T790M resistance mutations, quality of life, whether there is a potential role for earlier-generation TKIs after osimertinib failure, and overall survival. This review explores these issues for EGFR inhibitors and other molecularly targeted therapies.

[Pharmacist-led patient education and adverse event management in patients with non-small cell lung cancer receiving afatinib in a community-based, real-world clinical setting.](#) Khrystolubova N1, Shieh M1, Patel AJ2, Bailey R1. *J Oncol Pharm Pract*. 2019 Mar 4;1078155219833441. doi: 10.1177/1078155219833441. [Epub ahead of print]

**PURPOSE:** To describe the outcomes of a pharmacist-led multi-center, collaborative patient education and proactive adverse event management program in a community-based oncology setting. **METHODS:** Patients with EGFR mutation-positive (EGFRm+) non-small cell lung cancer, newly prescribed with oral afatinib, and monitored as part of the Florida Cancer Specialists patient management program, were included in a retrospective, observational analysis. During follow-up, data were collected on adverse event frequency, and changes in afatinib dosing. Data analyses were descriptive and exploratory in nature. **RESULTS:** The mean age of the 123 patients included in the analysis was 69 years, and 78% were female. At the time of the analysis, 3 patients had discontinued before receiving treatment, 89 patients had discontinued afatinib treatment, and 31 patients were continuing to receive afatinib treatment. The most common afatinib-related adverse events were diarrhea (85%), rash/skin reactions (58%), stomatitis/mucositis (19%), and paronychia (16%). Overall, 13% of patients discontinued due to afatinib-related adverse events. The median duration of treatment was 4 months in patients who discontinued due to adverse events, 6 months in those who discontinued for other reasons, and 18 months in those who were continuing to receive therapy. Afatinib dose-reductions were more frequent in patients continuing treatment versus those who discontinued due to adverse events (77% vs. 42%, respectively).

**CONCLUSIONS:** Findings suggest that adverse events in patients with EGFRm+ non-small cell lung cancer receiving afatinib can be successfully managed in a community-based, real-world setting with the help of collaborative pharmacist-led patient education, adverse event monitoring, and continuous support.

[Immunotherapy in Non-Small Cell Lung Cancer: Facts and Hopes.](#) Doroshov DB1,2, Sanmamed MF3,4,5,6, Hastings K2, et al. Clin Cancer Res. 2019 Mar 1. doi: 10.1158/1078-0432.CCR-18-1538. [Epub ahead of print]

Immune-checkpoint inhibitors (ICI), particularly inhibitors of the PD-1 axis, have altered the management of non-small cell lung cancer (NSCLC) over the last 10 years. First demonstrated to improve outcomes in second-line or later therapy of advanced disease, ICIs were shown to improve overall survival compared with chemotherapy in first-line therapy for patients whose tumors express PD-L1 on at least 50% of cells. More recently, combining ICIs with chemotherapy has been shown to improve survival in patients with both squamous and nonsquamous NSCLC, regardless of PD-L1 expression. However, PD-L1 and, more recently, tumor mutational burden have not proven to be straightforward indicative biomarkers. We describe the advances to date in utilizing these biomarkers, as well as novel markers of tumor inflammation, to ascertain which patients are most likely to benefit from ICIs. Ongoing translational work promises to improve the proportion of patients who benefit from these agents.

[Re-biopsy and liquid biopsy for patients with non-small cell lung cancer after EGFR-tyrosine kinase inhibitor failure.](#) Zhou J1, Zhao C2, Zhao J1, et al. Thorac Cancer. 2019 Apr;10(4):957-965. doi: 10.1111/1759-7714.13035. Epub 2019 Mar 18.

**BACKGROUND:** Re-biopsy is important for exploring resistance mechanisms, especially for non-small cell lung cancer (NSCLC) patients who develop resistance to EGFR-tyrosine kinase inhibitors (TKIs). Liquid biopsy using circulating tumor DNA has come into use for this purpose. This retrospective study investigated the status of re-biopsy and liquid biopsy in NSCLC patients with EGFR mutations and evaluated their effect on clinical strategies and prognosis. **METHODS:** Five hundred fifty-five NSCLC patients with resistance to EGFR-TKIs were included and divided into three groups: re-biopsy, liquid biopsy, and no re-biopsy. Amplification refractory mutation system (ARMS) PCR or super ARMS PCR was used to detect EGFR mutations. **RESULTS:** Three hundred eight (55.5%) patients underwent re-biopsy; 45.5% (140/308) were positive for T790M. The most common re-biopsy procedure was computed tomography-guided percutaneous core needle biopsy (60.1%), followed by effusion drainage (29.5%) and superficial lymph node biopsy (6.5%). One hundred eighteen (21.3%) patients underwent liquid biopsy; the T790M detection rate was 41.5% (49/118.) Of the 308 patients who underwent re-biopsy, 69 were examined for EGFR mutations with plasma. The concordance rate of T790M detection between tissue and plasma was 66.7%. A statistical difference in further treatment after EGFR-TKI failure was observed among all groups ( $P = 0.014$ ). Patients in the biopsy groups were more likely to receive third-generation EGFR-TKIs. Multivariate analysis showed that re-biopsy had a significant impact on overall survival ( $P < 0.001$ ). **CONCLUSION:** Re-biopsy plays a pivotal role in the management of patients with NSCLC and resistance to EGFR-TKIs. Liquid biopsy may be an alternative if difficulties performing re-biopsy exist.

[Multi-disciplinary proactive follow-up algorithm for patients with advanced NSCLC receiving afatinib.](#) Cheema PK1, Thawer A2, Leake J2, Cheng SY2, Khanna S2, Charles Victor J3. Support Care Cancer. 2019 Mar;27(3):1029-1039. doi: 10.1007/s00520-018-4392-x. Epub 2018 Aug 16.

**PURPOSE:** Afatinib is a standard first-line therapy for advanced EGFR-positive NSCLC. We implemented a pharmacist-led proactive follow-up algorithm to identify and manage early afatinib-related adverse events (AEs). **METHODS:** We conducted a retrospective chart review of all patients treated with afatinib after implementation of the algorithm at the Sunnybrook Odette Cancer Centre (Toronto, ON, Canada) from April 1, 2015 to July 31, 2016. Our in-house algorithm involved consultations in person and proactive pharmacist-led callbacks on days 5, 10, and 17. All AEs were graded and documented in real time and management based on toxicity grade was standardized. This study evaluated the impact of

our algorithm on real-world AEs. **RESULTS AND DISCUSSION:** Thirty-three patients were identified and reviewed. Median follow-up was 248 days. All patients experienced at least one drug-related AE; 18.2% were grade 3/4. The most common AEs were diarrhea 87.9%, rash 81.8%, stomatitis 57.6%, and paronychia 45.5%. Median dose of afatinib was 40 mg daily; 51.5% of patients had  $\geq 1$  dose reduction and 6.3% discontinued afatinib due to AEs. Proactive calls by the pharmacist identified 36.5% of all drug-related AEs, 33.3% of grade 3/4 AEs, 58.1% of first drug-related AEs and identified two patients that were non-compliant. Only 3.2% of AEs were identified by an emergency room/urgent clinic visit. **CONCLUSIONS:** This proactive multi-disciplinary AE management algorithm resulted in a low rate of urgent assessments and discontinuation due to toxicity while maintaining afatinib at ideal dose, thus providing a useful tool for centers prescribing afatinib.

### **[The Third-Generation EGFR Inhibitor, Osimertinib, Promotes c-FLIP Degradation, Enhancing Apoptosis Including TRAIL-Induced Apoptosis in NSCLC Cells with Activating EGFR Mutations.](#)**

Shi P1, Zhang S1, Zhu L2, Qian G3, Ren H4, Ramalingam SS3, Chen M4, Sun SY5. *Transl Oncol.* 2019 May;12(5):705-713. doi: 10.1016/j.tranon.2019.02.006. Epub 2019 Mar 9.

The third-generation EGFR inhibitor, osimertinib (AZD9291), selectively and irreversibly inhibits EGFR activating and T790 M mutants while sparing wild-type EGFR. Osimertinib is now an approved drug for non-small cell lung cancer (NSCLC) patients with activating EGFR mutations (first-line) or those who have become resistant to 1st generation EGFR inhibitors through the T790 M mutation (second-line). Unfortunately, all patients eventually relapse and develop resistance to osimertinib. Hence, it is essential to fully understand the biology underlying the development of resistance to osimertinib in order to improve its therapeutic efficacy and overcome resistance. Cellular FLICE-inhibitory protein (c-FLIP) is a truncated form of caspase-8 and functions as a key inhibitor of the extrinsic apoptotic pathway. The current study has demonstrated that osimertinib reduces c-FLIP levels via facilitating its degradation and enhances apoptosis induced by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) primarily in NSCLC with activating EGFR mutations. Moreover, modulation of c-FLIP expression levels, to some degree, also alters the sensitivities of EGFR mutant NSCLC cells to undergo osimertinib-induced apoptosis, suggesting that c-FLIP suppression is an important event contributing to the antitumor activity of osimertinib against EGFR mutant NSCLC.

**[Duration of treatment among patients prescribed afatinib or erlotinib as first-line therapy for EGFR mutation-positive non-small-cell lung cancer in the USA.](#)** Lim J1, Samuelsen C2, Golembesky A2, Shrestha S3, Wang L3, Griebisch I2. *Future Oncol.* 2019 Mar 19. doi: 10.2217/fon-2019-0052. [Epub ahead of print]

**AIM:** Evaluate duration of therapy among patients treated with afatinib or erlotinib as first-line therapy for non-small-cell lung cancer (NSCLC). **MATERIALS & METHODS:** NSCLC patients initiating afatinib or erlotinib between 2014 and 2017 were identified in three large claims databases in the USA. Propensity score matching was conducted to compare the duration of treatment between patients by treatment. **RESULTS:** Patients prescribed afatinib had a significantly longer median duration of treatment compared with those prescribed erlotinib (12.1 vs 9.9 months;  $p = 0.035$ ) and experienced a 14% reduction in risk of discontinuing therapy (adjusted hazard ratio: 0.86; CI: 0.75-0.99). **CONCLUSION:** First-line treatment duration in a real-world setting was significantly longer for patients prescribed afatinib compared with erlotinib.

**[Clinical Characteristics of Osimertinib Responder in Non-Small Cell Lung Cancer Patients with EGFR-T790M Mutation.](#)** Yoshimura A1, Yamada T2, Okura N3, et al. *Cancers (Basel).* 2019 Mar 15;11(3). pii: E365. doi: 10.3390/cancers11030365.

Osimertinib is a mutant-selective EGFR inhibitor that is effective against non-small cell lung cancer (NSCLC) in patients with the EGFR-T790M mutation, who are resistant to EGFR-tyrosine kinase inhibitors (EGFR-TKIs). However, the factors affecting response to osimertinib treatment are unknown. In this retrospective study, 27 NSCLC patients with the EGFR-T790M mutation were enrolled at five institutions in Japan. Among several parameters tested, the progression-free survival (PFS) associated with the initial EGFR-TKIs was positively correlated with the PFS after osimertinib treatment ( $p = 0.021$ ). The median PFS following osimertinib treatment and the overall survival (OS) were longer in patients who responded to osimertinib than in those who did not (17.7 months versus 3.5 months,  $p = 0.009$  and 24.2 months versus 13.5 months,  $p = 0.021$ , respectively). A multivariate analysis demonstrated that the PFS with initial EGFR-TKIs was significantly related to the PFS with osimertinib treatment ( $p = 0.035$ ), whereas osimertinib response was significantly related to the PFS and OS with osimertinib treatment ( $p = 0.016$  and  $p = 0.006$ , respectively). Our retrospective observations indicate that PFS following the initial EGFR-TKI treatment and the response rate to osimertinib might be promising predictors for effective osimertinib treatment in NSCLC patients with the EGFR-T790M mutation.

**[Choosing wisely first line immunotherapy in non-small cell lung cancer \(NSCLC\): what to add and what to leave out.](#)** Proto C1, Ferrara R2, Signorelli D1, et al. *Cancer Treat Rev.* 2019 Mar 28;75:39-51. doi: 10.1016/j.ctrv.2019.03.004. [Epub ahead of print]

Immunotherapy has dramatically changed the therapeutic scenario in treatment naïve advanced non-small cell lung cancer (NSCLC). While single agent pembrolizumab has become the standard therapy in patients with PD-L1 expression on tumor cells  $\geq 50\%$ , the combination of pembrolizumab or atezolizumab and platinum-based chemotherapy has emerged as an effective first line treatment regardless of PD-L1 expression both in squamous and non-squamous NSCLC without oncogenic drivers. Furthermore, double immune checkpoint inhibition has shown promising results in treatment naïve patients with high tumor mutational burden (TMB). Of note, the presence of both negative PD-L1 expression and low TMB may identify a subgroup of patients who has little benefit from immunotherapy combinations and for whom the best treatment option may still be platinum-based chemotherapy. To date, first-line single agent immune checkpoint blockade has demonstrated limited activity in EGFR mutated NSCLC and the combination of immunotherapy and targeted agents has raised safety concerns in both EGFR and ALK positive NSCLC patients. Finally, in EGFR mutated or ALK rearranged NSCLC, atezolizumab in combination with platinum-based chemotherapy and bevacizumab is emerging as a potential treatment option upon progression to first line tyrosine kinase inhibitors.

**[Mechanisms involved in IL-15 superagonist enhancement of anti-PD-L1 therapy.](#)** Knudson KM1, Hicks KC1, Alter S2, Schlom J3, Gameiro SR1. *Immunother Cancer.* 2019 Mar 21;7(1):82. doi: 10.1186/s40425-019-0551-y.

**BACKGROUND:** Immunotherapy targeting PD-1/PD-L1 fails to induce clinical responses in most patients with solid cancers. N-803, formerly ALT-803, is an IL-15 superagonist mutant and dimeric IL-15R $\alpha$ Sushi-Fc fusion protein complex that enhances CD8 $^+$  T and NK cell expansion and function and exhibits anti-tumor efficacy in preclinical models. Previous in vitro studies have shown that IL-15 increases PD-L1 expression, a negative regulator of CD8 $^+$  T and NK cell function. Most reported preclinical studies administered N-803 intraperitoneally not subcutaneously, the current clinical route of administration. N-803 is now being evaluated clinically in combination with PD-1/PD-L1 inhibitors. However, the mechanism of action has not been fully elucidated. Here, we examined the anti-tumor efficacy and immunomodulatory effects of combining N-803 with an anti-PD-L1 antibody in preclinical models of solid carcinomas refractory to anti-PD-L1 or N-803. **METHODS:** Subcutaneous N-803 and an anti-PD-L1 monoclonal antibody were administered as monotherapy or in combination to 4T1 triple negative breast and MC38-CEA colon tumor-bearing mice. Anti-tumor efficacy was evaluated, and a



comprehensive analysis of the immune-mediated effects of each therapy was performed on the primary tumor, lung as a site of metastasis, and spleen. **RESULTS:** We demonstrate that N-803 treatment increased PD-L1 expression on immune cells in vivo, supporting the combination of N-803 and anti-PD-L1. N-803 plus anti-PD-L1 was well-tolerated, reduced 4T1 lung metastasis and MC38-CEA tumor burden, and increased survival as compared to N-803 and anti-PD-L1 monotherapies. Efficacy of the combination therapy was dependent on both CD8+ T and NK cells and was associated with increased numbers of these activated immune cells in the lung and spleen. Most alterations to NK and CD8+ T cell phenotype and number were driven by N-803. However, the addition of anti-PD-L1 to N-803 significantly enhanced CD8+ T cell effector function versus N-803 and anti-PD-L1 monotherapies, as indicated by increased Granzyme B and IFN $\gamma$  production, at the site of metastasis and in the periphery. Increased CD8+ T cell effector function correlated with higher serum IFN $\gamma$  levels, without related toxicities, and enhanced anti-tumor efficacy of the N-803 plus anti-PD-L1 combination versus either monotherapy. **CONCLUSIONS:** We provide novel insight into the mechanism of action of N-803 plus anti-PD-L1 combination and offer preclinical proof of concept supporting clinical use of N-803 in combination with checkpoint inhibitors, including for patients non- and/or minimally responsive to either monotherapy.

**[Comparing the efficacy of concurrent EGFR-TKI and whole-brain radiotherapy vs EGFR-TKI alone as a first-line therapy for advanced EGFR-mutated non-small-cell lung cancer with brain metastases: a retrospective cohort study.](#)** He ZY<sup>1,2</sup>, Li MF<sup>1,2</sup>, Lin JH<sup>1,2</sup>, Lin D<sup>1,2</sup>, Lin RJ<sup>3</sup>. Cancer Manag Res. 2019 Mar 14;11:2129-2138. doi: 10.2147/CMAR.S184922. eCollection 2019.

**BACKGROUND:** Non-small-cell lung cancer (NSCLC) is a global public health problem, and brain is a common metastatic site in advanced NSCLC. Currently, whole-brain radiotherapy (WBRT) remains a major treatment for brain metastases, while EGFR-tyrosine kinase inhibitor (TKI) is the standard treatment for advanced NSCLC harboring EGFR mutations, which is also effective for brain metastases. However, whether EGFR-TKIs plus radiotherapy is superior to EGFR-TKIs alone for the treatment of advanced EGFR-mutant NSCLC with brain metastases remains controversial. This study aimed to compare the efficacy of concurrent EGFR-TKIs and WBRT vs EGFR-TKI alone in a retrospective cohort of advanced EGFR-mutant NSCLC with brain metastases. **PATIENTS AND METHODS:** The medical records of 104 treatment-naïve, advanced EGFR-mutant NSCLC patients with brain metastases were retrospectively reviewed, and there were 56 patients undergoing concurrent EGFR-TKI and WBRT, and 48 patients given EGFR-TKI alone, including 20 cases with salvage WBRT upon brain metastasis progression. The survival prognosis was compared between the two cohorts. **RESULTS:** The baseline clinicopathologic factors were balanced between the two cohorts. After a median follow-up of 23 months, 35.6% of the study subjects survived. Concurrent EGFR-TKI and WBRT significantly improved the median intracranial PFS (iPFS) compared with EGFR-TKI alone (17.7 vs 11.0 months,  $P=0.015$ ); however, no significant difference was seen in median overall survival between the two cohorts (28.1 vs 24.0 months,  $P=0.756$ ). In addition, the median iPFS was found to significantly vary in the number of brain metastases ( $\leq 3$  vs  $> 3$  metastases: 18.0 vs 12.5 months,  $P=0.044$ ). Subgroup analysis showed that concurrent EGFR-TKI and WBRT improved median iPFS compared with EGFR-TKI alone in patients with more than three brain metastases ( $P=0.001$ ); however, no significant difference was observed between the two regimens in patients with three or less brain metastases ( $P=0.526$ ). **CONCLUSION:** Our data demonstrate that concurrent EGFR-TKI and WBRT achieves longer iPFS than EGFR-TKI alone in advanced EGFR-mutant NSCLC with brain metastases. In advanced EGFR-mutant NSCLC with three or less brain metastases, EGFR-TKI alone may be an option as a first-line therapy.

**[Identification of genetic alterations associated with primary resistance to EGFR-TKIs in advanced non-small-cell lung cancer patients with EGFR sensitive mutations.](#)** Wang F<sup>1,2</sup>, Diao XY<sup>3</sup>, Zhang

X4, Shao Q4, Feng YF5,6, An X7, Wang HY8,9. *Cancer Commun (Lond)*. 2019 Mar 2;39(1):7. doi: 10.1186/s40880-019-0354-z.

**BACKGROUND:** Identification of activated epidermal growth factor receptor (EGFR) mutations and application of EGFR-tyrosine kinase inhibitors (EGFR-TKIs) have greatly changed the therapeutic strategies of non-small-cell lung cancer (NSCLC). However, the long-term efficacy of EGFR-TKI therapy is limited due to the development of drug resistance. The aim of this study was to investigate the correlation between the aberrant alterations of 8 driver genes and the primary resistance to EGFR-TKIs in advanced NSCLC patients with activated EGFR mutations. **METHODS:** We retrospectively reviewed the clinical data from 416 patients with stage III/IV or recurrent NSCLC who received an initial EGFR-TKI treatment, from April 2004 and March 2011, at the Sun Yat-sen University Cancer Center. Several genetic alterations associated with the efficacy of EGFR-TKIs, including the alterations in BIM, ALK, KRAS, PIK3CA, PTEN, MET, IGF1R, and ROS1, were detected by the routine clinical technologies. The progression-free survival (PFS) and overall survival (OS) were compared between different groups using Kaplan-Meier survival analysis with the log-rank test. A Cox regression model was used to estimate multivariable-adjusted hazard ratios (HRs) and their 95% confidence intervals (95% CIs) associated with the PFS and OS. **RESULTS:** Among the investigated patients, 169 NSCLC patients harbored EGFR-sensitive mutations. EGFR-mutant patients having PTEN deletion had a shorter PFS and OS than those with intact PTEN ( $P = 0.003$  for PFS, and  $P = 0.034$  for OS). In the combined molecular analysis of EGFR signaling pathway and resistance genes, we found that EGFR-mutant patients coexisted with aberrant alterations in EGFR signaling pathway and those having resistant genes had a statistically poorer PFS than those without such alterations ( $P < 0.001$ ). A Cox proportional regression model determined that PTEN deletion (HR = 4.29, 95% CI = 1.72-10.70) and low PTEN expression (HR = 1.96, 95% CI = 1.22-3.13), MET FISH+ (HR = 2.83, 95% CI = 1.37-5.86) were independent predictors for PFS in patients with EGFR-TKI treatment after adjustment for multiple factor. **CONCLUSIONS:** We determined that the coexistence of genetic alterations in cancer genes may explain primary resistance to EGFR-TKIs.

**[Pembrolizumab in patients with advanced non-small-cell lung cancer \(KEYNOTE-001\): 3-year results from an open-label, phase 1 study.](#)**

Leighl NB1, Hellmann MD2, Hui R3, Carcereny E4, et al. *Lancet Respir Med*. 2019 Apr;7(4):347-357. doi: 10.1016/S2213-2600(18)30500-9. Epub 2019 Mar 12.

**BACKGROUND:** The anti-programmed death 1 monoclonal antibody pembrolizumab has shown antitumour activity and is a first-line and second-line treatment option for patients with programmed death ligand 1 (PD-L1)-expressing advanced non-small-cell lung cancer. We report updated 3-year safety and efficacy outcomes from the phase 1 study, KEYNOTE-001. **METHODS:** KEYNOTE-001 is a multicohort, open-label, phase 1 study of pembrolizumab (2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks) in treatment naive or previously treated patients with locally advanced or metastatic non-small-cell lung cancer with measurable disease at baseline. Two cohorts were randomly assigned to a pembrolizumab dose by use of a computer-generated randomisation schedule at cohort-dependent ratios, and a further four cohorts were assigned to a pembrolizumab dose without randomisation. We present 3-year outcomes for the full analysis set of patients who received at least one dose of study treatment, pooled for all pembrolizumab doses. The primary efficacy endpoint was proportion of patients with objective response, analysed here as investigator-assessed response according to immune-related response criteria. Secondary efficacy endpoints included overall survival, duration of response, and progression-free survival. Safety endpoints included incidence of adverse events. This study is registered at ClinicalTrials.gov, number NCT01295827, and is ongoing. **FINDINGS:** Between May 8, 2012 and July 13, 2014, 550 patients (101 treatment naive and 449 previously treated) were enrolled. Median follow-up was 34.5 months at data cutoff (Sept 1, 2016). At 36 months, investigator-assessed objective response according to immune-related response criteria was achieved for 41 of 101 treatment naive patients (41% [95% CI 30.9-50.8]; median duration of response was 16.7 months [95% CI 12.6-not reached]) and 102

of 449 previously treated patients (23% [18.9-26.9]; 33.3 ([22.5-not reached]). The Kaplan-Meier estimate of overall survival at 36 months was 26.4% (95% CI 14.3-40.1) for treatment naive patients and 19.0% (15.0-23.4) for previously treated patients, with median overall survival of 22.3 months (95% CI 17.1-31.5) and 10.5 months (8.6-13.2). PD-L1 tumour proportion score  $\geq 50\%$  was associated with longer median overall survival (95% CI) versus tumour proportion score 1-49% (treatment naive: 34.9 [20.3-not reached] vs 19.5 [10.7-26.3] months; previously treated: 15.4 [10.5-18.5] vs 8.5 [6.0-12.7] months). Grade 3-5 treatment-related adverse events occurred in 66 patients (12%), and 30 (6%) discontinued owing to a treatment-related adverse event. The most frequent grade 3-4 treatment-related adverse events were pneumonitis (10 [2%] of 550) and fatigue (5 [1%] of 550). Overall, 227 patients (41%) of 550 had serious adverse events, of which 50 (9%) were treatment related. **INTERPRETATION:** Pembrolizumab provides durable response and long-term effects on overall survival, with tolerable safety, for treatment naive and previously treated patients with advanced non-small-cell lung cancer expressing PD-L1. **FUNDING:** Merck Sharp & Dohme Corp.

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## NSCLC - RADIOTHERAPY

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[\*\*A prospective, three-arm, randomized trial of EGCG for preventing radiation-induced esophagitis in lung cancer patients receiving radiotherapy.\*\*](#) Zhao H1, Jia L2, Chen G3, Li X1, Meng X1, Zhao X1, Xing L4, Zhu W5. *Radiother Oncol.* 2019 Mar 19. pii: S0167-8140(19)30104-5. doi: 10.1016/j.radonc.2019.02.022. [Epub ahead of print]

**BACKGROUND AND PURPOSE:** This trial investigated whether epigallocatechin-3-gallate (EGCG), a radioprotector, could be effective in the prevention and treatment of acute radiation-induced esophagitis (ARIE). **METHODS AND MATERIALS:** This is a phase II study of EGCG combined with chemoradiation in unresectable stage III non-small-cell lung cancer or limited stage small cell lung cancer. Patients were randomized into a prophylactic EGCG group (arm A), a therapeutic EGCG group after the occurrence of esophagitis (arm B) or conventional therapy group (arm C). Esophagitis grades, pain and dysphagia scores were recorded weekly. Adjusted esophagitis index (AEI), pain index (API) and dysphagia index (ADI) were calculated to reflect changes in esophagitis grade, pain score and dysphagia score throughout treatment. **RESULTS:** A total of 83 patients were eligible for toxicity analysis (arm A vs arm B vs arm C: N = 28:27:28). There was no significant difference in the baseline characteristics among three arms of the patients. The difference in the maximum esophagitis grade among three groups was statistically significant (P = 0.004). The maximum ARIE for patients with EGCG was significantly lower than for those with conventional therapy. The mean AEI of arm A was lower than that of arm B, while the mean AEI of arm C was the highest (arm A vs arm B, P = 0.028; arm B vs arm C, P = 0.002). Furthermore, API and ADI were significantly lower in patients receiving EGCG than in conventionally treated patients. **CONCLUSION:** The application of EGCG could effectively alleviate acute radiation esophagitis in advanced lung cancer without obvious side effects. Prophylactic application of EGCG had a slight advantage over therapeutic use in treatment of acute esophagitis.

[\*\*Deep Learning Applications in Chest Radiography and Computed Tomography: Current State of the Art.\*\*](#) Lee SM1, Seo JB1, Yun J2, et al. *J Thorac Imaging.* 2019 Mar;34(2):75-85. doi: 10.1097/RTI.0000000000000387.

Deep learning is a genre of machine learning that allows computational models to learn representations of data with multiple levels of abstraction using numerous processing layers. A distinctive feature of deep learning, compared with conventional machine learning methods, is that it can generate appropriate models for tasks directly from the raw data, removing the need for human-led feature extraction. Medical images are particularly suited for deep learning applications. Deep learning techniques have already demonstrated high performance in the detection of diabetic retinopathy on fundoscopic images and

metastatic breast cancer cells on pathologic images. In radiology, deep learning has the opportunity to provide improved accuracy of image interpretation and diagnosis. Many groups are exploring the possibility of using deep learning-based applications to solve unmet clinical needs. In chest imaging, there has been a large effort to develop and apply computer-aided detection systems for the detection of lung nodules on chest radiographs and chest computed tomography. The essential limitation to computer-aided detection is an inability to learn from new information. To overcome these deficiencies, many groups have turned to deep learning approaches with promising results. In addition to nodule detection, interstitial lung disease recognition, lesion segmentation, diagnosis and patient outcomes have been addressed by deep learning approaches. The purpose of this review article was to cover the current state of the art for deep learning approaches and its limitations, and some of the potential impact on the field of radiology, with specific reference to chest imaging.

**Circulating microRNAs as biomarkers of radiation-induced cardiac toxicity in non-small-cell lung cancer.** Hawkins PG1, Sun Y2, Dess RT1, et al. *Cancer Res Clin Oncol.* 2019 Mar 28. doi: 10.1007/s00432-019-02903-5. [Epub ahead of print]

**PURPOSE:** Radiation-induced cardiac toxicity (RICT) is an increasingly well-appreciated source of morbidity and mortality in patients receiving thoracic radiotherapy (RT). Currently available methods to predict RICT are suboptimal. We investigated circulating microRNAs (c-miRNAs) as potential biomarkers of RICT in patients undergoing definitive RT for non-small-cell lung cancer (NSCLC).

**METHODS:** Data from 63 patients treated on institutional trials were analyzed. Prognostic models of grade 3 or greater (G3 +) RICT based on pre-treatment c-miRNA levels ('c-miRNA'), mean heart dose (MHD) and pre-existing cardiac disease (PCD) ('clinical'), and a combination of these ('c-miRNA + clinical') were developed. Elastic net Cox regression and full cross validation were used for variable selection, model building, and model evaluation. Concordance statistic (c-index) and integrated Brier score (IBS) were used to evaluate model performance. **RESULTS:** MHD, PCD, and serum levels of 14 c-miRNA species were identified as jointly prognostic for G3 + RICT. The 'c-miRNA and 'clinical' models yielded similar cross-validated c-indices (0.70 and 0.72, respectively) and IBSs (0.26 and 0.28, respectively). However, prognostication was not improved by combining c-miRNA and clinical factors (c-index 0.70, IBS 0.28). The 'c-miRNA' and 'clinical' models were able to significantly stratify patients into high- and low-risk groups of developing G3 + RICT. Chi-square testing demonstrated a marginally significantly higher prevalence of PCD in patients with high- compared to low-risk c-miRNA profile ( $p = 0.09$ ), suggesting an association between some c-miRNAs and PCD. **CONCLUSIONS:** We identified a pre-treatment c-miRNA signature prognostic for G3 + RICT. With further development, pre- and mid-treatment c-miRNA profiling could contribute to patient-specific dose selection and treatment adaptation.

**Prophylactic Cranial Irradiation vs Observation in Patients With Locally Advanced Non-Small Cell Lung Cancer: A Long-term Update of the NRG Oncology/RTOG 0214 Phase 3 Randomized Clinical Trial.** Sun A1, Hu C2,3, Wong SJ4, Gore E4, Videtic G5, Dutta S6, Suntharalingam M7, Chen Y8, Gaspar LE9, Choy H10. *JAMA Oncol.* 2019 Mar 14. doi: 10.1001/jamaoncol.2018.7220. [Epub ahead of print]

**IMPORTANCE:** Brain metastasis (BM) rates are high in locally advanced non-small cell lung cancer (LA-NSCLC), approaching rates seen in small cell lung cancer, where prophylactic cranial irradiation (PCI) is standard of care. Although PCI decreases the incidence of BM in LA-NSCLC, a survival advantage has not yet been shown. **OBJECTIVE:** To determine if PCI improves survival in LA-NSCLC. **DESIGN, SETTING, AND PARTICIPANTS:** Radiation Therapy Oncology Group (RTOG) 0214 was a randomized phase 3 clinical trial in stage III NSCLC stratified by stage (IIIA vs IIIB), histologic characteristics (nonsquamous vs squamous) and therapy (no surgery vs surgery). The study took place at



291 institutions in the United States, Canada, and internationally. Of 356 patients with stage III NSCLC entered onto this study, 16 were ineligible; therefore, 340 patients were randomized. **INTERVENTION FOR CLINICAL TRIALS:** Observation vs PCI. **MAIN OUTCOMES AND MEASURES:** The primary outcome was overall survival (OS). The secondary end points were disease-free survival (DFS) and incidence of BM. **RESULTS:** Of the 340 total participants, mean (SD) age was 61 years; 213 of the participants were men and 127 were women. The median follow-up time was 2.1 years for all patients, and 9.2 years for living patients. The OS for PCI was not significantly better than observation (hazard ratio [HR], 0.82; 95% CI, 0.63-1.06; P = .12; 5- and 10-year rates, 24.7% and 17.6% vs 26.0% and 13.3%, respectively), while the DFS (HR, 0.76; 95% CI, 0.59-0.97; P = .03; 5- and 10-year rates, 19.0% and 12.6% vs 16.1% and 7.5% for PCI vs observation) and BM (HR, 0.43; 95% CI, 0.24-0.77; P = .003; 5- and 10-year rates, 16.7% vs 28.3% for PCI vs observation) were significantly different. Patients in the PCI arm were 57% less likely to develop BM than those in the observation arm. Younger patients (<60 years) and patients with nonsquamous disease developed more BM. On multivariable analysis, PCI was associated with decreased BM and improved DFS, but not improved OS. Multivariable analysis within the nonsurgical arm suggests that PCI effectively prolongs OS, DFS, and BM. **CONCLUSIONS AND RELEVANCE:** In patients with stage III LA-NSCLC without progression of disease after therapy, PCI decreased the 5- and 10-year rate of BM and improved 5- and 10-year DFS, but did not improve OS. Although this study did not meet its primary end point, the long-term results reveal many important findings that will benefit future trials. Identifying the appropriate patient population and a safe intervention is critical. **TRIAL REGISTRATION:**ClinicalTrials.gov identifier: NCT00048997.

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## SMALL CELL LUNG CANCER - SCLC

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[Immunotherapy for small cell lung cancer: mechanisms of resistance.](#) Hamilton G1, Rath B1. *Expert Opin Biol Ther.* 2019 May;19(5):423-432. doi: 10.1080/14712598.2019.1592155. Epub 2019 Mar 18. Small cell lung cancer (SCLC) is a highly malignant disease with a dismal prognosis that is currently being tested for the clinical activity of checkpoint inhibitors. SCLC is associated with smoking and exhibits a high mutational burden. However, low expression of PD-L1 and MHC antigens, as well low levels of immune cell infiltration and rapid tumor progress seems to limit the efficacy of anticancer immunity. Nevertheless, long-term survival was reported from studies using anti-PD-1/PD-L1 and CTLA-4 agents. Areas covered: Data of clinical trials of checkpoint inhibitors in SCLC show lower success rates compared to NSCLC. The mechanisms of resistance to immunotherapy are discussed for their relevance to SCLC patients. Expert opinion: Although some factors, such as a high mutation rate, favor immunotherapy for SCLC patients, downregulation of MHC class I, low expression of PD-L1, poor tumor infiltration by effector T cells, presence of myeloid-derived suppressor cells as well as regulatory T lymphocytes counteract the immune system activation by checkpoint inhibitors. Furthermore, this tumor develops avascular regions which have immunosuppressive effects and restrict access of lymphocytes and antibodies. In conclusion, immunotherapy in SCLC is effective in highly selected patients with good performance status and special and unknown preconditions contributing to long-lasting responses.

[Randomized controlled trial of lobaplatin plus etoposide vs. cisplatin plus etoposide as first-line therapy in patients with extensive-stage small cell lung cancer.](#) Cheng Y1, Fan Y2, Liu X3, et al. *Oncol Lett.* 2019 May;17(5):4701-4709. doi: 10.3892/ol.2019.10125. Epub 2019 Mar 8.

The majority of previous studies of lobaplatin in small cell lung cancer (SCLC) are small phase I-II studies. The present study aimed to verify the non-inferiority (in terms of efficacy) of lobaplatin plus etoposide (EL) vs. cisplatin plus etoposide (EP) in patients with previously untreated extensive-stage SCLC (ES-SCLC). This phase III non-inferiority randomized clinical trial enrolled patients at 17 sites between September 2010 and May 2013. Patients were randomized to EL (30 mg/m<sup>2</sup> lobaplatin on day 1

and 100 mg/m<sup>2</sup> etoposide on days 1-3, for 21-day cycles) or EP (80 mg/m<sup>2</sup> cisplatin on day 1 and 100 mg/m<sup>2</sup> etoposide on days 1-3, for 21-day cycles). The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate, disease control rate (DCR), toxicity and quality of life (QoL). A total of 234 patients were randomized to the EL (n=122) and EP (n=112) treatment groups. The median PFS, median OS and DCR were 5.1 vs. 5.3 months (P=0.786), 10.6 vs. 9.7 months (P=0.701) and 85.5 vs. 86.7% (P=0.848) in the EL vs. EP groups, respectively. Patients in the EL group had significantly lower frequencies of nephrotoxicity (2.5 vs. 11.7%; P=0.008), nausea (22.3 vs. 40.5%; P=0.003) and vomiting (14.1 vs. 35.1%; P<0.001) than those in the EP group. Overall, EL was not inferior to EP in terms of PFS and OS. The tolerance and QoL of the EL regimen were better than those of the EP regimen. EL is thus an alternative choice for the first-line treatment of ES-SCLC.

[Application of computed tomography-based radiomics signature analysis in the prediction of the response of small cell lung cancer patients to first-line chemotherapy.](#) Wei H1,2, Yang F3,4, Liu Z5, et al. *Exp Ther Med.* 2019 May;17(5):3621-3629. doi: 10.3892/etm.2019.7357. Epub 2019 Mar 7.

The aim of the present study was to investigate the utility of a computed tomography (CT)-based radiomics signature for the early prediction of the tumor response of small cell lung cancer (SCLC) patients to chemotherapy. A dataset including 92 patients from a clinical trial was retrospectively assembled. All of the patients received the standard first-line regimen of etoposide and cisplatin. According to the Response Evaluation Criteria in Solid Tumors 1.1, the patients were divided into two groups: Response and no response groups. A total of 21 radiomics features were extracted from CT images prior to and after two cycles of chemotherapy and a radiomics signature was constructed via a binary logistic regression model. The area under the receiver operating characteristics curve (AUC) was determined to evaluate the performance of the radiomics signature to predict the response to chemotherapy. The clinicopathological factors associated with chemotherapy in patients with SCLC were also evaluated, and a predictive model was established using a binary logistic regression analysis. The 21 radiological features were used to establish a radiomics signature that was significantly associated with the efficacy of SCLC chemotherapy (P<0.05). The performance of the radiomics signature to predict the chemotherapy efficacy (AUC=0.797) was better than that of the model using clinicopathological parameters (AUC=0.670). Therefore, the present study demonstrated that radiomics features may be promising prognostic imaging biomarkers to predict the response of SCLC patients to chemotherapy and may thus be utilized to guide appropriate treatment planning.

[Survival outcomes after whole brain radiotherapy for brain metastases in older adults with newly diagnosed metastatic small cell carcinoma: A national cancer database \(NCDB\) analysis.](#) Renz P1, Hasan S1, Wegner RE2. *J Geriatr Oncol.* 2019 Mar 12. pii: S1879-4068(18)30416-8. doi:

10.1016/j.jgo.2019.01.017. [Epub ahead of print]

**BACKGROUND:** Small cell lung cancer (SCLC) is an aggressive malignancy with a tendency to affect older adults and also metastasize to the brain. Older adults tolerate whole brain radiotherapy (WBRT) poorly with marginal survival benefit. We utilized the national cancer database (NCDB) to evaluate the survival outcomes following WBRT in older adults with SCLC and brain metastases. **METHODS:** We identified 1615 patients ≥75 years old diagnosed with SCLC and brain metastases. Patients were categorized by type of therapy: chemotherapy + WBRT (n = 576), chemotherapy alone (n = 238), WBRT alone (n = 360) and no chemotherapy or WBRT (n = 441). Clinical and demographic characteristics were reported for each treatment cohort with a subsequent multivariable regression analysis for survival.

**RESULTS:** Median patient age was 79 years. WBRT median dose was 30 Gy. At time of analysis, 1530 of the cohort had died, yielding a median OS of 2.9 months and 6 month survival of 31% for patients that received chemotherapy. For patients treated without chemotherapy, median OS with WBRT was

1.9 months compared to 1.2 months without ( $p < .0001$ ). For patients receiving chemotherapy with, and without WBRT, median OS was 5.6 months and 6.4 months, respectively ( $p = .43$ ). Multivariable cox regression revealed age  $> 80$ , extracranial disease, male sex, and rural location as predictors of increased risk of death. **CONCLUSION:** In older adult patients with SCLC brain metastasis, WBRT was associated with a modest increase in survival in patients not fit for chemotherapy, and there was no association with increased survival over chemotherapy alone.

**Inhibition of the Replication Stress Response Is a Synthetic Vulnerability in SCLC That Acts Synergistically in Combination with Cisplatin.**

Nagel R1,2, Avelar AT2, Aben N1,3, et al. Mol Cancer Ther. 2019 Apr;18(4):762-770. doi: 10.1158/1535-7163.MCT-18-0972. Epub 2019 Mar 14.

Small cell lung cancer (SCLC) is generally regarded as very difficult to treat, mostly due to the development of metastases early in the disease and a quick relapse with resistant disease. SCLC patients initially show a good response to treatment with the DNA damaging agents cisplatin and etoposide. This is, however, quickly followed by the development of resistant disease, which urges the development of novel therapies for this type of cancer. In this study, we set out to compile a comprehensive overview of the vulnerabilities of SCLC. A functional genome-wide screen where all individual genes were knocked out was performed to identify novel vulnerabilities of SCLC. By analysis of the knockouts that were lethal to these cancer cells, we identified several processes to be synthetic vulnerabilities in SCLC. We were able to validate the vulnerability to inhibition of the replication stress response machinery by use of Chk1 and ATR inhibitors. Strikingly, SCLC cells were more sensitive to these inhibitors than nontransformed cells. In addition, these inhibitors work synergistically with either etoposide and cisplatin, where the interaction is largest with the latter. ATR inhibition by VE-822 treatment in combination with cisplatin also outperforms the combination of cisplatin with etoposide in vivo. Altogether, our study uncovered a critical dependence of SCLC on the replication stress response and urges the validation of ATR inhibitors in combination with cisplatin in a clinical setting.

**Use of targeted next generation sequencing to characterize tumor mutational burden and efficacy of immune checkpoint inhibition in small cell lung cancer.**

Ricciuti B1, Kravets S2, Dahlberg SE2, et al. J Immunother Cancer. 2019 Mar 28;7(1):87. doi: 10.1186/s40425-019-0572-6.

**BACKGROUND:** Clinically-available biomarkers to identify the fraction of patients with small cell lung cancer (SCLC) who respond to immune-checkpoint inhibitors (ICIs) are lacking. High nonsynonymous tumor mutational burden (TMB), as assessed by whole exome sequencing, correlates with improved clinical outcomes for patients with SCLC treated with ICIs. Whether TMB as assessed by targeted next generation sequencing (NGS) is associated with improved efficacy of ICIs in patients with SCLC is currently unknown. Here we determined whether TMB by targeted NGS is associated with efficacy of ICIs in patients with SCLC. **METHODS:** We collected clinicopathologic data from patients with relapsed or refractory SCLC which underwent targeted NGS with TMB assessment by the Dana-Farber Cancer Institute OncoPanel platform. The relationship between TMB and clinical outcomes after treatment with ICIs was investigated. **RESULTS:** Among the 52 patients treated with ICIs, we found no significant difference in the objective response rate (ORR) between patients with a TMB above the 50th percentile ("TMB high") and those with a TMB at or below the 50th percentile ("TMB low"). The median progression-free survival (mPFS) and median overall survival (mOS) were significantly longer in patients with a high TMB compared to those with a low TMB (mPFS: 3.3 versus 1.2 months, HR: 0.37 [95% CI: 0.20-0.69],  $P < 0.01$ ; mOS: 10.4 versus 2.5 months, HR: 0.38 [95% CI: 0.19-0.77],  $P < 0.01$ ). The one-year PFS and OS rates improved with increasing mutational load when TMB was divided into tertiles. **CONCLUSIONS:** These findings show that targeted NGS, a readily available clinical diagnostic test, can be used to identify patients with SCLC who are most likely to benefit from treatment with immune checkpoint inhibitors.

**Relationships Between Smoking Status and Psychological Distress, Optimism, and Health Environment Perceptions at Time of Diagnosis of Actual or Suspected Lung Cancer.**

Choi SH1, Chan RR, Lehto RH. *Cancer Nurs.* 2019 Mar/Apr;42(2):156-163. doi: 10.1097/NCC.0000000000000579.

**BACKGROUND:** While much research and practice resources have addressed smoking cessation among cancer patients, less emphasis has been placed on personal psychological and environment factors associated with smoking at the time of diagnosis. **OBJECTIVE:** The aim of this study was to examine differences in psychological distress, optimism, and perceptions of the health environment/illness experience based on smoking status in patients with current, former, and no smoking history with newly diagnosed suspected or actual lung cancer. **METHODS:** Data were derived from a descriptive study of 52 patients (34 men and 18 women aged 37-83 years) undergoing diagnostic evaluation for actual or suspected lung cancer. Descriptive statistics were used to characterize data. Analysis of variance,  $\chi$ , and Spearman correlation tests were used to determine relationships among main study variables (smoking status, anxiety, worry, perceived cognitive functioning, optimistic outlook, health environment/illness experience perceptions). **RESULTS:** Current smoking status was associated with higher psychological distress (anxiety and worry) among patients facing a new suspected or actual cancer diagnosis. **CONCLUSIONS:** The study was able to provide important information relative to smoking status and psychological distress at the time of diagnosis of suspected or actual lung cancer. Findings demonstrate needs for assessment and targeted interventions to reduce psychological distress and to promote long-term adaptation in patients smoking at time of diagnosis. **IMPLICATIONS FOR PRACTICE:** Nurses are positioned to provide support and resources for cancer patients. It is critical that smoking cessation interventions also address nicotine craving, emotion regulation, and adaptive coping skills.

**Exercise Training in Patients With Non-Small Cell Lung Cancer During In-Hospital Chemotherapy Treatment: A RANDOMIZED CONTROLLED TRIAL.**

Rutkowska A1, Jastrzebski D, Rutkowski S, Żebrowska A, Stanula A, Szczegielniak J, Ziora D, Casaburi R. *J Cardiopulm Rehabil Prev.* 2019 Mar;39(2):127-133. doi: 10.1097/HCR.0000000000000410.

**PURPOSE:** The aim of this study was to perform a randomized trial to assess the impact of exercise training in patients with non-small cell lung cancer during chemotherapy on several outcomes in comparison to a control group (CG). **METHODS:** The exercise training group (ETG) consisted of 20 patients and the CG consisted of 10 patients. In the ETG, a 4-wk in-hospital exercise training program was performed in 2-wk cycles interspersed with consecutive rounds of chemotherapy with cytostatic drugs. The exercise training program was individualized and included warm-up, respiratory muscle exercise, training on a cycle ergometer or treadmill, and Nordic walking. CG participants were assessed before and after 6 wk of chemotherapy alone. **RESULTS:** Comparing pre- and post-intervention values, the ETG demonstrated an increase in 6-min walk distance ( $486 \pm 92$  vs  $531 \pm 103$  m,  $P = .01$ ). In a battery of physical performance tests: Up and Go Test ( $6.3 \pm 1.0$  vs  $6.0 \pm 1.1$  sec,  $P = .01$ ); chair stand ( $13.3 \pm 2.8$  vs  $14.3 \pm 3.4$  repetitions,  $P = .001$ ); and arm curl ( $18.4 \pm 3.1$  vs  $20.4 \pm 3.5$  repetitions,  $P = .001$ ) all improved significantly. Spirometry values also improved: FEV1 % predicted ( $76 \pm 16$  vs  $84 \pm 15$ ,  $P = .01$ ), FVC % predicted ( $87 \pm 14$  vs  $95 \pm 13$ ,  $P = .01$ ), and FEV1/FVC ( $73 \pm 13\%$  vs  $76 \pm 12\%$ ,  $P = .04$ ). The exercise training was well tolerated, without any adverse events due to exercise. There were no significant improvements in the CG. **CONCLUSIONS:** This study suggests that planned, individualized, and supervised exercise programs in patients with advanced lung cancer during chemotherapy are a practical and beneficial intervention for enhancing mobility and physical fitness.



### [Development and validation of the caregiver roles and responsibilities scale in cancer caregivers.](#)

Shilling V1, Starkings R2, Jenkins V2, Cella D3, Fallowfield L2. Qual Life Res. 2019 Mar 18. doi: 10.1007/s11136-019-02154-4. [Epub ahead of print]

**PURPOSE:** The caregiver roles and responsibilities scale (CRRS) was developed to facilitate formal assessment of broad life impacts for informal (i.e. unpaid) caregivers to people with cancer. Here we report the development and initial validation. **METHODS:** The CRRS was developed from the thematic analysis of two interview studies with cancer patients (stage III-IV breast, gynaecological, lung or melanoma) and caregivers. In the evaluation studies, participants completed the CRRS alongside the Caregiver Quality of Life-Cancer, the main criterion measure for concurrent validity, and the WHOQOL-BREF for additional convergent validity data. Questionnaires were completed at baseline, 7-days and 2-months. Demographic data and patient characteristics were collected at baseline. **RESULTS:** Two-hundred and forty-five caregivers to people with stage I-IV breast, colorectal, gynaecological, head and neck, lung or renal cancer or melanoma completed the CRRS at least once. The final 41 core items selected comprised five subscales: Support and Impact, Lifestyle, Emotional Health and Wellbeing, Self-care and Financial Wellbeing as well as three standalone items. Missing data rate was low (0.6%); there were no ceiling or floor effects for total scores. Cronbach's alpha was 0.92 for the CRRS-41; 0.75-0.87 for the subscales. CRRS showed good test-retest reliability (ICC = 0.91), sensitivity to change and the predicted pattern of correlation with validation measures  $r = 0.75-0.89$ . The standalone 7-item jobs and careers subscale requires further validation. **CONCLUSIONS:** Initial evaluation shows the CRRS has good validity and reliability and is a promising tool for the assessment of the effects of cancer and cancer treatment on the lives and wellbeing of informal caregivers.

[Evaluation of the quality of life after surgical removal of lung cancer.](#) Szeliga E1, Czenczek-Lewandowska E2, Kontek A1, Wolan-Nieroda A1, Guzik A1, Walicka-Cupryś K1. Adv Respir Med. 2019 Mar 4. doi: 10.5603/ARM.a2019.0003. [Epub ahead of print]

**BACKGROUND:** Morbidity and mortality attributed to lung cancer remain at high levels, especially where men are concerned. The surgery for lung cancer involves removing neoplastic lesions in order to save the largest possible part of the healthy lung. Of importance is also pre- and post-surgical rehabilitation. The aim of this thesis is to gauge the quality of life of patients who have had their lung cancer surgically removed. **METHODS:** The study was conducted on 72 patients (52 men and 20 women). The patients were examined prior to, a week after and six months following surgery. The investigation employed the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires, as well as a visual analogue pain scale (VAS). **RESULTS:** The study confirmed a decreased quality of life in all of the investigated domains. The only visible improvement over a span of six months following the surgery was observed in the (overall) symptom scale ( $p=0.0312$ ). The functional scale and the symptomatic scale for lung cancer patients improved slightly ( $p=1.0000$ ). **CONCLUSION:** In comparison to the pre-surgical period, the quality of patients' lives after surgical removal of lung cancer decreased drastically. After six months the situation improved slightly; however, the patients did not return to their pre-surgical state.

[Palliative Radiation Therapy for Vertebral Metastases and Metastatic Cord Compression in Patients Treated With Anti-PD-1 Therapy.](#) Fareed MM1, Pike LRG1, Bang A2, et al. Front Oncol. 2019 Mar 29;9:199. doi: 10.3389/fonc.2019.00199. eCollection 2019.

**BACKGROUND:** There is increasing use of immune checkpoint blockade (ICB) across multiple cancer types, including in patients at risk for vertebral metastases and cord compression. These patients are often treated with palliative radiotherapy (PRT); however, data evaluating the combination of PRT and ICB in patients with vertebral metastases is limited. Furthermore, patients with cord compression are generally excluded from prospective clinical trials. Therefore, we retrospectively evaluated outcomes following PRT and PD-1 inhibition in patients with vertebral metastases. **METHODS:** We performed a

retrospective chart review of 37 consecutive patients (total 57 lesions) treated with radiation for vertebral metastases who also received PD-1 inhibition. Patient, treatment and outcomes data were abstracted from the medical records. **RESULTS:** Histologies included non-small cell lung cancer (n = 21), renal cell carcinoma (n = 9) and melanoma (n = 7). Out of 57 lesions, 18 involved >1 segments of the vertebral column. There were isolated lesions in thoracic (16), lumbar (9), cervical (6), and sacral (8) vertebrae. Presenting symptoms included pain (19), numbness (10), and weakness (3). Eleven patients were asymptomatic. Radiologic cord compression was present in 12, epidural extension in 28 and compression fracture in 14. Eleven patients underwent surgical decompression prior to the onset of RT. Median radiation dose was 24 Gy (range 8-30 Gy). Stereotactic radiation was delivered in 4 patients; 33 patients received conformal RT. 21 patients received PD-1 inhibition after RT, 9 before RT and 7 with RT. Seven patients received concurrent CTLA-4 inhibitors with anti-PD-1 therapy. Treatment was in general well-tolerated. Toxicities included fatigue (6), transient pain flare (1), nausea/vomiting (1) and G1 skin changes (1). All patients reported some degree of pain relief. Numbness/weakness was improved in 6 of 13 patients with baseline symptoms (46%) and this was more likely in patients that received vertebral radiation after starting PD-1 inhibitors (71 vs. 17%, p = 0.04). Most patients (22 of 33 evaluable patients, 67%) had stability of irradiated lesions on subsequent follow up imaging performed at median of 30 days from RT, whereas 3 had a complete local response and 4 had a partial local response. **CONCLUSIONS:** We demonstrate that PRT administered to vertebral metastases was well-tolerated and effective in patients treated with PD-1 inhibitors. There was an encouraging rate of pain reduction and neurological improvement.

[Systematic screening and assessment of psychosocial well-being and care needs of people with cancer.](#) Schouten B1, Avau B, Bekkering GTE, Vankrunkelsven P, Mebis J, Hellings J, Van Hecke A. Cochrane Database Syst Rev. 2019 Mar 26;3:CD012387. doi: 10.1002/14651858.CD012387.pub2.

**BACKGROUND:** Receiving a diagnosis of cancer and the subsequent related treatments can have a significant impact on an individual's physical and psychosocial well-being. To ensure that cancer care addresses all aspects of well-being, systematic screening for distress and supportive care needs is recommended. Appropriate screening could help support the integration of psychosocial approaches in daily routines in order to achieve holistic cancer care and ensure that the specific care needs of people with cancer are met and that the organisation of such care is optimised. **OBJECTIVES:** To examine the effectiveness and safety of screening of psychosocial well-being and care needs of people with cancer. To explore the intervention characteristics that contribute to the effectiveness of these screening interventions. **SEARCH METHODS:** We searched five electronic databases in January 2018: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO, and CINAHL. We also searched five trial registers and screened the contents of relevant journals, citations, and references to find published and unpublished trials. **SELECTION CRITERIA:** We included randomised controlled trials (RCTs) and non-randomised controlled trials (NRCTs) that studied the effect of screening interventions addressing the psychosocial well-being and care needs of people with cancer compared to usual care. These screening interventions could involve self-reporting of people with a patient-reported outcome measures (PROMs) or a semi-structured interview with a screening interventionist, and comprise a solitary screening intervention or screening with guided actions. We excluded studies that evaluated screening integrated as an element in more complex interventions (e.g. therapy, coaching, full care pathways, or care programmes). **DATA COLLECTION AND ANALYSIS:** Two review authors independently extracted the data and assessed methodological quality for each included study using the Cochrane tool for RCTs and the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool for NRCTs. Due to the high level of heterogeneity in the included studies, only three were included in meta-analysis. Results of the remaining 23 studies were analysed narratively.

**MAIN RESULTS:** We included 26 studies (18 RCTs and 8 NRCTs) with sample sizes of 41 to 1012 participants, involving a total of 7654 adults with cancer. Two studies included only men or women; all other studies included both sexes. For most studies people with breast, lung, head and neck, colorectal, prostate cancer, or several of these diagnoses were included; some studies included people with a broader range of cancer diagnosis. Ten studies focused on a solitary screening intervention, while the remaining 16 studies evaluated a screening intervention combined with guided actions. A broad range of intervention instruments was used, and were described by study authors as a screening of health-related quality of life (HRQoL), distress screening, needs assessment, or assessment of biopsychosocial symptoms or overall well-being. In 13 studies, the screening was a self-reported questionnaire, while in the remaining 13 studies an interventionist conducted the screening by interview or paper-pencil assessment. The interventional screenings in the studies were applied 1 to 12 times, without follow-up or from 4 weeks to 18 months after the first interventional screening. We assessed risk of bias as high for eight RCTs, low for five RCTs, and unclear for the five remaining RCTs. There were further concerns about the NRCTs (1 = critical risk study; 6 = serious risk studies; 1 = risk unclear). Due to considerable heterogeneity in several intervention and study characteristics, we have reported the results narratively for the majority of the evidence. In the narrative synthesis of all included studies, we found very low-certainty evidence for the effect of screening on HRQoL (20 studies). Of these studies, eight found beneficial effects of screening for several subdomains of HRQoL, and 10 found no effects of screening. One study found adverse effects, and the last study did not report quantitative results. We found very low-certainty evidence for the effect of screening on distress (16 studies). Of these studies, two found beneficial effects of screening, and 14 found no effects of screening. We judged the overall certainty of the evidence for the effect of screening on HRQoL to be very low. We found very low-certainty evidence for the effect of screening on care needs (seven studies). Of these studies, three found beneficial effects of screening for several subdomains of care needs, and two found no effects of screening. One study found adverse effects, and the last study did not report quantitative results. We judged the overall level of evidence for the effect of screening on HRQoL to be very low. None of the studies specifically evaluated or reported adverse effects of screening. However, three studies reported unfavourable effects of screening, including lower QoL, more unmet needs, and lower satisfaction. Three studies could be included in a meta-analysis. The meta-analysis revealed no beneficial effect of the screening intervention on people with cancer HRQoL (mean difference (MD) 1.65, 95% confidence interval (CI) -4.83 to 8.12, 2 RCTs, 6 months follow-up); distress (MD 0.0, 95% CI -0.36 to 0.36, 1 RCT, 3 months follow-up); or care needs (MD 2.32, 95% CI -7.49 to 12.14, 2 RCTs, 3 months follow-up). However, these studies all evaluated one specific screening intervention (CONNECT) in people with colorectal cancer. In the studies where some effects could be identified, no recurring relationships were found between intervention characteristics and the effectiveness of screening interventions. **AUTHORS' CONCLUSIONS:** We found low-certainty evidence that does not support the effectiveness of screening of psychosocial well-being and care needs in people with cancer. Studies were heterogeneous in population, intervention, and outcome assessment. The results of this review suggest a need for more uniformity in outcomes and reporting; for the use of intervention description guidelines; for further improvement of methodological certainty in studies and for combining subjective patient-reported outcomes with objective outcomes.

**[Patient reported outcomes for cancer patients receiving immunotherapy: opportunities for palliative care - A Systematic Review.](#)**

Hall ET1, Singhal S2, Dickerson J2, Gabster B2, Wong HN3, Aslakson RA4, Schapira L5. *J Pain Symptom Manage.* 2019 Mar 21. pii: S0885-3924(19)30132-0. doi: 10.1016/j.jpainsymman.2019.03.015. [Epub ahead of print]

**CONTEXT:** Immune checkpoint inhibitors (ICIs) are increasingly used to treat a variety of cancers, but comparatively little is known about patient-reported outcomes (PROs) and health-related quality of life (HRQoL) among patients receiving these novel therapies. **OBJECTIVES:** We performed a systematic

review to examine PROs and HRQoL among cancer patients receiving ICIs as compared to other anticancer therapies. **METHODS:** We systematically searched PubMed, CINAHL, Embase, Web of Science, and Scopus, using search terms representing ICIs, PROs and HRQoL on August 10, 2018. Eligible articles were required to involve cancer patients treated with ICIs and to report PROs and/or HRQoL data. **RESULTS:** We screened 1,453 references and included 15 publications representing 15 randomized controlled trials in our analysis. Studies included several cancer types (melanoma, lung cancer, genitourinary cancer, and head/neck cancer), utilized four different ICIs (nivolumab, pembrolizumab, atezolizumab, and ipilimumab), and compared ICIs to a wide range of therapies (chemotherapy, targeted therapies, other immunotherapy strategies, and placebo). Studies utilized a total of seven different PROs to measure HRQoL, most commonly the European Organisation for the Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30) (n = 12, 80%). PRO data were reported in a variety of formats and at a variety of time points throughout treatment which made direct comparison challenging. Some trials (n=11, 73%) reported PROs on specific symptoms. In general, patients receiving ICIs had similar to improved HRQoL and experiences when compared to other therapies. **CONCLUSION:** Despite the broad clinical trials experience of ICI therapies across cancer types, relatively few randomized studies reported patient PROs and HRQoL data. Available data suggest that ICIs are well-tolerated in terms of HRQoL compared to other anticancer therapies although the conclusions are limited by the heterogeneity of trial designs and outcomes. Currently used instruments may fail to capture important symptomatology unique to ICIs, underscoring a need for PROs designed specifically for ICIs.

#### **Quality of Life in Patients with Advanced Non-Small-Cell Lung Cancer Receiving Palliative Chemotherapy.**

Daroszewski C1, Stasiewicz M2, Jaźwińska-Tarnawska E3, et al. *Adv Exp Med Biol.* 2019 Mar 2. doi: 10.1007/5584\_2019\_346. [Epub ahead of print]

The goal of this study was to explore quality of life in patients with advanced non-small-cell lung cancer (NSCLC) in an attempt to single out features that could help predict the possibility of non-completion of chemotherapy. The survey tool was the Quality of Life Questionnaire Core-30 (QLQ-C30) with the module Lung Cancer 13 (LC-13) developed by the European Organization for Research and Treatment of Cancer. The assessment of quality of life (QoL) was performed in 58 patients with advanced NSCLC before palliative chemotherapy and it was repeated in 43 patients who completed at least three cycles of chemotherapy. We found that the patients who failed to complete the chemotherapy course distinctly showed, in contradistinction to those who completed it, poor physical functioning in ( $67.6 \pm 16.3$  vs.  $78.3 \pm 21.3$  points, respectively,  $p < 0.05$ ) and the lack of appetite ( $27.1 \pm 38.0$  vs.  $48.9 \pm 37.5$  points, respectively  $p < 0.05$ ). At the end of palliative chemotherapy alopecia, sore throat, and constipation significantly worsened QoL, but global health status remained unchanged. In conclusion, poor physical functioning and loss of appetite seem to harbingers a risk of non-completion of chemotherapy in advanced NSCLC.

#### **Holistic Needs of People with Thoracic Cancer Identified by the Sheffield Profile for Assessment and Referral to Care Questionnaire©.**

Wilcock A1, Hussain A2, Maddocks M2. *J Palliat Med.* 2019 Mar 8. doi: 10.1089/jpm.2018.0540. [Epub ahead of print]

**BACKGROUND:** A holistic needs assessment is recommended in people with cancer at key stages, including soon after diagnosis. For people with thoracic cancer, there is a lack of data obtained routinely at this time point. **OBJECTIVE:** To identify the most common and/or distressing supportive and palliative needs present soon after diagnosis using a specifically developed questionnaire. **METHODS:** As part of a local rehabilitation service, patients within three to six weeks of a diagnosis of thoracic cancer were invited to complete the Sheffield Profile for Assessment and Referral to Care (SPARC©) questionnaire. **RESULTS:** For a 26-month period, 738 patients completed the questionnaire, representing



about 70% of all patients diagnosed with thoracic cancer during this time. Respondents had a median [interquartile range] of 15 (11-21) symptoms or issues, with 2 (0-5), 4 (2-7), and 7 (5-11) causing "very much," "quite a bit," and "a little" distress or bother, respectively. The top five most frequent needs causing any degree of distress or bother were physical, present in 68%-80% of patients: feeling tired, shortness of breath, cough, feeling sleepy in the day, changes in weight. Two psychological issues followed: worrying about effects of the illness on others, feeling anxious, both present in 67%. Despite most patients reporting talking to health professionals about their condition, 20%-30% wanted further information. **CONCLUSIONS:** These findings represent the largest cohort of patients with thoracic cancer completing the SPARC questionnaire soon after diagnosis, and provide detailed information on the high level of need that thoracic oncology services must be able to respond to.

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## COMPLEMENTARY & ALTERNATIVE THERAPY

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[TCM therapies combined with chemotherapy for preventing recurrence and metastasis in postoperative II to IIIA NSCLC: A protocol for a systematic review and meta-analysis.](#) Chen S1,2, Zhang Z1,2, Zhang X2, et al. *Medicine (Baltimore)*. 2019 Mar;98(9):e14724. doi: 10.1097/MD.00000000000014724.

**BACKGROUND:** Traditional Chinese Medicine (TCM) therapies have been combined with chemotherapy for preventing Recurrence and metastasis in postoperative II to IIIA non-small-cell lung cancer (NSCLC) and the associated better disease-free survival (DFS), but its effects remain elusive. The purpose of this review is to assess the efficacy of TCM therapies as a treatment for postoperative II to IIIA NSCLC. **METHODS AND ANALYSIS:** Seventh databases will be searched for relevant studies from inception to the present date. We will include randomized controlled trials assessing TCM therapies combined with chemotherapy for preventing Recurrence and metastasis in postoperative II to IIIA NSCLC. The methodological qualities, including the risk of bias, will be evaluated using the Cochrane risk of bias assessment tool, while confidence in the cumulative evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. **ETHICS AND DISSEMINATION:** Ethical approval is not required, as this study is based on the review of published research. This review will be published in a peer-reviewed journal and disseminated both electronically and in print. **PROSPERO REGISTRATION NUMBER:** The protocol for this systematic review has been registered on PROSPERO under the number CRD42019116594.

[Network analysis and mechanisms of action of Chinese herb-related natural compounds in lung cancer cells.](#) Lin YJ1, Liang WM2, Chen CJ3, et al. *Phytomedicine*. 2019 Mar 13;58:152893. doi: 10.1016/j.phymed.2019.152893. [Epub ahead of print]

**BACKGROUND:** Chinese herbal medicines (CHMs) are a resource of natural compounds (ingredients) and their potential chemical derivatives with anticancer properties, some of which are already in clinical use. Bei-Mu (BM), Jie-Geng (JG), and Mai-Men-Dong-Tang (MMDT) are important CHMs prescribed for patients with lung cancer that have improved the survival rate. **HYPOTHESIS/PURPOSE:** The aim of this study was to systemically investigate the mechanisms of action of these CHM products in lung cancer cells. **METHODS:** We used a network pharmacology approach to study CHM product-related natural compounds and their lung cancer targets. In addition, the underlying anti-lung cancer effects of the natural compounds on apoptosis, cell cycle progression, autophagy, and the expression of related proteins was investigated in vitro. **RESULTS:** Ingredient-lung cancer target network analysis identified 20 natural compounds. Three of these compounds, ursolic acid, 2-(3R)-8,8-dimethyl-3,4-dihydro-2H-pyrano(6,5-f)chromen-3-yl)-5-methoxyphenol, and licochalcone A, inhibited the proliferation of A549 lung cancer cells in a dose-dependent manner. Signal pathway analyses suggested that these three ingredients may target cellular apoptosis, anti-apoptosis, and cell cycle-related proteins. These three ingredients induced

apoptosis through the regulation of the expression of apoptotic and anti-apoptotic proteins, including B-cell lymphoma-2 and full-length and cleaved poly(ADP-ribose) polymerase proteins. They also induced cell cycle arrest in S and G2/M phases and autophagy in A549 cells. **CONCLUSION:** The pharmacological mechanisms of ingredients from MMDT on lung cancer may be strongly associated with their modulatory effects on apoptosis, autophagy, cell cycle progression, and cell proliferation.

**Herbal Medicines for Irinotecan-Induced Diarrhea.** Tang L1, Li X1, Wan L1, Xiao Y1, Zeng X1, Ding H1. *Front Pharmacol.* 2019 Mar 29;10:182. doi: 10.3389/fphar.2019.00182. eCollection 2019. Irinotecan (CPT-11), a water-soluble derivative of camptothecin, belongs to the class of DNA topoisomerase I inhibitors and has been approved worldwide for the treatment of advanced colorectal cancer, lung cancer, and malignant lymphoma. Although CPT-11-based chemotherapy is widely used, severe gastrointestinal (GI) toxicity, especially late-onset diarrhea, is a common adverse reaction, limiting clinical application of the drug. The incidence of grade 3 or 4 diarrhea is high, with 20-40% of CPT-11-treated patients experiencing this adverse effect. High-dose loperamide and octreotide are generally recommended for treatment of CPT-11-induced diarrhea. However, in clinical practice, loperamide is associated with a significant failure rate and the beneficial effects of octreotide are controversial. An accumulating number of recent studies have suggested that medicinal herbs and their derived phytochemicals may be effective complementary treatments for CPT-11-induced diarrhea. In this mini-review, we briefly summarize currently available literatures regarding the formulae and herbs/natural products used as adjuvants in animal and clinical studies for the treatment of diarrhea caused by CPT-11.

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## MISCELLANEOUS WORKS

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**Early-Stage NSCLC: Advances in Thoracic Oncology 2018.** Osarogiagbon RU1, Veronesi G2, Fang W3, Ekman S4, Suda K5, Aerts JG6, Donington J7. *J Thorac Oncol.* 2019 Mar 7. pii: S1556-0864(19)30199-6. doi: 10.1016/j.jtho.2019.02.029. [Epub ahead of print] 2018 was a banner year for all thoracic oncology, but especially for early-stage NSCLC. Three seminal events occurred in the approximately 18 months from mid-2017 to the end of 2018: in June 2017 at the American Society of Clinical Oncology Annual Meeting a small, relatively unheralded study from Max Diehn's group at Stanford University reported on the use of a novel "cancer personalized profiling by deep sequencing" circulating tumor-DNA technology to identify minimal residual disease in patients after curative-intent radiation or surgery for NSCLC; in April 2018 at the American Association for Cancer Research Annual Meeting, Drew Pardoll presented a small pilot study of 21 patients who had received two doses of preoperative nivolumab; in September 2018, at the 19th World Conference on Lung Cancer, Harry J. De Koning presented the long-awaited results of the Dutch-Belgian Lung Cancer Screening Trial (NELSON). These three seminal studies, along with others which are reviewed in this paper, promise to accelerate our progress towards a world in which lung cancer is identified early, more patients undergo curative-intent treatment that achieves the promised cure, and those at risk for failure after treatment are identified early, when the cancer remains most vulnerable. The day is around the corner when lung cancer is defanged and no longer the worldwide terror it currently is. We herein present an overview of the most recent body of work that moves us inexorably towards that day.

**Association of Expanded VA Hospice Care With Aggressive Care and Cost for Veterans With Advanced Lung Cancer.** Mor V1,2, Wagner TH3,4,5, Levy C6,7, et al. *JAMA Oncol.* 2019 Mar 28. doi: 10.1001/jamaoncol.2019.0081. [Epub ahead of print]

**IMPORTANCE:** Medicare hospice beneficiaries discontinue disease-modifying treatments because the hospice benefit limits access. While veterans have concurrent access to hospice care and Veterans Affairs (VA) Medical Center (VAMC)-provided treatments, the association of this with changes in treatment and

costs of veterans' end-of-life care is unknown. **OBJECTIVE:** To determine whether increasing availability of hospice care, without restrictions on disease-modifying treatments, is associated with reduced aggressive treatments and medical care costs at the end of life. **DESIGN, SETTING, AND PARTICIPANTS:** A modified difference-in-difference study design, using facility fixed effects, compared patient outcomes during years with relatively high vs lower hospice use. This study evaluated 13 085 veterans newly diagnosed with stage IV non-small cell lung cancer (NSCLC) from 113 VAMCs with a minimum of 5 veterans diagnosed with stage IV NSCLC per year, between 2006 and 2012. Data analyses were conducted between January 2017 and July 2018. **EXPOSURES:** Using VA inpatient, outpatient, pharmacy claims, and similar Medicare data, we created VAMC-level annual aggregates of all patients who died of cancer for hospice use, cancer treatment, and/or concurrent receipt of both in the last month of life, dividing all VAMC years into quintiles of exposure to hospice availability. **MAIN OUTCOMES AND MEASURES:** Receipt of aggressive treatments (2 or more hospital admissions within 30 days, tube feeding, mechanical ventilation, intensive care unit [ICU] admission) and total costs in the first 6 months after diagnosis. **RESULTS:** Of the 13 085 veterans included in the study, 12 858 (98%) were men; 10 531 (81%) were white, and 5949 (46%) were older than 65 years. Veterans with NSCLC treated in a VAMC in the top hospice quintile (79% hospice users), relative to the bottom quintile (55% hospice users), were more than twice as likely to have concurrent cancer treatment after initiating hospice care (adjusted odds ratio [AOR], 2.28; 95% CI, 1.67-3.31). Nonetheless, for veterans with NSCLC seen in VAMCs in the top hospice quintile, the AOR of receiving aggressive treatment in the 6 months after diagnosis was 0.66 (95% CI, 0.53-0.81), and the AOR of ICU use was 0.78 (95% CI, 0.62-0.99) relative to patients seen in VAMCs in the bottom hospice quintile. The 6-month costs were lower by an estimated \$266 (95% CI, -\$358 to -\$164) per day for the high-quintile group vs the low-quintile group. There was no survival difference. **CONCLUSIONS AND RELEVANCE:** Increasing the availability of hospice care without restricting treatment access for veterans with advanced lung cancer was associated with less aggressive medical treatment and significantly lower costs while still providing cancer treatment.

### [Impact of estrogen monotherapy on survival in women with stage III-IV non-small cell lung cancer.](#)

Heilbroner SP1, Xanthopoulos EP2, Buono D3, et al. *Lung Cancer*. 2019 Mar;129:8-15. doi: 10.1016/j.lungcan.2018.12.021. Epub 2018 Dec 24.

**OBJECTIVES:** Women with lung cancer have better survival than men. The reasons are unknown, but estrogen is hypothesized to improve survival. Our objective was to examine the association between estrogen monotherapy and cancer-specific and overall survival in elderly women with non-small cell lung cancer (NSCLC). **MATERIALS AND METHODS:** We used the SEER-Medicare database to identify women  $\geq 65$  years old who were diagnosed with stage III or IV NSCLC. Estrogen monotherapy (EM) was defined as at least one estrogen claim without any progesterone claims 6 months prior to diagnosis. To assess cancer-specific survival and overall survival, we used Kaplan-Meier and multivariate Cox modeling with propensity score adjustments. As an exploratory analysis, we also examined the effect of combined estrogen and progesterone hormonal therapy on survival using Cox modeling. **RESULTS:** We identified 6958 women in our initial cohort: 283 used EM (4%) and 6675 (96%) did not. The median follow-up time was 46.5 months in the EM patients and 49.5 months in the non-EM patients. In a Kaplan-Meier analysis, median overall survival was 8.2 months in patients who receive EM and 6.2 months in those who did not ( $p = 0.004$ ). In our 1:4 propensity-matched cohort, median follow-up was 46.5 in the EM group and 50.6 in the non-EM group; median overall survival was 8.0 months in the EM group and 6.4 months in the non-EM group ( $p = 0.02$ ). In a multivariate Cox regression of the matched cohort, EM was significantly associated with overall survival (HR 0.84; 95% CI 0.73 - 0.97). All results were similar for cancer-specific survival. In our exploratory analysis, combined Estrogen-Progesterone did significantly impact overall survival (HR 0.84; 95% CI 0.71-0.99,  $p = 0.04$ ) but did not appear to effect

cancer-specific survival (HR 0.91; 95% CI 0.77-1.09, p = 0.30). **CONCLUSION:** EM was associated with a significant improvement in cancer-specific survival and overall survival in women with late stage NSCLC.

**Lung cancer survival among never smokers.** Casal-Mouriño A1, Valdés L2, Barros-Dios JM3, Ruano-Ravina A4. *Cancer Lett.* 2019 Jun 1;451:142-149. doi: 10.1016/j.canlet.2019.02.047. Epub 2019 Mar 6. Lung cancer incidence among never smokers has increased in recent decades with 10-30% of all lung cancers occurring in never smokers, where exposure to residential radon is the leading cause of this disease. Lung cancer survival is low, ranging from 12% to 16% at 5 years of diagnosis. There is scant evidence to date on survival from this disease in never smokers. We aim to evaluate lung cancer survival in never smokers and ascertain whether there might be differences regarding smokers, through a systematic review applying predefined inclusion and exclusion criteria. 17 Studies were included. Never-smoker lung cancer patients seem to experience longer survival times than do smokers or ex-smokers. Lung cancer in never smokers displays distinctive clinical characteristics, is more frequent among women, is diagnosed at more advanced stages, and the predominant histologic type is adenocarcinoma. Further studies are necessary to ascertain lung cancer survival among never smokers.

**Impact of Primary Care Access on Mortality of Lung Cancer Patients in an Underserved Community.** Su CT1,2, Chau V1, Halmos B3, Shah CD1, et al. *Am J Clin Oncol.* 2019 Mar;42(3):298-303. doi: 10.1097/COC.0000000000000516.

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

**Natural history, clinical course and predictors of interval time from initial diagnosis to development of subsequent NSCLC brain metastases.** Smith DR1, Bian Y1, Wu CC1, et al. *J Neurooncol.* 2019 Mar 14. doi: 10.1007/s11060-019-03149-4. [Epub ahead of print]

**PURPOSE:** Non-small cell lung cancer (NSCLC) brain metastases are associated with substantial morbidity and mortality. During recent years, accompanying dramatic improvements in systemic disease control, NSCLC brain metastases have emerged as an increasingly relevant clinical problem. However, optimal surveillance practices remain poorly defined. This purpose of this study was to further



characterize the natural history, clinical course and risk factors associated with earlier development of subsequent NSCLC brain metastases to better inform clinical practice and help guide survivorship care. **METHODS:** We retrospectively reviewed all institutional NSCLC brain metastasis cases treated with radiotherapy between 1997 and 2015. Exclusion criteria included presence of brain metastases at initial NSCLC diagnosis and incomplete staging information. Interval time to brain metastases and subsequent survival were characterized using Kaplan-Meier and multivariate Cox regression analyses. **RESULTS:** Among 105 patients within this cohort, median interval time to development of brain metastases was 16 months. Median interval times were 29, 19, 16 and 13 months for Stage I-IV patients, respectively ( $P = 0.016$ ). Additional independent predictors for earlier development of NSCLC brain metastases included non-adenocarcinomatous histopathology (HR 3.036,  $P < 0.001$ ), no prior surgical resection (HR 1.609,  $P = 0.036$ ) and no prior systemic therapy (HR 3.560,  $P = 0.004$ ). Median survival following intracranial progression was 16 months. Delayed development of brain metastases was associated with better prognosis (HR 0.970,  $P < 0.001$ ) but not survival following intracranial disease onset. **CONCLUSIONS:** Collectively, our results provide valuable insights into the natural history of NSCLC brain metastases. NSCLC stage, histology, prior surgical resection and prior systemic therapy emerged as independent predictors for interval time to brain metastases.

[The impact of copay assistance on patient out-of-pocket costs and treatment rates with ALK inhibitors.](#) Seetasith A1, Wong W2, Tse J3, Burudpakdee C1. *J Med Econ.* 2019 May;22(5):414-420. doi: 10.1080/13696998.2019.1580200. Epub 2019 Mar 1.

**INTRODUCTION:** The patient cost burden of oral anticancer medicines has been associated with prescription abandonment, delayed treatment initiation, and poorer health outcomes in the US. Since 2011, several small molecule tyrosine kinase inhibitors have been approved for the treatment of non-small cell lung cancer (NSCLC) patients with rearrangement of the anaplastic lymphoma kinase (ALK) gene. The objective of this study was to measure the impact of copay assistance on patient cost sharing and treatment patterns in patients prescribed oral ALK inhibitors (ALKi's). **METHODS:** Patterns of claims approval/rejection and payment/reversal, out-of-pocket (OOP) costs, and treatment persistence were reported for patients identified in the IQVIA Formulary Impact Analyzer database from January 2013 to August 2017 linked to a medical claims database. The primary study cohorts were patients with copay assistance, including manufacturer's copay cards, other discount cards, or free-trial vouchers, on the index ALKi claim, and patients without copay assistance at any time during the follow-up period. **RESULTS:** In total, 3,143 patients were included in analyses related to claim patterns, and 1,685 patients were included in analyses related to treatment persistence. Copay assistance decreased the OOP cost for the first approved ALKi by \$1,930, on average. Patients with copay assistance picked up ALKi prescriptions from the pharmacy sooner than patients without copay assistance (2.6 days vs 25.7 days). In adjusted analyses, patients with copay assistance had 88.2% lower risk of abandoning their first approved prescription and 24.3% lower risk of discontinuing treatment with the first observed ALKi (all  $p < 0.001$ ). **CONCLUSION:** Copay assistance reduced the patient cost burden for ALKi's and was associated with patients picking up their ALKi prescriptions, beginning ALKi treatment sooner, and remaining on treatment.

[Lung Cancer Patient Perceptions of the Value of an Outreach Thoracic Surgical Clinic.](#) Mohammad Z1, Mitchell KG1, Nelson DB1, Robb C1, Jreissaty C1, Tu J1, Vaporciyan AA1, Sepesi B1, Antonoff MB2. *Ann Thorac Surg.* 2019 Mar 27. pii: S0003-4975(19)30415-1. doi: 10.1016/j.athoracsur.2019.02.059. [Epub ahead of print]

**BACKGROUND:** While specialty outreach clinics have been associated with improved outcomes and access to care, their role for patients with non-small cell lung cancer (NSCLC) has not been described. We sought to characterize perceptions of the utility of a specialty outreach clinic among patients with

suspected NSCLC. **METHODS:** Surveys were administered to patients who were suspected to have NSCLC and were seen at an outreach thoracic surgery clinic (2016-2017). The clinic was located approximately 20 miles from the academic cancer center. **RESULTS:** 69 patients completed surveys. The median distance traveled to the clinic was 43.5 miles (IQR 5.0-111.3). Among patients traveling  $\geq 50$  miles, the overwhelming majority (27/32, 84.4%) cited physician expertise as the primary benefit of treatment at the clinic. Moreover, compared to patients living in closer proximity, they were more willing to travel  $\geq 100$  miles to have surgery (71.0% vs 26.7%,  $p=0.001$ ) or to consult with a surgeon (71.0% vs 25.8%,  $p<0.001$ ). Patients for whom it was very important to receive care close to home (33/68, 48.5%) were less willing to travel  $\geq 100$  miles for consultation [surgeon (33.3% vs 65.6%,  $p=0.011$ ); medical oncologist (33.3% vs 65.6%,  $p=0.011$ ); radiation oncologist (33.3% vs 64.5%,  $p=0.015$ )] and for treatment [surgery (33.3% vs 65.6%,  $p=0.011$ ); chemotherapy (36.7% vs 60.7%,  $p=0.067$ ); radiotherapy (33.3% vs 64.3%,  $p=0.018$ )]. **CONCLUSIONS:** Many patients value receiving oncologic care close to home and are sensitive to distance required to travel for care. Thoracic surgical outreach clinics may provide a benefit for lung cancer patients in the settings of initial consultation, preoperative, and postoperative care.