



## Caring Ambassadors Lung Cancer Program Literature Review, December 2020

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### SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

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**[Update 2020: Management of Non-Small Cell Lung Cancer](#)** Lung. 2020 Dec;198(6):897-907. doi: 10.1007/s00408-020-00407-5. Epub 2020 Nov 11. Mariam Alexander 1 , So Yeon Kim 2 , Haiying Cheng 3

The past decade has seen a revolution of new advances in the management of non-small cell lung cancer (NSCLC) with remarkable progresses in screening, diagnosis, and treatment. The advances in systemic treatment have been driven primarily by the development of molecularly targeted therapeutics, immune checkpoint inhibitors, and anti-angiogenic agents, all of which have transformed this field with significantly improved patient outcomes. This review will address updates in lung cancer screening, liquid biopsy, and immunotherapy in the front-line setting. We discuss recent advances and highlight the plethora of new approvals of molecular-targeted therapy for subgroups of NSCLC patients with sensitizing EGFR, ALK, ROS1, RET, BRAF V600E, MET, and NTRK alterations.

**[Disparities of National Lung Cancer Screening Guidelines in the US Population](#)** J Natl Cancer Inst. 2020 Nov 1;112(11):1136-1142. doi: 10.1093/jnci/djaa013. Summer S Han 1 2 3 , Eric Chow 1 , Kevin Ten Haaf 4 , Iakovos Toumazis 5 6 , Pianpian Cao 7 , Mehrad Bastani 5 6 , Martin Tammemagi 8 , Jihyoun Jeon 7 , Eric J Feuer 9 , Rafael Meza 7 , Sylvia K Plevritis 2 5 6

**BACKGROUND:** Current US Preventive Services Task Force (USPSTF) lung cancer screening guidelines are based on smoking history and age (55-80 years). These guidelines may miss those at higher risk, even at lower exposures of smoking or younger ages, because of other risk factors such as race, family history, or comorbidity. In this study, we characterized the demographic and clinical profiles of those selected by risk-based screening criteria but were missed by USPSTF guidelines in younger (50-54 years) and older (71-80 years) age groups. **METHODS:** We used data from the National Health Interview Survey, the CISNET Smoking History Generator, and results of logistic prediction models to simulate lifetime lung cancer risk-factor data for 100 000 individuals in the 1950-1960 birth cohorts. We calculated age-specific 6-year lung cancer risk for each individual from ages 50 to 90 years using the PLCOm2012 model and evaluated age-specific screening eligibility by USPSTF guidelines and by risk-based criteria (varying thresholds between 1.3% and 2.5%). **RESULTS:** In the 1950 birth cohort, 5.4% would have

been ineligible for screening by USPSTF criteria in their younger ages but eligible based on risk-based criteria. Similarly, 10.4% of the cohort would be ineligible for screening by USPSTF in older ages. Notably, high proportions of blacks were ineligible for screening by USPSTF criteria at younger (15.6%) and older (14.2%) ages, which were statistically significantly greater than those of whites (4.8% and 10.8%, respectively;  $P < .001$ ). Similar results were observed with other risk thresholds and for the 1960 cohort. **CONCLUSIONS:** Further consideration is needed to incorporate comprehensive risk factors, including race and ethnicity, into lung cancer screening to reduce potential racial disparities.

### **Can a Broad Molecular Screen Based on Circulating Tumor DNA Aid in Early Cancer Detection?**

J Appl Lab Med. 2020 Nov 1;5(6):1372-1377. doi: 10.1093/jalm/jfaa138. Clare Fiala 1 , Eleftherios P Diamandis 1 2 3

Early detection of cancer has been a major research focus for almost a century. Current methods for early cancer detection suffer from suboptimal sensitivity and specificity, especially when used for population screening. For most major cancers, including breast, prostate, lung, ovarian, and pancreatic cancer, population screening is still controversial or is not recommended by expert bodies. Circulating tumor DNA (ctDNA) is an exciting new cancer biomarker with potential applicability to all cancer types. Recent investigations have shown that genetic alterations or epigenetic modifications in ctDNA could be used for cancer detection with a liquid biopsy (i.e., a tube of blood). Tests based on ctDNA have attracted considerable attention for various applications, such as patient management, prognosis, early diagnosis, and population screening. Recently, new biotechnology companies were founded, with the goal of revolutionizing early cancer detection by using ctDNA. We previously examined this technology, as published by various academic laboratories and of one leading company, Grail, and drew attention to potential obstacles. After 3 years of intense development, this technology seems to have made some progress. Here, we will analyze the latest clinical data presented by Grail in October 2019, during the inaugural American Society of Clinical Oncology (ASCO) 2019 Breakthrough Conference. Despite considerable technical improvements, it seems that the sensitivity and specificity of the Grail test as a pan-cancer screening tool are still too low for clinical use. The prospects that this test could be further improved are also discussed.

### **The promises and challenges of early non-small cell lung cancer detection: patient perceptions, low-dose CT screening, bronchoscopy and biomarkers**

Mol Oncol. 2020 Nov 30. doi: 10.1002/1878-0261.12864. Online ahead of print. Lukas Kalinke 1 , Ricky Thakrar 1 , Sam M Janes 1

Lung cancer survival statistics are sobering with survival ranking among the poorest of all cancers despite the addition of targeted therapies and immunotherapies. However, improvements in tools for early detection hold promise. The Netherlands-Leuven Longkanker Screenings Onderzoek (NELSON) trial recently corroborated the findings from the previous National Lung Screening Trial (NLST) low dose CT screening trial in reducing lung cancer mortality. Biomarker research and development is increasing at pace as the molecular life histories of lung cancers become further unravelled. Low dose CT screening (LDCT) is effective but targets only those at the highest risk and is burdensome on healthcare. An optimally designed CT screening programme at best will only detect a low proportion of overall lung cancers as only those at very high risk meet screening criteria. Biomarkers that help risk stratify suitable patients for LDCT screening, and those that assist in determining which LDCT detected nodules are likely to represent malignant disease are needed. Some biomarkers have been proposed as standalone lung cancer diagnosis tools. Bronchoscopy technology is improving, with better capacity to identify and obtain samples from early lung cancers. Clinicians need to be aware of each early lung cancer detection method's inherent limitations. We anticipate that the future of early lung cancer diagnosis will involve a synergistic, multimodal approach, combining several early detection methods.

[State Variation in Low-Dose CT Scanning for Lung Cancer Screening in the United States](#) J Natl Cancer Inst. 2020 Nov 12;djaa170. doi: 10.1093/jnci/djaa170. Online ahead of print. Stacey A Fedewa 1 , Ella A Kazerooni 2 , Jamie L Studts 3 , Robert Smith 1 , Priti Bandi 1 , Ann Goding Sauer 1 , Megan Cotter 1 , Helmhne M Sineshaw 1 , Ahmedin Jemal 1 , Gerard A Silvestri 4

**BACKGROUND:** Annual lung cancer screening (LCS) with low dose chest computed tomography in older current and former smokers (ie., eligible adults) has been recommended since 2013. Uptake has been slow and variable across the United States (US). We estimated the LCS rate and growth at the national and state level between 2016-2018. **METHODS:** The American College of Radiology's Lung Cancer Screening Registry (LCSR) was used to capture screening events. Population-based surveys, US Census, and cancer registry data were used to estimate the number of eligible adults and lung cancer mortality (ie, burden). Lung cancer screening rates (SR) in eligible adults and rate ratios (SRR) with 95% confidence intervals (CI) were used to measure changes by state and year. **RESULTS:** Nationally, the SR was steady between 2016 (3.3%, 95%CI =3.3% to 3.7%) and 2017 (3.4%, 95%CI =3.4% to 3.9%), increasing to 5.0% (95%CI = 5.0 to 5.7) in 2018 (2018 vs 2016 SRR = 1.52, 95%CI = 1.51 to 1.62). In 2018, several Southern states with a high lung-cancer burden (eg, Mississippi, West Virginia, Arkansas) had relatively low SRs (<4%) among eligible adults, whereas several Northeastern states with lower lung cancer burden (eg, Massachusetts, Vermont, New Hampshire) had the highest SRs (12.8-15.2%). The exception was Kentucky, which had the nation's highest lung cancer mortality rate and one of the highest SRs (13.7%). **CONCLUSIONS:** Less than 1 in 20 eligible adults received LCS nationally, and uptake varied widely across states. LCS rates were not aligned with lung cancer burden across states, except for Kentucky, which has supported comprehensive efforts to implement LCS.

[Liquid Biopsy of Non-Plasma Body Fluids in Non-Small Cell Lung Cancer: Look Closer to the Tumor!](#) Cells. 2020 Nov 16;9(11):2486. doi: 10.3390/cells9112486. Lucile Durin 1 , Anne Pradines 2 3 , Céline Basset 4 , Bryan Ulrich 5 , Laura Keller 2 3 , Vincent Dongay 1 , Gilles Favre 2 3 6 , Julien Mazieres 1 2 6 , Nicolas Guibert 1 2 6

Liquid biopsy is a rapidly emerging field due to an increasing number of oncogenic drivers and a better understanding of resistance mechanisms to targeted therapies in non-small cell lung cancer (NSCLC). The sensitivity of the most widely used blood-based assays is, however, limited in particular in cases of low tumor volume where shed of tumor-derived material can be limited. A negative result thus requires biopsy confirmation using minimally invasive sampling procedures that can result in small specimens, which are often not suitable for genotyping. Liquid biopsy is not limited to plasma, and tumor DNA circulating in other body fluids such as urine, pleural fluid, cerebrospinal fluid, or cytology specimen-derived supernatant can be exploited. In comparison to cell blocks, these fluids in close contact to the tumor may contain a more abundant and less analytically demanding tumor DNA. In this review, we discuss the potential applications of circulating tumor DNA derived from cytology samples in NSCLC, from early stage (screening, nodule characterization) to metastatic disease.

[Liquid biopsy is a valuable tool in the diagnosis and management of lung cancer](#) J Thorac Dis. 2020 Nov;12(11):7048-7056. doi: 10.21037/jtd.2020.04.20. Matthew J Cecchini 1 , Eunhee S Yi 1

Liquid biopsy refers to the use of various body fluids to test for circulating biological elements derived from the tumor. Liquid biopsy has taken on an increasingly important role in lung cancer diagnosis, molecular characterization, surveillance, monitoring, and determining mechanisms of resistance. These assays can utilize various sources of cell-free DNA (cfDNA) including blood, pleural fluid, urine, and others to detect tumor associated alterations. With the increasing power of next-generation sequencing technologies and the development of assays such as digital droplet PCR, rare tumor alleles can be detected in cfDNA to determine key characteristics of the tumor. Current assays, while effective, are still challenged by limited sensitivity and capacity to single genes or small panels of genes, though this is

rapidly expanding. Nevertheless, testing of cfDNA has been shown to be valuable in detecting resistance to targeted inhibitors, particularly for detection of T790M in EGFR and monitoring response to therapy. With the continued development of more powerful and sensitive assays, these techniques will empower clinicians to better characterize early stage disease and can be used in the screening of high-risk patients, which may eliminate the requirement for tissue diagnosis in some settings. That said, since the majority of these alterations are not specific to lung cancer, there will continue to be a need for tissue in at least the initial diagnosis. Used in conjunction with tissue sampling, these assays will assist the treating clinician and the pathologist to better characterize individual tumors, even in the setting of limited tissue.

[Reproducible and Interpretable Spiculation Quantification for Lung Cancer Screening](#) Comput Methods Programs Biomed. 2020 Nov 13;105839. doi: 10.1016/j.cmpb.2020.105839. Online ahead of print. Wookjin Choi <sup>1</sup>, Saad Nadeem <sup>2</sup>, Sadeh R Alam <sup>3</sup>, Joseph O Deasy <sup>3</sup>, Allen Tannenbaum <sup>4</sup>, Wei Lu <sup>3</sup>

Spiculations are important predictors of lung cancer malignancy, which are spikes on the surface of the pulmonary nodules. In this study, we proposed an interpretable and parameter-free technique to quantify the spiculation using area distortion metric obtained by the conformal (angle-preserving) spherical parameterization. We exploit the insight that for an angle-preserved spherical mapping of a given nodule, the corresponding negative area distortion precisely characterizes the spiculations on that nodule. We introduced novel spiculation scores based on the area distortion metric and spiculation measures. We also semi-automatically segment lung nodule (for reproducibility) as well as vessel and wall attachment to differentiate the real spiculations from lobulation and attachment. A simple pathological malignancy prediction model is also introduced. We used the publicly-available LIDC-IDRI dataset pathologists (strong-label) and radiologists (weak-label) ratings to train and test radiomics models containing this feature, and then externally validate the models. We achieved AUC = 0.80 and 0.76, respectively, with the models trained on the 811 weakly-labeled LIDC datasets and tested on the 72 strongly-labeled LIDC and 73 LUNGx datasets; the previous best model for LUNGx had AUC = 0.68. The number-of-spiculations feature was found to be highly correlated (Spearman's rank correlation coefficient  $\rho=0.44$ ) with the radiologists' spiculation score. We developed a reproducible and interpretable, parameter-free technique for quantifying spiculations on nodules. The spiculation quantification measures was then applied to the radiomics framework for pathological malignancy prediction with reproducible semi-automatic segmentation of nodule. Using our interpretable features (size, attachment, spiculation, lobulation), we were able to achieve higher performance than previous models. In the future, we will exhaustively test our model for lung cancer screening in the clinic.

[RNF213 gene mutation in circulating tumor DNA detected by targeted next-generation sequencing in the assisted discrimination of early-stage lung cancer from pulmonary nodules](#) Thorac Cancer. 2020 Nov 16. doi: 10.1111/1759-7714.13741. Online ahead of print. Ning Jiang <sup>1</sup>, Jie Zhou <sup>3</sup>, Wenhao Zhang <sup>3</sup>, et al.

**BACKGROUND:** To distinguish early-stage lung cancer from benign disease in pulmonary nodules, especially lesions with ground-glass opacity (GGO), we assessed gene mutations of ctDNA in peripheral blood using targeted next-generation sequencing (NGS). **METHODS:** Single pulmonary nodule patients without mediastinal lymph nodes and symptoms that were hard to diagnose by chest CT and lung cancer biomarker measurement in multiple medical centers were enrolled into the study. All patients accepted minimally invasive surgery but refused preoperative biopsy. Gene mutations in preoperative blood samples were detected by targeted NGS. Mutations with significant differences between lung tumors and benign lesions, as grouped by postoperative pathology, were screened. Protein expression was determined by immunohistochemistry. Highly expressed genes were selected as biomarkers to verify the mutations in peripheral blood. **RESULTS:** In the training set, the RNF213, KMT2D, CSMD3 and LRP1B genes were



mutated more frequently in early-stage lung cancer (27 cases) than in benign nodules (15 cases) ( $P < 0.05$ ). High expression of the RNF213 gene in lung cancers and low expression in benign diseases were seen by immunohistochemistry. The RNF213 gene was mutated in 25% of lung cancer samples in the validation set of 28 samples and showed high specificity (100%). In GGO patients, RNF213 was mutated more frequently in early-stage lung cancer compared to benign diseases ( $P < 0.05$ ). **CONCLUSIONS:** RNF213 gene mutations were observed more frequently in early-stage lung cancer, but not in benign nodules. Mutation of the RNF213 gene in peripheral blood may be a high specificity biomarker for the assisted early diagnosis of lung cancer in pulmonary nodules. **KEY POINTS:** Significant findings of the study: In peripheral venous blood and tumor tissue, RNF213 gene mutated more frequently in lung cancer than benign pulmonary nodules. **WHAT THIS STUDY ADDS:** Detection mutation of the RNF213 gene in peripheral blood may be a high specificity method for the assisted early diagnosis of lung cancer in pulmonary nodules.

### [Multi-Window CT Based Radiological Traits for Improving Early Detection in Lung Cancer](#)

**Screening** Cancer Manag Res. 2020 Nov 27;12:12225-12238. doi: 10.2147/CMAR.S246609. eCollection 2020. Hong Lu 1 2, Jongphil Kim 3, Jin Qi 1 2, Qian Li 1, Ying Liu 1, Matthew B Schabath 4, Zhaoxiang Ye 1, Robert J Gillies 2, Yoganand Balagurunathan 2 5

**RATIONALE AND OBJECTIVES:** Evaluate ability of radiological semantic traits assessed on multi-window computed tomography (CT) to predict lung cancer risk. **MATERIALS AND METHODS:** A total of 199 participants were investigated, including 60 incident lung cancers and 139 benign positive controls. Twenty lung window features and 2 mediastinal window features were extracted and scored on a point scale in three screening rounds. Multivariate logistic regression analysis was used to explore the association of these radiological traits with the risk of developing lung cancer. The areas under the receiver operating characteristic curve (AUROC), sensitivity, specificity, and positive predictive value (PPV) were computed to evaluate the best predictive model. **RESULTS:** Combining mediastinal window-specific features with the lung window features-based model significantly improves performance compared to individual window features. Model performance is consistent both at baseline and the first follow-up scan, with an AUROC increased from 0.822 to 0.871 ( $p = 0.009$ ) and from 0.877 to 0.917 ( $p = 0.008$ ), respectively, for single to multi-window feature models. We also find that the multi-window CT based model showed better specificity and PPV, with PPV at the second follow-up scan improved to 0.953. **CONCLUSION:** We find combining window semantic features improves model performance in identifying cancerous nodules. We also find that lung window features are more informative compared to mediastinal features in predicting malignancy.

### [Understanding the Associations between Smoking-Related Risk Perception, Interest in Quitting Smoking, and Interest in Lung Cancer Screening among Homeless Adult Smokers](#)

Int J Environ Res Public Health. 2020 Nov 27;17(23):E8817. doi: 10.3390/ijerph17238817. Pooja Agrawal 1, Matthew Taing 2 3, Tzu-An Chen 2 3, Sean M Reuven 2 3, Michael S Businelle 4, Darla E Kendzor 4, Eric H Bernicker 5, Lorraine R Reitzel 2 3

Individuals experiencing homelessness smoke cigarettes at high rates, suffer a disproportionate incidence of lung cancer, but are unlikely to be screened to enhance early detection. Understanding correlates of lung cancer screening (LCS) interest within this vulnerable group may lend insight into prevention and treatment efforts and reduce their smoking-related morbidity and mortality. This study sought to understand how risk perception and interest in quitting smoking relate to LCS interest among homeless adults. Participants comprised a convenience sample of CO-verified current smokers ( $N = 310$ ; 72.6% men, Mage = 43 + 11.7) from a homeless shelter in Dallas, TX. Participants self-reported risk perception, interest in quitting smoking, and interest in LCS. The average risk perception was 6.7 + 3.2 (range 0-10), 74.8% ( $n = 232$ ) agreed or strongly agreed with interest in LCS, and 65.8% ( $n = 204$ ) were interested in

quitting smoking. Greater interest in quitting smoking, but not greater risk perception, was associated with greater interest in LCS (adjusted OR: 1.968, (95% CI: 1.213, 3.191),  $p = 0.006$ ). Risk perception and interest in quitting smoking did not interact in their association with interest in LCS. Results suggest that homeless smokers with an interest in quitting may be receptive to LCS: a diagnostic tool by which cancers can be caught at earlier stages and prior to metastasis. However, few in the current sample would be eligible for LCS based on current guidelines; results have implications for altered screening practices among chronic smokers experiencing homelessness.

**[Artificial Intelligence Tools for Refining Lung Cancer Screening](#)** J Clin Med. 2020 Nov 27;9(12):E3860. doi: 10.3390/jcm9123860. J Luis Espinoza <sup>1</sup> <sup>2</sup>, Le Thanh Dong <sup>3</sup>

Nearly one-quarter of all cancer deaths worldwide are due to lung cancer, making this disease the leading cause of cancer death among both men and women. The most important determinant of survival in lung cancer is the disease stage at diagnosis, thus developing an effective screening method for early diagnosis has been a long-term goal in lung cancer care. In the last decade, and based on the results of large clinical trials, lung cancer screening programs using low-dose computer tomography (LDCT) in high-risk individuals have been implemented in some clinical settings, however, this method has various limitations, especially a high false-positive rate which eventually results in a number of unnecessary diagnostic and therapeutic interventions among the screened subjects. By using complex algorithms and software, artificial intelligence (AI) is capable to emulate human cognition in the analysis, interpretation, and comprehension of complicated data and currently, it is being successfully applied in various healthcare settings. Taking advantage of the ability of AI to quantify information from images, and its superior capability in recognizing complex patterns in images compared to humans, AI has the potential to aid clinicians in the interpretation of LDCT images obtained in the setting of lung cancer screening. In the last decade, several AI models aimed to improve lung cancer detection have been reported. Some algorithms performed equal or even outperformed experienced radiologists in distinguishing benign from malignant lung nodules and some of those models improved diagnostic accuracy and decreased the false-positive rate. Here, we discuss recent publications in which AI algorithms are utilized to assess chest computer tomography (CT) scans imaging obtaining in the setting of lung cancer screening.

**[Primary Care Physician Perceptions of Shared Decision Making in Lung Cancer Screening](#)**

J Cancer Educ. 2020 Nov 23. doi: 10.1007/s13187-020-01925-9. Online ahead of print. Mohammad Abubaker-Sharif <sup>1</sup>, Christine Shusted <sup>2</sup>, Pamela Myers <sup>3</sup>, Ronald Myers <sup>4</sup>

The Centers for Medicare and Medicaid Services (CMS) supports lung cancer screening (LCS) with annual low-dose computed tomography (LDCT) for patients who undergo shared decision-making (SDM) about LCS. Unfortunately, SDM and LCS rates are low in primary care, and, as a result, the potential benefits of LCS are not being realized. The research team interviewed 16 primary care physicians in a large urban medical center (7 in Family and Community Medicine and 9 in Internal Medicine) on their views of SDM and LCS. Interview audio-recordings were transcribed. Coders analyzed the interview transcripts independently using direct content analysis to identify major themes and subthemes. Results of interview analyses show that physicians were aware of LCS but believed that they and their patients would benefit from receiving more information about screening guidelines. Physicians knew about SDM and felt that SDM performance could help to identify issues that are important to patients and may affect their receptivity to LCS. However, many physicians expressed concerns about the time required for SDM and completing SDM about LCS when other issues need to be addressed. They also acknowledged the challenge of engaging patients, especially those with low health literacy, in SDM. In practice, some physicians reported instead of engaging eligible patients in SDM, they simply encourage them to screen. Importantly, most physicians said that they would like to receive training in SDM. Findings from this study indicate that primary care physicians support the dissemination of information about LCS and

understand the importance of SDM. Physicians also feel that performing SDM in routine care is challenging but are receptive to additional training in SDM. Health systems should take steps to support SDM and LCS performance in primary care.

**[Comparison of clinical diagnostic value of spiral CT with different dose in patients with early-stage peripheral lung cancer](#)** Clin Transl Oncol. 2020 Nov 22. doi: 10.1007/s12094-020-02503-7. Online ahead of print. Y J Sun 1 , J Lou 2 , Q L Xu 3 , Y G Xing 4 , X Z Zhao 5 , L L Zhao 6 , X N Wang 7

**PURPOSE:** To compare the clinical diagnostic value of spiral CT scan with different dose in patients with early-stage peripheral lung cancer. **METHODS:** A total of 163 cases of patients with early-stage peripheral lung cancer who came to People's Hospital of Rizhao for treatment from June 2014 to January 2017 were retrospectively analyzed. A total of 78 cases of patients who received low-dose CT scanning were the low-dose group, another 84 cases of patients who received routine dose CT scanning were the routine dose group. Multislice helical CT (MSCT) scanning was performed in both groups, with tube voltage of 120 kV. Tube current was 25 m A in the low-dose group and 250 m A in the routine dose group. In addition, a total of 80 patients with lobar pneumonia were added as the control group of diagnostic sensitivity, specificity and accuracy. Pathological diagnosis was taken as the gold standard to compare the diagnostic sensitivity, specificity and accuracy of the two groups. **RESULTS:** The image quality, nodules and signs of the two groups were compared, and the results of radiation dose of the two groups were compared. The diagnostic sensitivity, specificity and accuracy of the low-dose group were 82.05%, 87.50% and 84.81%, respectively. The diagnostic sensitivity, specificity and accuracy of the routine dose group were 85.71%, 86.25% and 85.97%, respectively. The diagnostic value of the two groups was not statistically significant ( $p > 0.05$ ). However, the radiation dose in the low-dose group was significantly lower than that in the routine group. **CONCLUSION:** Low-dose MSCT scanning can meet the clinical requirements for imaging diagnosis of peripheral lung cancer, and can reduce the radiation dose of patients.

**[Lung cancer screening eligibility and use with low-dose computed tomography: Results from the 2018 Behavioral Risk Factor Surveillance System cross-sectional survey](#)** Cancer. 2020 Nov 18. doi: 10.1002/cncr.33322. Online ahead of print. Anand K Narayan 1 , Yasha Gupta 2 , Brent P Little 1 ,

Joanne O Shepard 1 , Efren J Flores 1

**BACKGROUND:** In randomized controlled trials, lung cancer screening with low-dose chest computed tomography (LCS) has been reported to reduce lung cancer mortality. Although initial studies suggested that only approximately 5% of eligible patients have undergone LCS, recent studies have indicated that use of LCS may be increasing nationwide. The objective of the current study was to estimate recent LCS use using cross-sectional survey data from the 2018 Behavioral Risk Factor Surveillance System (BRFSS) survey. **METHODS:** The BRFSS is a nationally representative, cross-sectional telephone survey of adults in the United States (response rate of approximately 50%). The 2018 BRFSS survey included questions regarding LCS eligibility and use in 8 states. The primary outcome was the percentage of participants (aged 55-79 years with a smoking history of >30 pack-years) who reported undergoing LCS. Logistic regression analyses evaluated the association between LCS use and sociodemographic characteristics, adjusted for potential confounders and accounting for complex survey design elements. **RESULTS:** A total of 26,910 participants were included, 9.9% of whom were eligible for LCS (95% CI, 8.8%-10.6%). Of the eligible patients, 19.2% reported undergoing LCS (95% CI, 14.0%-24.4%). Approximately 16.4% of current smokers were eligible for LCS (95% CI, 14.2%-18.6%). In our multiple variable analyses of eligible patients, age, sex, marital status, current smoking status, and race were not found to be associated with statistically significant differences in reported LCS ( $P > .05$ ). Retired patients, patients with personal physicians, and patients who did not complete a high school education were more likely to report receiving LCS ( $P < .05$ ). **CONCLUSIONS:** Compared with previously published studies,

the results of the current study suggested that LCS use is increasing. However, LCS use remains low (19%) among eligible participants.

[Urban-Rural Disparities in Access to Low-Dose Computed Tomography Lung Cancer Screening in Missouri and Illinois](#) *Prev Chronic Dis.* 2020 Nov 5;17:E140. doi: 10.5888/pcd17.200202. Karthik W Rohatgi 1 2 , Christine M Marx 1 , Marquita W Lewis-Thames 3 , Jingxia Liu 1 , Graham A Colditz 1 , Aimee S James 1

**INTRODUCTION:** Low-dose computed tomography (LDCT) lung cancer screening is recommended for current and former smokers who meet eligibility criteria. Few studies have quantitatively examined disparities in access to LDCT screening. The objective of this study was to examine relationships between 1) rurality, sociodemographic characteristics, and access to LDCT lung cancer screening and 2) screening access and lung cancer mortality. **METHODS:** We used census block group and county-level data from Missouri and Illinois. We defined access to screening as presence of an accredited screening center within 30 miles of residence as of May 2019. We used mixed-effects logistic models for screening access and county-level multiple linear regression models for lung cancer mortality. **RESULTS:** Approximately 97.6% of metropolitan residents had access to screening, compared with 41.0% of nonmetropolitan residents. After controlling for sociodemographic characteristics, the odds of having access to screening in rural areas were 17% of the odds in metropolitan areas (95% CI, 12%-26%). We observed no association between screening access and lung cancer mortality. Southeastern Missouri, a rural and impoverished area, had low levels of screening access, high smoking prevalence, and high lung cancer mortality. **CONCLUSION:** Although access to LDCT is lower in rural areas than in urban areas, lung cancer mortality in rural residents is multifactorial and cannot be explained by access alone. Targeted efforts to implement rural LDCT screening could reduce geographic disparities in access, although further research is needed to understand how increased access to screening could affect uptake and rural disparities in lung cancer mortality.

[Computer-Tailored Decision Support Tool for Lung Cancer Screening: Community-Based Pilot Randomized Controlled Trial](#) *J Med Internet Res.* 2020 Nov 3;22(11):e17050. doi: 10.2196/17050.

Lisa Carter-Harris # 1 , Robert Skipworth Comer # 2 , James E Slaven Ii # 3 , Patrick O Monahan # 3 , Emilee Vode # 4 , Nasser H Hanna # 3 , DuyKhanh Pham Ceppa # 3 , Susan M Rawl # 4

**BACKGROUND:** Lung cancer screening is a US Preventive Services Task Force Grade B recommendation that has been shown to decrease lung cancer-related mortality by approximately 20%. However, making the decision to screen, or not, for lung cancer is a complex decision because there are potential risks (eg, false positive results, overdiagnosis). Shared decision making was incorporated into the lung cancer screening guideline and, for the first time, is a requirement for reimbursement of a cancer screening test from Medicare. Awareness of lung cancer screening remains low in both the general and screening-eligible populations. When a screening-eligible person visits their clinician never having heard about lung cancer screening, engaging in shared decision making to arrive at an informed decision can be a challenge. Methods to effectively prepare patients for these clinical encounters and support both patients and clinicians to engage in these important discussions are needed. **OBJECTIVE:** The aim of the study was to estimate the effects of a computer-tailored decision support tool that meets the certification criteria of the International Patient Decision Aid Standards that will prepare individuals and support shared decision making in lung cancer screening decisions. **METHODS:** A pilot randomized controlled trial with a community-based sample of 60 screening-eligible participants who have never been screened for lung cancer was conducted. Approximately half of the participants (n=31) were randomized to view LungTalk-a web-based tailored computer program-while the other half (n=29) viewed generic information about lung cancer screening from the American Cancer Society. The outcomes that were compared included lung cancer and screening knowledge, lung cancer screening health beliefs (perceived



risk, perceived benefits, perceived barriers, and self-efficacy), and perception of being prepared to engage in a discussion about lung cancer screening with their clinician. **RESULTS:** Knowledge scores increased significantly for both groups with greater improvement noted in the group receiving LungTalk (2.33 vs 1.14 mean change). Perceived self-efficacy and perceived benefits improved in the theoretically expected directions. **CONCLUSIONS:** LungTalk goes beyond other decision tools by addressing lung health broadly, in the context of performing a low-dose computed tomography of the chest that has the potential to uncover other conditions of concern beyond lung cancer, to more comprehensively educate the individual, and extends the work of nontailored decision aids in the field by introducing tailoring algorithms and message framing based upon smoking status in order to determine what components of the intervention drive behavior change when an individual is informed and makes the decision whether to be screened or not to be screened for lung cancer.

### **Patient Adherence to Screening for Lung Cancer in the US: A Systematic Review and Meta-**

**analysis** JAMA Netw Open. 2020 Nov 2;3(11):e2025102. doi: 10.1001/jamanetworkopen.2020.25102.

Maria A Lopez-Olivo 1 , Kristin G Maki 1 , Noah J Choi 1 , Richard M Hoffman 2 , Ya-Chen Tina Shih 1 , Lisa M Lowenstein 1 , Rachel S Hicklen 3 , Robert J Volk 1

**IMPORTANCE:** To be effective in reducing deaths from lung cancer among high-risk current and former smokers, screening with low-dose computed tomography must be performed periodically.

**OBJECTIVE:** To examine lung cancer screening (LCS) adherence rates reported in the US, patient characteristics associated with adherence, and diagnostic testing rates after screening. **DATA SOURCES:** Five electronic databases (MEDLINE, Embase, Scopus, CINAHL, and Web of Science) were searched for articles published in the English language from January 1, 2011, through February 28, 2020.

**STUDY SELECTION:** Two reviewers independently selected prospective and retrospective cohort studies from 95 potentially relevant studies reporting patient LCS adherence.

**DATA EXTRACTION AND SYNTHESIS:** Quality appraisal and data extraction were performed independently by 2 reviewers using the Newcastle-Ottawa Scale for quality assessment. A random-effects model meta-analysis was conducted when at least 2 studies reported on the same outcome. Reporting followed the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guideline. **MAIN OUTCOMES**

**AND MEASURES:** The primary outcome was LCS adherence after a baseline screening. Secondary measures were the patient characteristics associated with adherence and the rate of diagnostic testing after screening. **RESULTS:** Fifteen studies with a total of 16 863 individuals were included in this systematic review and meta-analysis. The pooled LCS adherence rate across all follow-up periods (range, 12-36 months) was 55% (95% CI, 44%-66%). Regarding patient characteristics associated with adherence rates, current smokers were less likely to adhere to LCS than former smokers (odds ratio [OR], 0.70; 95% CI, 0.62-0.80); White patients were more likely to adhere to LCS than patients of races other than White (OR, 2.0; 95% CI, 1.6-2.6); people 65 to 73 years of age were more likely to adhere to LCS than people 50 to 64 years of age (OR, 1.4; 95% CI, 1.0-1.9); and completion of 4 or more years of college was also associated with increased adherence compared with people not completing college (OR, 1.5; 95% CI, 1.1-2.1). Evidence was insufficient to evaluate diagnostic testing rates after abnormal screening scan results.

The main source of variation was attributable to the eligibility criteria for screening used across studies. **CONCLUSIONS AND RELEVANCE:** In this study, the pooled LCS adherence rate after a baseline screening was far lower than those observed in large randomized clinical trials of screening. Interventions to promote adherence to screening should prioritize current smokers and smokers from minority populations.

[Role of Surgical Intervention in Unresectable Non-Small Cell Lung Cancer](#) J Clin Med. 2020 Nov 29;9(12):E3881. doi: 10.3390/jcm9123881. Shigeki Suzuki 1 , Taichiro Goto 2

With the development of systemic treatments with high response rates, including tyrosine kinase inhibitors and immune checkpoint inhibitors, some patients with unresectable lung cancer now have a chance to undergo radical resection after primary treatment. Although there is no general consensus regarding the definition of "unresectable" in lung cancer, the term "resectable" refers to technically resectable and indicates that resection can provide a favorable prognosis to some extent. Unresectable lung cancer is typically represented by stage III and IV disease. Stage III lung cancer is a heterogeneous disease, and in some patients with technically resectable non-small cell lung cancer (NSCLC), multimodality treatments, including induction chemoradiotherapy followed by surgery, are the treatments of choice. The representative surgical intervention for unresectable stage III/IV NSCLC is salvage surgery, which refers to surgical treatment for local residual/recurrent lesions after definitive non-surgical treatment. Surgical intervention is also used for an oligometastatic stage IV NSCLC. In this review, we highlight the role of surgical intervention in patients with unresectable NSCLC, for whom an initial complete resection is technically difficult. We further describe the history of and new findings on salvage surgery for unresectable NSCLC and surgery for oligometastatic NSCLC.

[Institution-level differences in quality and outcomes of lung cancer resections in the United States](#)

Chest. 2020 Nov 13;S0012-3692(20)35134-5. doi: 10.1016/j.chest.2020.10.075. Online ahead of print. Raymond U Osarogiagbon 1 , Helmhne M Sineshaw 2 , Chun Chieh Lin 2 , Ahmedin Jemal 2

**BACKGROUND:** Institution-level disparities in non-small cell lung cancer (NSCLC) survival may be driven by reversible differences in care-delivery processes. We quantified the impact of differences in readily identifiable quality metrics on long-term survival disparities in resected NSCLC. **RESEARCH QUESTION:** how do reversible differences in oncologic quality of care contribute to institution-level disparities in early-stage NSCLC survival? **STUDY DESIGN AND METHODS:** We retrospectively analyzed patients in the National Cancer Data Base with NSCLC resections from 2004-2015 within institutions categorized as Community, Comprehensive Community, Integrated Network, Academic, and National Cancer Institute (NCI)-Designated Cancer Programs. We estimated percentages and adjusted odds ratios for 6 potentially avoidable poor-quality markers: incomplete resection, non-examination of lymph nodes, non-anatomic resection, non-evidence-based use of adjuvant chemotherapy, non-evidence-based use of adjuvant radiation therapy and 60-day postoperative mortality. By sequentially eliminating patients with poor-quality markers and calculating adjusted hazard ratios, we quantified their overall survival impact. **RESULTS:** Of 169,775 patients, 7%, 46%, 10%, 24% and 12% had surgery at Community, Comprehensive Community, Integrated Network, Academic and NCI-Designated Cancer Programs, with 5-year overall survival rates 52%, 56%, 58%, 60% and 66%, respectively. After the sequential elimination process, using NCI-Designated Cancer Centers as reference, the adjusted hazard ratio for 5-year overall survival changed from 1.47 (95% CI 1.41-1.53), 1.29 (1.25-1.33), 1.18 (1.14-1.23) and 1.20 (1.16-1.24) for Community, Comprehensive Community, Integrated Networks and Academic Cancer Programs to 1.35 (1.28-1.42), 1.22 (1.17-1.26), 1.16 (1.11-1.22), and 1.17 (1.12-1.21), respectively ( $p < .001$  for all comparisons to NCI-designated programs). Differences in quality of surgical resection and postoperative care accounted for 11-25% of the inter-institutional survival disparities. **INTERPRETATION:** Targeting 6 readily-identified poor-quality markers narrowed, but did not eliminate, institutional survival disparities. The greatest impact was in community programs. Residual

factors driving persistent institution-level long-term NSCLC survival disparities must be characterized in order to eliminate them

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

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### [Treatment Sequencing for Anaplastic Lymphoma Kinase-Rearranged Non-Small-Cell Lung Cancer](#)

Drugs. 2020 Nov 23. doi: 10.1007/s40265-020-01445-2. Online ahead of print. Diego Kauffmann-Guerrero 1 , Kathrin Kahnert 1 , Rudolf M Huber 2

Non-small-cell lung cancer (NSCLC) accounts for about 85% of all lung cancer cases and is the leading cause of cancer-related deaths. Most NSCLC patients are diagnosed with advanced disease and require systemic treatment. Despite emerging advances in chemotherapy and immunotherapy, the prognosis of stage IV patients remains poor. However, the discovery of oncogenic driver mutations including mutations in the epidermal growth factor receptor (EGFR), the anaplastic lymphoma kinase (ALK) and others, characterize a subset of patients with the opportunity of targeted therapies. Fusions between the ALK and echinoderm microtubule-associated protein-like 4 (EML4) are present in ~ 3-5% of patients with NSCLC. Several first-, second-, and third-generation ALK tyrosine kinase inhibitors (TKIs) have been developed in the last decade and have tremendously changed treatment options and outcomes of ALK-positive NSCLC patients. With increasing treatment options, treatment sequence decisions have become more and more complex. ALK-mutations, fusion variants, or activation of by-pass pathways result in treatment resistance during the course of treatment in nearly all patients. Mutation-guided treatment sequencing can lead to better outcomes, and re-biopsy or liquid-biopsy should be performed whenever possible in case of disease progression in ALK-rearranged patients. In the future, combinational treatment of ALK TKIs with other pathway-inhibitors might further improve patients' treatment options and outcomes. Here, we review the data for currently available ALK TKIs, discuss approaches of treatment sequencing, and give an outlook on emerging developments.

### [High Prevalence and Early Occurrence of Skeletal Complications in EGFR Mutated NSCLC](#)

[Patients With Bone Metastases](#) Front Oncol. 2020 Nov 12;10:588862. doi: 10.3389/fonc.2020.588862. eCollection 2020. Marta Laganà 1 , Cristina Gurizzan 1 , Elisa Roca 1 , et al.

**OBJECTIVES:** The prevalence of Skeletal Related Adverse Events (SREs) in EGFR mutated non-small cell lung cancer (NSCLC) patients with bone metastases, treated with modern tyrosine kinase inhibitors (TKIs), has been scarcely investigated. **MATERIALS AND METHODS:** We retrospectively evaluated the data of EGFR mutated NSCLC patients with bone metastases treated with TKIs in 12 Italian centers from 2014 to 2019, with the primary aim to explore type and frequency of SREs. **RESULTS:** Seventy-seven out of 274 patients enrolled (28%) developed at least one major SRE: 55/274 (20%) bone fractures, 30/274 (11%) spinal cord compression, 5/274 (2%) hypercalcemia. Median time to the onset of SRE was 3.63 months. Nine patients (3%) underwent bone surgery and 150 (55%) radiation therapy on bone. SREs were more frequently observed within the 12 months from TKI start than afterwards (71 vs 29%,  $p = 0.000$ ). Patient Performance Status and liver metastases were independently associated with the risk of developing SREs. Median TKI exposure and overall survival were 11 and 28 months, respectively. Bone resorption inhibitors were associated with a lower risk of death (HR 0.722, 95% CI: 0.504-1.033,  $p = 0.075$ ) although not statistically significant at multivariate analysis. **CONCLUSION:** Bone metastatic NSCLC patients with EGFR mutated disease, treated with EGFR TKIs, have a relatively long survival expectancy and are at high risk to develop SREs. The early SRE occurrence after the TKI start provides the rationale to administer bone resorption inhibitors.

[Impact of prior chemoradiotherapy-related variables on outcomes with durvalumab in unresectable Stage III NSCLC \(PACIFIC\)](#) Lung Cancer. 2020 Nov 26;151:30-38. doi:

10.1016/j.lungcan.2020.11.024. Online ahead of print. Corinne Faivre-Finn 1 , David R Spigel 2 , et al.

**INTRODUCTION:** The PACIFIC trial demonstrated that durvalumab significantly improved progression-free and overall survival (PFS/OS), versus placebo, in patients with Stage III NSCLC and stable or responding disease following concurrent, platinum-based chemoradiotherapy (CRT). A range of CT and RT regimens were permitted, and used, in the trial. We report post-hoc, exploratory analyses of clinical outcomes from PACIFIC according to CRT-related variables. **METHODS:** Patients were randomized 2:1 (1-42 days post-CRT) to up to 12 months durvalumab (10 mg/kg intravenously every 2 weeks) or placebo. Efficacy and safety were analyzed in patient subgroups defined by the following baseline variables: platinum-based CT (cisplatin/carboplatin); vinorelbine, etoposide, or taxane-based CT (all yes/no); total RT dose (<60 Gy/60-66 Gy/>66 Gy); time from last RT dose to randomization (<14 days/≥14 days); and use of pre-CRT induction CT (yes/no). Treatment effects for time-to-event endpoints were estimated by hazard ratios (HRs) from unstratified Cox-proportional-hazards models. **RESULTS:** Overall, 713 patients were randomized, of whom 709 received treatment in either the durvalumab (n/N = 473/476) or placebo arms (n/N = 236/237). Durvalumab improved PFS, versus placebo, across all subgroups (median follow up, 14.5 months; HR range, 0.34-0.63). Durvalumab improved OS across most subgroups (median follow up, 25.2 months; HR range, 0.35-0.86); however, the 95 % confidence interval (CI) of the estimated treatment effect crossed one for the subgroups of patients who received induction CT (HR, 0.78 [95 % CI, 0.51-1.20]); carboplatin (0.86 [0.60-1.23]); vinorelbine (0.79 [0.49-1.27]); and taxane-based CT (0.73 [0.51-1.04]); and patients who were randomized ≥14 days post-RT (0.81 [0.62-1.06]). Safety was broadly similar across the CRT subgroups. **CONCLUSION:** Durvalumab prolonged PFS and OS irrespective of treatment variables related to prior CRT to which patients with Stage III NSCLC had previously stabilized or responded. Limited patient numbers and imbalances in baseline factors in each subgroup preclude robust conclusions.

[Immune checkpoint inhibitor therapy may increase the incidence of treatment-related necrosis after stereotactic radiosurgery for brain metastases: a systematic review and meta-analysis](#) Eur

Radiol. 2020 Nov 25. doi: 10.1007/s00330-020-07514-0. Online ahead of print. Pyeong Hwa Kim 1 , Chong Hyun Suh 2 , Ho Sung Kim 1 , et al.

**OBJECTIVES:** TO compare the incidence of treatment-related necrosis between combination SRS+ICI therapy and SRS therapy alone in patients with brain metastases from melanoma and non-small cell lung cancer (NSCLC). **METHODS:** A systematic literature search of Ovid-MEDLINE and EMBASE was performed up to August 10, 2020. The difference in the pooled incidence of treatment-related necrosis after SRS+ICI or SRS alone was evaluated. The cumulative incidence of treatment-related necrosis at the specific time point after the treatment was calculated and plotted. Subgroup and meta-regression analyses were additionally performed. **RESULTS:** Sixteen studies (14 on melanoma, 2 on NSCLC) were included. In NSCLC brain metastasis, the reported incidences of treatment-related necrosis in SRS+ICI and SRS alone ranged 2.9-3.4% and 0-2.9%, respectively. Meta-analysis was conducted including 14 studies on melanoma brain metastasis. The incidence of treatment-related necrosis was higher in SRS+ICI than SRS alone (16.0% vs. 6.5%; p = 0.065; OR, 2.35). The incidence showed rapid increase until 12 months after the SRS when combined with ICI therapy (14%; 95% CI, 8-22%) and its pace of increase slowed thereafter. Histopathologic diagnosis as the reference standard for treatment-related necrosis and inclusion of only symptomatic cases were the source of heterogeneity in SRS+ICI. **CONCLUSIONS:** Treatment-related necrosis tended to occur 2.4 times more frequently in the setting of combination SRS+ICI therapy compared with SRS alone in melanoma brain metastasis showing high cumulative incidence within the first year. Treatment-related necrosis should be considered when SRS+ICI combination therapy is used for melanoma brain metastasis, especially in the first year.



**Immunotherapy Moves to the Early-Stage Setting in Non-Small Cell Lung Cancer: Emerging Evidence and the Role of Biomarkers** Cancers (Basel). 2020 Nov 20;12(11):3459. doi:

10.3390/cancers12113459. Xabier Mielgo-Rubio <sup>1</sup>, Virginia Calvo <sup>2</sup>, Javier Luna <sup>3</sup>, et al. Despite numerous advances in targeted therapy and immunotherapy in the last decade, lung cancer continues to present the highest mortality rate of all cancers. Targeted therapy based on specific genomic alterations, together with PD-1 and CTLA-4 axis blocking-based immunotherapy, have significantly improved survival in advanced non-small cell lung cancer (NSCLC) and both therapies are now well-established in this clinical setting. However, it is time for immunotherapy to be applied in patients with early-stage disease, which would be an important qualitative leap in the treatment of lung cancer patients with curative intent. Preliminary data from a multitude of studies are highly promising, but therapeutic decision-making should be guided by an understanding of the molecular features of the tumour and host. In the present review, we discuss the most recently published studies and ongoing clinical trials, controversies, future challenges and the role of biomarkers in the selection of best therapeutic options.

**Efficacy of pembrolizumab in patients with brain metastasis caused by previously untreated non-small cell lung cancer with high tumor PD-L1 expression** Lung Cancer. 2020 Nov 15;S0169-

5002(20)30684-X. doi: 10.1016/j.lungcan.2020.11.009. Online ahead of print. Kazushige Wakuda <sup>1</sup>, Michitoshi Yabe <sup>2</sup>, Hiroaki Kodama <sup>2</sup>, et al.

**OBJECTIVES:** Pembrolizumab is recommended for patients with previously untreated non-small cell lung cancer (NSCLC) with a programmed death ligand 1 (PD-L1) tumor proportion score (TPS) of  $\geq 1\%$ . The KEYNOTE-024 study described the efficacy of pembrolizumab in patients with previously untreated NSCLC who had a PD-L1 TPS of at least 50%. However, patients with untreated brain metastasis (BM) were excluded from many clinical trials. Therefore, we assessed the efficacy of pembrolizumab against BM of NSCLC with high tumor PD-L1 expression. **MATERIALS AND METHODS:** We retrospectively reviewed patients who received pembrolizumab as first-line treatment against NSCLC with PD-L1 TPS  $\geq 50\%$  between March 2017 and September 2019. Treatment efficacy was compared between patients with (BM group) and without BM (non-BM group). In addition, the BM group was divided into patients who previously received treatment for BM before pembrolizumab (BM-T group) and those with no prior treatment for BM (BM-not T group). **RESULTS:** Eighty-seven patients (23 BM group and 64 non-BM group) were assessable for efficacy. No significant differences in patient characteristics were found between the BM and non-BM groups, but proportion of patients with stage IV at diagnosis was significantly higher in the BM group. Median progression-free survival (PFS) (6.5 months vs. 7.0 months) and overall survival (OS) (21.6 months vs. 24.6 months) did not significantly differ between the two groups. The response rate of BM was 70%. The BM group was subdivided into 13 patients in the BM-T group and 10 patients in the BM-not T group. No significant differences in patient characteristics were found between the two groups, but maximum diameter of BM and proportion of patients with symptomatic BM were significantly greater in the BM-T group. PFS and OS did not significantly differ between the two groups. The median PFS of BM was 13.6 months in the BM-T group and 18.6 months in the BM-not T group. **CONCLUSION:** Pembrolizumab may be effective for BM caused by previously untreated NSCLC with high PD-L1 tumor expression.

**Immunotherapy for Lung Cancer-Improving Outcomes in Patients With Locally Advanced Non-Small Cell Lung Cancer With Immunotherapy** Cancer J. Nov/Dec 2020;26(6):548-554. doi:

10.1097/PPO.0000000000000485. Lova Sun <sup>1</sup>, Charu Aggarwal Patients with locally advanced non-small cell lung cancer (NSCLC), a heterogenous group encompassing stage IIIA-IIIC disease, often have surgically unresectable cancer and are managed with concurrent chemoradiation. Since the establishment of platinum-based chemoradiation as standard of care for

unresectable locally advanced NSCLC, various strategies including escalating radiation dose, targeted therapies, antiangiogenic agents, and induction or consolidation chemotherapy have failed to show improvement in outcomes. However, recently, use of consolidation immunotherapy with durvalumab following concurrent chemoradiation therapy has been associated with improvement in survival and has led to a paradigm shift. In this review, we will summarize results from trials of immunotherapy in locally advanced NSCLC and comment on ongoing trials and potential future investigations.

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## NSCLC - RADIOTHERAPY

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### [Validating impact of pretreatment tumor growth rate on outcome of early-stage lung cancer treated with stereotactic body radiation therapy](#) Thorac Cancer. 2020 Nov 30. doi: 10.1111/1759-7714.13744.

Online ahead of print.

**BACKGROUND:** To assess correlation of pretreatment specific growth rate (SGR) value of  $0.43 \times 10^{-2}$  with overall and failure-free survival of patients with early-stage non-small cell lung cancer (NSCLC) treated with stereotactic body radiation therapy (SBRT).

**METHODS:** A retrospective chart review of 160 patients with pathologically confirmed stage I NSCLC treated with SBRT between June 2010 and December 2012 in a large, tertiary cancer institute was undertaken. Both diagnostic and archived planning CT were uploaded to the treatment planning system to determine tumor volume at diagnosis (GTV1) and planning time (GTV2). The time (t) between both CTs was recorded. SGR was calculated using GTV1, GTV2, and t. The median SGR ( $0.43 \times 10^{-2}$ ) from our previous data was used to group patients into low and high SGR cohorts. Log-rank test was used to compare overall (OS) and failure-free survivals (FFS) of SGR groups. **RESULTS:** The median time interval between diagnostic and planning CT scans was 87 days. The median OS was 38 and 66 months for high and low SGR cohorts, respectively ( $P = 0.03$ ). The median FFS was 27 and 55 months for high and low SGR cohorts, respectively ( $P = 0.005$ ). High SGR ( $P < 0.05$ ), male gender ( $P = <0.01$ ), and GTV2 ( $P = <0.05$ ) were associated with poorer FFS.

**CONCLUSIONS:** High SGR was associated with poorer outcome in patients with early-stage NSCLC treated with SBRT. SGR can be used in conjunction with other well-known predictive factors to formulate a practical predictive model to identify subgroups of the patient at higher risk of recurrence after SBRT.

### [Safety and Efficacy of Stereotactic Body Radiotherapy in Ultracentral Lung Tumors Using a Risk-optimized Fractionation Scheme](#) Clin Lung Cancer. 2020 Nov 18;S1525-7304(20)30336-3. doi:

10.1016/j.clcc.2020.11.003. Online ahead of print. Sebastian Regnery 1, Tanja Eichkorn 1, Fabian Weykamp 1, et al.

**BACKGROUND:** Delivery of stereotactic body radiotherapy (SBRT) to ultracentral lung tumors remains a major challenge, with potentially excessive SBRT-related toxicity. This study investigates a risk-optimized approach to ultracentral SBRT in an elderly and comorbid patient cohort. **PATIENTS AND**

**METHODS:** Analysis encompassed 129 patients (mean age:  $70 \pm 11$  years, median Charlson comorbidity index: 4 [range, 3-5]) following risk-adapted SBRT to central or ultracentral primary and secondary lung tumors between 2012 and 2019 (78 central, 51 ultracentral). Ultracentral tumors were defined by planning target volume overlap with the proximal bronchial tree. Whereas ultracentral tumors were treated with a risk-optimized fractionation scheme of 50 Gy in 10 fractions, central tumors received higher-fractionated 60 Gy in 8 fractions. Outcome parameters and toxicity for ultracentral and central tumors were assessed using Kaplan-Meier and competing risk analyses. **RESULTS:** Local failure rate was not significantly increased in ultracentral tumors compared with central tumors (2-year local failure rate ultracentral, 26.9%; 95% confidence interval [CI], 12.2%-44.2%; central, 14.6%; 95% CI, 6.6%-25.5%;  $P = .17$ ). Overall survival was similar in both groups (2-year overall survival central, 55.4%; 95%

CI, 44.5%-68.9%; ultracentral, 54.9%; 95% CI, 40.8%-73.9%;  $P = .6$ ). Toxicity was moderate, with toxicity  $\geq$  grade 3 rates of 15.3% (95% CI, 5.9%-28.9%) for ultracentral and 7.3% (95% CI, 2.7%-15.0%) for central tumors after 2 years ( $P = .27$ ). No grade 4 toxicity and only 1 potential grade 5 toxicity were observed in the ultracentral cohort. **CONCLUSION:** Risk-optimized SBRT to ultracentral lung tumors is a reasonably effective and safe treatment alternative in frail patients

**[Benefit of dosimetry distribution for patients with multiple brain metastases from non-small cell lung cancer by a Cyberknife stereotactic radiosurgery \(SRS\) system](#)** BMC Cancer. 2020 Nov

25;20(1):1144. doi: 10.1186/s12885-020-07624-4. Xuyao Yu 1 , Yuwen Wang 2 , Zhiyong Yuan 1 , Hui Yu 3 , Yongchun Song 1 , Lujun Zhao 1 , Ping Wang 4

**BACKGROUND:** In order to obtain a high dose conformal index of tumor and steep dose fall-off in healthy tissues for brain metastasis stereotactic radiosurgery (SRS), the aim of this study was to investigate SRS planning optimization by comparing one multiple-lesions plan (MLP) with multiple single-lesion plans (SLPs) for patients with multiple brain metastases using the Cyberknife (CK) system. **METHODS:** Fifty non-small cell lung cancer (NSCLC) patients (28 males and 22 females) with 2-4 brain metastases, inter-tumour distances less than 3 cm, were retrospectively replanned with the original prescription dose (12-32 Gy) in the original fractions (1-3). Two different clinical CK SRS plans (SLPs and MLP) were generated for the same patients with the same collimator and prescription isodose line (62-68%) by the CK Multiplan System. Both SLPs and MLP were able to achieve  $> 95\%$  PTV volume covered prescription dose and met the Timmerman 2011 organs at risk (brainstem, optic nerve and pituitary) constraints. **RESULTS:** Compared with those in the SLPs, the maximum dose ( $D_{max}$ ) and mean dose ( $D_{mean}$ ) of brainstem in the MLP were reduced 0.22-3.13% (2.62%) and 2.71-12.56% (5.57%), respectively, all  $P < 0.05$ . Meanwhile, the volumes of the whole brain minus the tumors that received a single dose equivalent of 8-16 Gy (V8Gy-V16Gy) were effectively reduced in the MLP. The treatment time parameters, the total number of beams and monitor units, of the MLP were reduced by 3.31 and 1.47% ( $P < 0.05$ ), respectively. Although there were a few differences in the conformity index (CI) and homogeneity index (HI) between the two treatment plans, the differences were not statistically significant ( $P = 2.94$  and  $1.08 > 0.05$ ). **CONCLUSION:** One multiple-lesions plan for brain metastases could achieve higher precision in the target and lower doses in healthy tissue while shortening the treatment time and improving the treatment efficiency over multiple single-lesion plans.

**[Radiation and immunotherapy: emerging mechanisms of synergy](#)** J Thorac Dis. 2020

Nov;12(11):7011-7023. doi: 10.21037/jtd-2019-cptn-07. William G Breen 1 , Konstantinos Leventakos 2 , Haidong Dong 3 , Kenneth W Merrell 1

Immunotherapy (IO) has become a standard treatment in patients with metastatic and locally advanced non-small cell lung cancer (NSCLC), and is now being tested in patients with early stage disease. IO agents currently in use for lung cancer target PD-1, PD-L1, and CTLA-4. While survival and tumor control have improved with IO, many patients have limited or short responses to IO. Therefore, methods to improve the systemic response to IO are needed. Radiation therapy (RT) is an integral component of lung cancer treatment, and may improve systemic response to IO by increasing antigen presentation, increasing co-stimulatory signaling, increasing T-cells recruitment, upregulating PD-L1, increasing tumor stromal lymphocyte infiltration, and altering the microenvironment. IO after definitive chemoradiation is now standard treatment in unresectable stage III NSCLC following publication of the PACIFIC clinical trial. For early stage NSCLC, IO is being investigated in conjunction with stereotactic body radiotherapy (SBRT). The benefit of adding RT to IO in patients with metastatic disease may be especially pronounced in patients with low baseline PD-L1 expression, potentially when delivered as a short course of SBRT, as supported by the PEMBRO-RT clinical trial. Current and ongoing clinical trials are evaluating the optimal radiation dose, timing, and sequencing of RT with IO.

[Systemic Effects of Radiation Therapy-Induced Abscopal Responses in Patients with Advanced Lung Cancer](#) Oncology. 2020 Nov 20;1-14. doi: 10.1159/000510287. Online ahead of print. Mark A D'Andrea 1 , G Kesava Reddy 2

**BACKGROUND:** Out-of-field tumor regression effects of radiation therapy (abscopal response) have been sporadically observed in the past, but they have only recently gained significant importance due to the use of innovative high-precision radiation delivery devices for the treatment of various cancers including non-small cell lung cancer (NSCLC). In this study, we provide a detailed overview of the current state of knowledge and clinical experience of radiation therapy-induced abscopal effects in patients with advanced NSCLC. **SUMMARY:** Peer-reviewed published clinical evidence on the abscopal effect of radiation therapy was collected using electronic databases such as MEDLINE via PubMed and Google Scholar. The clinical data on the abscopal effect of radiation therapy were reviewed and the outcomes have been summarized. Most studies describing the abscopal effects of radiation therapy in patients with advanced NSCLC have been in the form of either case reports or small cohort studies. Although the exact molecular mechanisms for the abscopal effect are yet to be established, current evidence indicates that tumor cell destruction induced by local radiation therapy releases tumor antigens, which stimulate the immune system of the host to activate the body's immune effector cells systemically and trigger the regression of distant nonirradiated cancer cells. These off-target antitumor effects of radiation therapy provide an opportunity to explore the use of the radiation therapy in combination with novel immunotherapy agents to maximize treatment outcomes in patients with advanced NSCLC and other cancers. Key Message: The findings suggest that radiation therapy has the ability to induce abscopal effects with an increased potential to boost these effects when it is used in combination with immunotherapy for the treatment of patients with advanced NSCLC and other cancers. Clinical trials investigating radiation therapy-induced abscopal effects may lead to a dramatic change in its use especially when it is combined with immunotherapy for the treatment of patients with advanced NSCLC.

[Radiotherapy and Immunotherapy Combinations for Lung Cancer](#) Curr Oncol Rep. 2020 Nov 19;23(1):4. doi: 10.1007/s11912-020-00993-w. Vishesh Agrawal 1 , Kimberly Thomas Benjamin 2 , Eric C Ko 3 4

**PURPOSE OF REVIEW:** Positive results from recent immunotherapy trials of non-small cell lung cancer (NSCLC) have coincided with a greater appreciation for the impact of radiation therapy (RT) on tumor immunity. Here, we summarize key clinical findings and ongoing efforts to combine immunotherapy and RT for the treatment of NSCLC. **RECENT FINDINGS:** The role of immunotherapy for NSCLC has expanded significantly following the pivotal approvals of nivolumab and pembrolizumab for metastatic NSCLC, maintenance durvalumab in unresectable stage III NSCLC, and atezolizumab for metastatic NSCLC. Several small early-phase trials have demonstrated the ability of RT to elicit clinically significant tumor immunity. These positive findings support current trial efforts combining RT with immunotherapy for NSCLC. Recently initiated trials of RT and immunotherapy hold significant promise in expanding the therapeutic options for NSCLC. Optimization of therapy will require careful patient selection to yield meaningful improvements in clinical outcomes.

[Stereotactic body radiotherapy \(SBRT\) for central and ultracentral node-negative lung tumors](#) J Thorac Dis. 2020 Nov;12(11):7024-7031. doi: 10.21037/jtd-2019-cptn-01. Dawn Owen 1 , Terence T Sio 2

Advancements in imaging and radiotherapy (RT) techniques have allowed for remarkably precise delivery of high radiation dose per treatment fraction to intrathoracic targets. As a non-invasive therapeutic modality (compared to surgery), stereotactic body radiotherapy (SBRT) is an attractive option for patients with early-stage non-small cell lung cancers and oligometastases, especially for older patients with



significant comorbidities and pre-existing pulmonary dysfunction. However, the outcomes and side effect profile of SBRT are highly dependent on tumor location, especially if the tumor is located centrally (within 2 cm of the proximal bronchial tree (PBT)] or ultracentrally (touching or within 1 cm of the mediastinum, esophagus, and PBT). In this focused review, we will examine the contemporary practice and principles of using hypofractionated RT or SBRT for central and ultracentral thoracic tumors. We will identify future directions on how this practice may be incorporated into the increasingly complicated modern paradigm of lung cancer treatments which now include immunotherapy along with proton beam radiotherapy.

**[A Randomised Phase III Trial of Palliative Radiotherapy \(PRT\) versus Concurrent Chemotherapy and PRT \(C-PRT\) in Patients with Good Performance Status, Locally Advanced or Metastatic NSCLC with symptoms due to intrathoracic disease who are not suitable for radical Chemo-radiotherapy: Results of the Trans-Tasman Radiation Oncology Group \(TROG\) 11.03 Trial](#)**

Pract Radiat Oncol. 2020 Nov 30;S1879-8500(20)30298-8. doi: 10.1016/j.prro.2020.11.009. Online ahead of print. M Lehman 1 , A Bernard 2 , A See 3 , M King 4 , M Michael 5

**PURPOSE:** We compared intrathoracic symptom response rate, quality of life (QOL) and toxicity in patients with Non-small cell Lung cancer (NSCLC) not suitable for radical chemo-radiotherapy (C-RT), experiencing symptoms from intrathoracic disease, who were randomized to receive palliative radiation therapy (PRT36/12) or concurrent chemotherapy and PRT (C-PRT40/20). **METHODS AND**

**MATERIALS:** We included patients with stage III or IV NSCLC, Eastern Co-operative Oncology Group (ECOG) Performance status 0-1, experiencing at least one of dyspnea, cough, hemoptysis or chest pain. The primary outcome was a change in intrathoracic response rate from baseline to six weeks post completion of therapy using (1) a composite measure, the Intrathoracic Symptom Burden Index (ISBI) and (2) individual symptom scores measured by the EORTC QLQ-C30 and QLQ-LC 13 instruments.

**RESULTS:** 76 patients were recruited with 68 eligible for analysis. 42.6% and 57.4% had stage III and IV disease respectively. The ISBI was significantly lower at 6 weeks post treatment than at baseline (adjusted mean difference -8.77, SE 2.67, 95%CI [-13.97, -3.58],  $p < 0.01$ ) for the entire cohort with no difference between trial arms ( $p = 0.34$ ). Both treatments provided effective palliation of individual symptoms with no significant difference between trial arms. QOL during treatment was significantly better for patients receiving C-PRT (40/20). There was no difference between arms in overall QOL between baseline and 6 weeks post treatment. There was no difference in toxicity between treatment arms during treatment nor between baseline and 6 weeks post treatment. There was no difference in progression-free survival (PFS). A non-statistically significant 3month improvement in median survival favored C-PRT(40/20). **CONCLUSION:** PRT(36/12) and C-PRT(40/20) provide effective symptom palliation in patients with stage III NSCLC not suitable for radical C-RT and in patients with Stage IV disease. Chemotherapy added to PRT(40/20) does not provide superior symptomatic relief in this patient cohort.

**[Radiation and immunotherapy: emerging mechanisms of synergy](#)** J Thorac Dis. 2020

Nov;12(11):7011-7023. doi: 10.21037/jtd-2019-cptn-07. William G Breen 1 , Konstantinos Leventakos 2 , Haidong Dong 3 , Kenneth W Merrell 1

Immunotherapy (IO) has become a standard treatment in patients with metastatic and locally advanced non-small cell lung cancer (NSCLC), and is now being tested in patients with early stage disease. IO agents currently in use for lung cancer target PD-1, PD-L1, and CTLA-4. While survival and tumor control have improved with IO, many patients have limited or short responses to IO. Therefore, methods to improve the systemic response to IO are needed. Radiation therapy (RT) is an integral component of lung cancer treatment, and may improve systemic response to IO by increasing antigen presentation, increasing co-stimulatory signaling, increasing T-cells recruitment, upregulating PD-L1, increasing tumor

stromal lymphocyte infiltration, and altering the microenvironment. IO after definitive chemoradiation is now standard treatment in unresectable stage III NSCLC following publication of the PACIFIC clinical trial. For early stage NSCLC, IO is being investigated in conjunction with stereotactic body radiotherapy (SBRT). The benefit of adding RT to IO in patients with metastatic disease may be especially pronounced in patients with low baseline PD-L1 expression, potentially when delivered as a short course of SBRT, as supported by the PEMBRO-RT clinical trial. Current and ongoing clinical trials are evaluating the optimal radiation dose, timing, and sequencing of RT with IO.

[Validating impact of pretreatment tumor growth rate on outcome of early-stage lung cancer treated with stereotactic body radiation therapy](#) Thorac Cancer. 2020 Nov 30. doi: 10.1111/1759-7714.13744.

Online ahead of print. Soha Atallah 1 2, Lisa W Le 3, Andrea Beznak 4 5, Robert MacRae 1 2, Andrew J Hope 4 5, Jason Pantarotto 1 2

**BACKGROUND:** To assess correlation of pretreatment specific growth rate (SGR) value of  $0.43 \times 10^{-2}$  with overall and failure-free survival of patients with early-stage non-small cell lung cancer (NSCLC) treated with stereotactic body radiation therapy (SBRT). **METHODS:** A retrospective chart review of 160 patients with pathologically confirmed stage I NSCLC treated with SBRT between June 2010 and December 2012 in a large, tertiary cancer institute was undertaken. Both diagnostic and archived planning CT were uploaded to the treatment planning system to determine tumor volume at diagnosis (GTV1) and planning time (GTV2). The time (t) between both CTs was recorded. SGR was calculated using GTV1, GTV2, and t. The median SGR ( $0.43 \times 10^{-2}$ ) from our previous data was used to group patients into low and high SGR cohorts. Log-rank test was used to compare overall (OS) and failure-free survivals (FFS) of SGR groups. **RESULTS:** The median time interval between diagnostic and planning CT scans was 87 days. The median OS was 38 and 66 months for high and low SGR cohorts, respectively ( $P = 0.03$ ). The median FFS was 27 and 55 months for high and low SGR cohorts, respectively ( $P = 0.005$ ). High SGR ( $P < 0.05$ ), male gender ( $P = <0.01$ ), and GTV2 ( $P = <0.05$ ) were associated with poorer FFS. **CONCLUSIONS:** High SGR was associated with poorer outcome in patients with early-stage NSCLC treated with SBRT. SGR can be used in conjunction with other well-known predictive factors to formulate a practical predictive model to identify subgroups of the patient at higher risk of recurrence after SBRT.

[Accumulation of the delivered dose based on cone-beam CT and deformable image registration for non-small cell lung cancer treated with hypofractionated radiotherapy](#) BMC Cancer. 2020 Nov

16;20(1):1112. doi: 10.1186/s12885-020-07617-3. Bin Wang 1, Da Quan Wang 1, Mao Sheng Lin 1, et al.

**BACKGROUND:** This study aimed to quantify the dosimetric differences between the planned and delivered dose to tumor and normal organs in locally advanced non-small cell lung cancer (LANSCLC) treated with hypofractionated radiotherapy (HRT), and to explore the necessity and identify optimal candidates for adaptive radiotherapy (ART). **METHODS:** Twenty-seven patients with stage III NSCLC were enrolled. Planned radiation dose was 51Gy in 17 fractions with cone-beam CT (CBCT) acquired at each fraction. Virtual CT was generated by deformable image registration (DIR) of the planning CT to CBCT for dose calculation and accumulation. Dosimetric parameters were compared between original and accumulated plans using Wilcoxon signed rank test. Correlations between dosimetric differences and clinical variables were analyzed using Mann-Whitney U test or Chi-square test. **RESULTS:** Patients had varied gross tumor volume (GTV) reduction by HRT (median reduction rate 11.1%, range - 2.9-44.0%). The V51 of planning target volume for GTV (PTV-GTV) was similar between original and accumulated plans (mean, 88.2% vs. 87.6%,  $p = 0.452$ ). Only 11.1% of patients had above 5% relative decrease in V51 of PTV-GTV in accumulated plans. Compared to the original plan, limited increase (median relative increase  $< 5\%$ ) was observed in doses of total lung (mean dose, V20 and V30), esophagus (mean dose,

maximum dose) and heart (mean dose, V30 and V40) in accumulated plans. Less than 30% of patients had above 5% relative increase of lung or heart doses. Patients with quick tumor regression or baseline obstructive pneumonitis showed more notable increase in doses to normal structures. Patients with baseline obstructive atelectasis showed notable decrease (10.3%) in dose coverage of PTV-GTV. **CONCLUSIONS:** LANSCLC patients treated with HRT had sufficient tumor dose coverage and acceptable normal tissue dose deviation. ART should be applied in patients with quick tumor regression and baseline obstructive pneumonitis/atelectasis to spare more normal structures.

[Stereotactic body radiation therapy mitigates radiation induced lymphopenia in early stage non-small cell lung cancer](#) PLoS One. 2020 Nov 30;15(11):e0241505. doi: 10.1371/journal.pone.0241505. eCollection 2020.

**INTRODUCTION:** Radiation-induced lymphopenia (RIL) occurs during treatment with conventional radiation in multiple organ sites. Development of RIL portends poor prognosis. Stereotactic body radiation therapy (SBRT) spares RIL in pancreatic cancer, but has not been examined in other sites commonly treated with SBRT. This work examines if SBRT similarly spares RIL in patients with non-small cell lung cancer (NSCLC). **MATERIALS AND METHODS:** Retrospective analysis was done at a single institution on 40 distinct cases of SBRT for early stage NSCLC from 2006-2017. Incidentally collected lymphocyte counts collected within 6 months of SBRT treatment were analyzed to determine if RIL occurred. The presence of RIL was correlated with location of initial failure and survival endpoints. Kaplan-Meier curves were constructed with significance defined at the level  $p < 0.05$ . **RESULTS:** RIL was observed in 35% of the analyzed patients. Patterns of failure and survival data were comparable to prior SBRT literature. There was no observed association in two year local, nodal, or distant failure, progression free survival, or overall survival based on the presence of RIL. **DISCUSSION:** SBRT spares RIL in NSCLC compared to historical rates observed with conventionally fractionated radiation. As understanding of the role of the immune system in cancer control continues to evolve, the importance of RIL sparing techniques take on increasing importance. This study represents further analysis of RIL sparing in SBRT in an early stage NSCLC cohort without the confounding influence of chemotherapy.

[Combined Immunotherapy and Stereotactic Radiotherapy Improves Neurologic Outcomes in Patients with Non-small-cell Lung Cancer Brain Metastases](#) Clin Lung Cancer. 2020 Nov 10;S1525-7304(20)30324-7. doi: 10.1016/j.clcc.2020.10.014. Online ahead of print.

Tom L Enright 1 , Jacob S Witt 2 , Adam R Burr 2 , Poonam Yadav 2 , Ticiana Leal 3 , Andrew M Baschnagel 4

**BACKGROUND:** The purpose of this study was to compare the outcomes of patients with non-small cell lung cancer (NSCLC) brain metastases treated with stereotactic radiotherapy (SRT) alone versus SRT and immune checkpoint inhibitors (ICIs). **PATIENTS AND METHODS:** Patients treated for their first diagnosis of intracranial metastases with SRT or SRT plus ICI were retrospectively identified. Overall survival (OS), local control (LC), distant brain failure (DBF), neurologic death, and rates of radiation necrosis were calculated. Univariate (UVA) and multivariable (MVA) analyses with competing risk analysis were performed. **RESULTS:** Seventy-seven patients with 132 lesions were analyzed, including 44 patients with 68 lesions in the SRT group and 33 patients with 64 lesions in the SRT plus ICI group. There were no differences in baseline factors between groups. Use of ICI predicted for decreased DBF (hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.24-0.84;  $P = .01$ ), decreased rates of neurologic death (HR, 0.29; 95% CI, 0.10-0.85;  $P = .02$ ), and better OS (HR, 0.46; 95% CI, 0.23-0.91;  $P = .03$ ). Two-year LC was 97% for the SRT + ICI group, and 86% for the SRT-alone group ( $P = .046$ ). Actuarial 2-year DBF was 39% for the SRT + ICI group and 66% for the SRT alone group ( $P = .016$ ). On MVA, ICI use persisted in predicting lower incidence of neurologic death (HR, 0.25; 95% CI, 0.09-0.72;  $P = .01$ ) and DBF (HR, 0.47; 95% CI, 0.25-0.85;  $P = .01$ ) when adjusted for competing risk of death.

**CONCLUSION:** In this cohort of patients with NSCLC brain metastases, ICI use combined with SRT predicted for improved LC and OS and decreased DBF and risk of neurologic death.

**[Whole-Brain Radiotherapy Can Improve the Survival of Patients with Multiple Brain Metastases from Non-Small Cell Lung Cancer Treated by Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors](#)**

Cancer Manag Res. 2020 Nov 6;12:11333-11340. doi: 10.2147/CMAR.S279096. eCollection 2020. Cheng Chen # 1 2 , Yan Wu 2 , Bao Ling Liu 2 , Hong Wei Wang 2 , Jian Hua Ma # 2 , Ju Ying Zhou # 1

**OBJECTIVE:** To observe whether whole-brain radiotherapy (WBRT) can bring survival benefits to patients with multiple brain metastases (BM) from non-small cell lung cancer (NSCLC) treated by epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) and determine the best time for WBRT intervention. **METHODS:** A retrospective analysis was performed on 148 patients diagnosed with EGFR gene-mutated NSCLC. All patients had multiple BM and received EGFR-TKI targeted therapy, which was performed to observe whether WBRT can bring survival benefits, and whether the choice of WBRT timing affects the survival of patients. **RESULTS:** Among the 148 patients with NSCLC treated with EGFR-TKI, 76 received WBRT; 72 were without WBRT. WBRT can reduce the intracranial progression rate in the patients (19.7% vs 33.3%,  $P=0.040$ ), thus improving the intracranial progression-free survival (iPFS) (median iPFS: 11.9 months versus 10.2 months,  $P=0.039$ ) and overall survival (OS) (median OS: 21.0 months versus 16.7 months,  $P=0.043$ ). Multivariate analysis showed that WBRT (HR=0.606; 95% CI: 0.403-0.912,  $P=0.016$ ) and the low Eastern Cooperative Oncology Group performance status (HR=1.884; 95% CI: 1.120-3.170,  $P=0.017$ ) are independent prognostic factors in all patients. Further subgroup analysis showed that the choice of WBRT time had no effect on patient survival. **CONCLUSION:** WBRT can improve the survival of patients with multiple BM from NSCLC receiving EGFR-TKI targeted therapy and is an independent prognostic factor. The choice of RT time has no effect on patient survival.

**[SABRTooth: a randomised controlled feasibility study of stereotactic ablative radiotherapy \(SABR\) with surgery in patients with peripheral stage I nonsmall cell lung cancer considered to be at higher risk of complications from surgical resection](#)**

Eur Respir J. 2020 Nov 12;56(5):2000118. doi: 10.1183/13993003.00118-2020. Print 2020 Nov. Kevin N Franks 1 2 3 , Lucy McParland 4 3 , Joanne Webster 4 , et al.

**OBJECTIVES:** Stereotactic ablative radiotherapy (SABR) is a well-established treatment for medically inoperable peripheral stage I nonsmall cell lung cancer (NSCLC). Previous nonrandomised evidence supports SABR as an alternative to surgery, but high-quality randomised controlled trial (RCT) evidence is lacking. The SABRTooth study aimed to establish whether a UK phase III RCT was feasible. **DESIGN AND METHODS:** SABRTooth was a UK multicentre randomised controlled feasibility study targeting patients with peripheral stage I NSCLC considered to be at higher risk of surgical complications. 54 patients were planned to be randomised 1:1 to SABR or surgery. The primary outcome was monthly average recruitment rates. **RESULTS:** Between July 2015 and January 2017, 318 patients were considered for the study and 205 (64.5%) were deemed ineligible. Out of 106 (33.3%) assessed as eligible, 24 (22.6%) patients were randomised to SABR (n=14) or surgery (n=10). A key theme for nonparticipation was treatment preference, with 43 (41%) preferring nonsurgical treatment and 19 (18%) preferring surgery. The average monthly recruitment rate was 1.7 patients against a target of three. 15 patients underwent their allocated treatment: SABR n=12, surgery n=3. **CONCLUSIONS:** We conclude that a phase III RCT randomising higher risk patients between SABR and surgery is not feasible in the National Health Service. Patients have pre-existing treatment preferences, which was a barrier to recruitment. A significant proportion of patients randomised to the surgical group declined and chose



SABR. SABR remains an alternative to surgery and novel study approaches are needed to define which patients benefit from a nonsurgical approach.

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## SMALL CELL LUNG CANCER - SCLC

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[Integrated Immunohistochemical Study on Small-Cell Carcinoma of the Lung Focusing on Transcription and Co-Transcription Factors](#) *Diagnostics (Basel)*. 2020 Nov 13;10(11):949. doi: 10.3390/diagnostics10110949. Younosuke Sato <sup>1</sup>, Isamu Okamoto <sup>2</sup>, Hiroki Kameyama <sup>3</sup>, et al. Small-cell lung cancer (SCLC) is an aggressive malignant cancer that is classified into four subtypes based on the expression of the following key transcription and co-transcription factors: ASCL1, NEUROD1, YAP1, and POU2F3. The protein expression levels of these key molecules may be important for the formation of SCLC characteristics in a molecular subtype-specific manner. We expect that immunohistochemistry (IHC) of these molecules may facilitate the diagnosis of the specific SCLC molecular subtype and aid in the appropriate selection of individualized treatments. We attempted IHC of the four key factors and 26 candidate SCLC target molecules selected from the gene expression omnibus datasets of 47 SCLC samples, which were grouped based on positive or negative results for the four key molecules. We examined differences in the expression levels of the candidate targets and key molecules. ASCL1 showed the highest positive rate in SCLC samples, and significant differences were observed in the expression levels of some target molecules between the ASCL1-positive and ASCL1-negative groups. Furthermore, the four key molecules were coordinately and simultaneously expressed in SCLC cells. An IHC study of ASCL1-positive samples showed many candidate SCLC target molecules, and IHC could become an essential method for determining SCLC molecular subtypes.

[Circulating Tumor DNA as a Prognostic Determinant in Small Cell Lung Cancer Patients Receiving Atezolizumab](#) *J Clin Med*. 2020 Nov 27;9(12):E3861. doi: 10.3390/jcm9123861. Guillaume Herbreteau <sup>1</sup>, Alexandra Langlais <sup>2</sup>, Laurent Greillier <sup>3</sup>, et al.

**BACKGROUND:** The IFCT-1603 trial evaluated atezolizumab in small cell lung cancer (SCLC). The purpose of the present study was to determine whether circulating tumor DNA (ctDNA), prospectively collected at treatment initiation, was associated with the prognosis of SCLC, and whether it identified patients who benefited from atezolizumab. **METHODS:** 68 patients were included in this study: 46 patients were treated with atezolizumab and 22 with conventional chemotherapy. Circulating DNA was extracted from plasma and NGS (Next Generation Sequencing) looked for mutations in the TP53, RB1, NOTCH1, NOTCH2, and NOTCH3 genes. ctDNA was detectable when at least one somatic mutation was identified, and its relative abundance was quantified by the variant allele fraction (VAF) of the most represented mutation. **RESULTS:** We found that 49/68 patients (70.6%) had detectable baseline ctDNA. The most frequently identified mutations were TP53 (32/49; 65.3%) and RB1 (25/49; 51.0%). Patients with detectable ctDNA had a significantly lower disease control rate at week 6 compared with patients with no detectable ctDNA, regardless of the nature of the treatment. Detection of ctDNA was associated with a poor OS prognosis. The detection of ctDNA at a relative abundance greater than the median value was significantly associated with poor overall survival (OS) and progression free survival (PFS). Interestingly, the benefit in overall survival (OS) associated with low ctDNA was more pronounced in patients treated with atezolizumab than in patients receiving chemotherapy. Among patients whose relative ctDNA abundance was below the median, those treated with atezolizumab tended to have higher OS than those in the chemotherapy arm. **CONCLUSION:** ctDNA is strongly associated with the prognosis of SCLC patients treated with second-line immunotherapy. Its analysis seems justified for future SCLC clinical trials.

[Epigenetic landscape of small cell lung cancer: small image of a giant recalcitrant disease](#) Semin Cancer Biol. 2020 Nov 18;S1044-579X(20)30240-6. doi: 10.1016/j.semcancer.2020.11.006. Online ahead of print. Parvez Khan 1 , Jawed Akhtar Siddiqui 1 , Shailendra Kumar Maurya 1 , et al.

Small cell lung cancer (SCLC) is a particular subtype of lung cancer with high mortality. Recent advances in understanding SCLC genomics and breakthroughs of immunotherapy have substantially expanded existing knowledge and treatment modalities. However, challenges associated with SCLC remain enigmatic and elusive. Most of the conventional drug discovery approaches targeting altered signaling pathways in SCLC end up in the 'grave-yard of drug discovery', which mandates exploring novel approaches beyond inhibiting cell signaling pathways. Epigenetic modifications have long been documented as the key contributors to the tumorigenesis of almost all types of cancer, including SCLC. The last decade witnessed an exponential increase in our understanding of epigenetic modifications for SCLC. The present review highlights the central role of epigenetic regulations in acquiring neoplastic phenotype, metastasis, aggressiveness, resistance to chemotherapy, and immunotherapeutic approaches of SCLC. Different types of epigenetic modifications (DNA/histone methylation or acetylation) that can serve as predictive biomarkers for prognostication, treatment stratification, neuroendocrine lineage determination, and development of potential SCLC therapies are also discussed. We also review the utility of epigenetic targets/epidrugs in combination with first-line chemotherapy and immunotherapy that are currently under investigation in preclinical and clinical studies. Altogether, the information presents the inclusive landscape of SCLC epigenetics and epidrugs that will help to improve SCLC outcomes.

[AMG 757, a Half-Life Extended, DLL3-Targeted Bispecific T-Cell Engager, Shows High Potency and Sensitivity in Preclinical Models of Small Cell Lung Cancer](#) Clin Cancer Res. 2020 Nov 17;clinres.2845.2020. doi: 10.1158/1078-0432.CCR-20-2845. Online ahead of print. Michael J Giffin 1 , Keegan Cooke 1 , Edward K Lobenhofer 2 , et al.

**PURPOSE:** Small cell lung cancer (SCLC) is an aggressive neuroendocrine tumor with a high relapse rate, limited therapeutic options, and poor prognosis. We investigated the antitumor activity of AMG 757, a half-life extended bispecific T-cell engager molecule targeting delta-like ligand 3 (DLL3) - a target selectively expressed in SCLC tumors but with minimal normal tissue expression. **METHODS:** AMG 757 efficacy was evaluated in SCLC cell lines and in orthotopic and patient-derived xenograft (PDX) mouse SCLC models. Following AMG 757 administration, changes in tumor volume, pharmacodynamic changes in tumor-infiltrating T cells (TILs), and the spatial relationship between the appearance of TILs and tumor histology were examined. Tolerability was assessed in nonhuman primates (NHP). **RESULTS:** AMG 757 showed potent and specific killing of even those SCLC cell lines with very low DLL3 expression (< 1000 molecules per cell). AMG 757 effectively engaged systemically administered human T cells, induced T cell activation, and redirected T cells to lyse tumor cells to promote significant tumor regression and complete responses in PDX models of SCLC and in orthotopic models of established primary lung SCLC and metastatic liver lesions. AMG 757 was well tolerated with no AMG 757-related adverse findings up to the highest tested dose (4.5 mg/kg weekly) in NHP. AMG 757 exhibits an extended half-life in NHP which is projected to enable intermittent administration in patients. **CONCLUSIONS:** AMG 757 has a compelling safety and efficacy profile in preclinical studies making it a viable option for targeting DLL3-expressing SCLC tumors in the clinical setting.

[Ex Vivo Expansion and Drug Sensitivity Profiling of Circulating Tumor Cells from Patients with Small Cell Lung Cancer](#) Cancers (Basel). 2020 Nov 16;12(11):3394. doi: 10.3390/cancers12113394. Hsin-Lun Lee 1 2 3 , Jeng-Fong Chiou 1 2 3 4 , Peng-Yuan Wang 5 6 , et al.

Small cell lung cancer (SCLC) represents one of the most aggressive malignancies among cancer types. Not only tumor sample availability is limited, but also the ability for tumor cells to rapidly acquire drug resistance are the rate-limiting bottlenecks for overall survival in current clinical settings. A liquid biopsy

capable of capturing and enriching circulating tumor cells (CTCs), together with the possibility of drug screening, is a promising solution. Here, we illustrate the development of a highly efficient ex vivo CTC expansion system based on binary colloidal crystals substrate. Clinical samples were enrolled from 22 patients with SCLC in the study. The CTCs were enriched and expanded from the collected peripheral blood samples. Expanded cells were analyzed for protein expression and observed for drug sensitivity with the use of immunofluorescence and ATP titer evaluation, respectively. Successful CTC spheroid proliferation was established after 4 weeks within 82% of all the collected peripheral blood samples from enrolled patients. Upon immunofluorescence analysis, the enriched cells showed positive markers for EpCAM, TTF-1, synaptophysin and negative for CD45. Additionally, the expanded CTCs demonstrated marked heterogeneity in the expression of E-cadherin and N-cadherin. In a preliminary case series, the drug sensitivity of patient-derived CTC to cisplatin and etoposide was studied to see the correlation with the corresponding therapeutic outcome. In conclusion, our study demonstrates that it is possible to efficiently expand CTCs from SCLC within a clinically relevant time frame; the biomarker information generated from enriched CTCs can assist the selection of effective drugs and improve disease outcome.

### **Clinicopathological features and prognostic implications of ASCL1 expression in surgically resected small cell lung cancer**

Thorac Cancer. 2020 Nov 15. doi: 10.1111/1759-7714.13705. Online ahead of print. Jiacong Wei # 1 , Li Liu # 1 , Yiyang Guo 2 , Jinyao Zhang 2 , Xin Wang 1 , Jiyan Dong 1 , Puyuan Xing 2 , Jianming Ying 1 , Lin Yang 1 , Junling Li 2

**BACKGROUND:** Small cell lung cancer (SCLC) is one of the most aggressive lung cancers. Treatment of SCLC has remained unchanged during the past decades. Preclinical studies have revealed ASCL1 as a transcription regulator in the neuroendocrine (NE) differentiation and carcinogenesis of SCLC. However, there are few studies on correlation of ASCL1 expression and clinicopathological factors in resected SCLCs. Here, we aimed to analyze the ASCL1 expression of SCLC and investigate its associations with clinicopathological factors and survival. **METHODS:** A total of 247 surgically resected pure SCLC specimens were included in this retrospective study, all of which were processed using tissue microarrays for immunohistochemistry analysis of ASCL1. A total of 48 of 247 cases were tested by NanoString for mRNA expression analysis on 50 SCLC related genes. Statistical analysis was performed using R studio and SPSS software. **RESULTS:** NE scores of 48 pure SCLC specimens were calculated by analyzing 50 preselected genes. A significant correlation between NE score with both ASCL1 mRNA expression and ASCL1 protein expression were observed. For the entire cohort of 247 patients, ASCL1 was highly expressed in 42.5% of pure SCLC patients according to IHC results. Significant differences were observed between ASCL1 high and low expression groups in variables including staging, lymph node metastasis, nerve invasion and overall survival. **CONCLUSIONS:** In limited staged pure SCLC, ASCL1 expression was positively correlated with NE signature, pTNM stage, nerve invasion and OS. ASCL1 may therefore serve as a potential biomarker to predict prognosis as well as in the selection of patients for therapies targeting ASCL1-regulated downstream molecules

### **Camrelizumab Plus Apatinib in Extensive-Stage Small-Cell Lung Cancer (PASSION): A Multicenter, Two-Stage, Phase 2 Trial**

J Thorac Oncol. 2020 Nov 6;S1556-0864(20)30806-6. doi: 10.1016/j.jtho.2020.10.002. Online ahead of print. Yun Fan 1 , Jun Zhao 2 , Qiming Wang 3 , et al.

**INTRODUCTION:** Treatment options in second-line extensive-stage small-cell lung cancer (ED-SCLC) setting are limited. PASSION (ClinicalTrials.gov identifier: NCT03417895) was a phase 2 study of camrelizumab plus apatinib in ED-SCLC after platinum-based chemotherapy. **METHODS:** In Stage 1, patients were randomized (1:1:1) to receive camrelizumab 200 mg every 2 weeks plus apatinib 375 mg once daily (QD), 5 days on/2 days off, or 7 days on/7 days off (six patients each cohort). Based on the tolerability during the first 28-day cycle and efficacy data in Stage 1, one cohort was chosen to expand to 45 patients in Stage 2. The primary endpoint was objective response rate (ORR). **RESULTS:** From Apr

20, 2018 to Mar 12, 2019, 59 patients were enrolled, with 47 patients in the QD cohort. In the QD cohort, confirmed ORR reached 34.0% (95% CI 20.9–49.3), the median progression-free survival (PFS) was 3.6 months, and the median overall survival (OS) was 8.4 months. Chemotherapy-sensitive and chemotherapy-resistant patients (defined as patients with disease relapsed  $\geq 90$  and  $< 90$  days after platinum-based chemotherapy, respectively) had comparable confirmed ORR (37.5% versus 32.3%), median PFS (3.6 versus 2.7 months), and median OS (9.6 versus 8.0 months). Treatment-related adverse events (TRAEs) of grade  $\geq 3$  were reported in 43 (72.9%) of 59 patients. Five (8.5%) patients discontinued due to TRAEs. **CONCLUSION:** Camrelizumab plus apatinib showed potential antitumor activity in both chemotherapy-sensitive and chemotherapy-resistant ED-SCLC patients who had failed platinum-based chemotherapy with acceptable toxicity profile. This phase 2 data warrant further clinical studies of camrelizumab plus apatinib in SCLC.

[Advances and Therapeutic Perspectives in Extended-Stage Small-Cell Lung Cancer](#) Cancers (Basel). 2020 Nov 1;12(11):3224. doi: 10.3390/cancers12113224. Thomas Pierret 1 , Anne-Claire Toffart 1 , Matteo Giaj Levra 1 , Denis Moro-Sibilot 1 , Elisa Gobbini 1 2

Extended small cell lung cancer (ED-SCLC) is a very aggressive disease, characterized by rapid growth and an early tendency to relapse. In contrast to non-small cell lung cancer, no therapeutic innovation has improved survival in patients with ED-SCLC over the past 20 years. Recently, immunotherapy has shown an important role in the management of these patients, emerging as the treatment of first choice in combination with chemotherapy and completely changing the therapeutic paradigm. However, patients' selection for this strategy is still challenging due to a lack of reliable predictive biomarkers. Conversely, the immunotherapy efficacy beyond the first line is pretty disappointing and innovative chemotherapies or target agents seem to be more promising in this setting. Some of them are also under evaluation as an upfront strategy and they will probably change the treatment algorithm in the next future. This proposal provides a comprehensive overview of available treatment strategies for ED-SCLC patients, highlighting their strengths and weaknesses

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## PALLIATIVE AND SUPPORTIVE CARE

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[Social needs and health-related quality of life among African American cancer survivors: Results from the Detroit Research on Cancer Survivors study](#) Cancer. 2020 Nov 23. doi: 10.1002/cncr.33286. Online ahead of print. Theresa A Hastert 1 2 , Jean A McDougall 3 , Shaila M Strayhorn 4 , Mrudula Nair 1 2 , Jennifer L Beebe-Dimmer 1 2 , Ann G Schwartz 1 2

**BACKGROUND:** Social needs may affect cancer survivors' health-related quality of life (HRQOL) above and beyond sociodemographic and cancer-related factors. The purpose of this study was to estimate associations between social needs and HRQOL. **METHODS:** Results included data from 1754 participants in the Detroit Research on Cancer Survivors cohort, a population-based study of African American survivors of breast, colorectal, lung, and prostate cancer. Social needs included items related to food insecurity, utility shutoffs, housing instability, not getting health care because of cost or a lack of transportation, and perceptions of neighborhood safety. HRQOL was measured with the validated Functional Assessment of Cancer Therapy-General (FACT-G). Linear regression models controlled for demographic, socioeconomic, and cancer-related factors. **RESULTS:** More than one-third of the survivors (36.3%) reported social needs including 17.1% of survivors reported 2 or more. The prevalence of social needs ranged from 14.8% for food insecurity to 8.9% for utility shutoffs. FACT-G score differences associated with social needs were -12.2 (95% confidence interval [CI] to -15.2 to -9.3) for not getting care because of a lack of transportation, -11.3 (95% CI, -14.2 to -8.4) for housing instability, -10.1 (95% CI, -12.7 to -7.4) for food insecurity, -9.8 (95% CI, -12.7 to -6.9) for feeling unsafe in the neighborhood, -8.6 (95% CI, -11.7 to -5.4) for utility shutoffs, and -6.7 (95% CI, -9.2 to -4.1) for not



getting care because of cost. **CONCLUSIONS:** Social needs were common in this cohort of African American cancer survivors and were associated with clinically significant differences in HRQOL. Clinical oncology care and survivorship care planning may present opportunities to screen for and address social needs to mitigate their impact on survivors' HRQOL.

**Implications of pneumonitis after chemoradiation and durvalumab for locally advanced non-small cell lung cancer** J Thorac Dis. 2020 Nov;12(11):6690-6700. doi: 10.21037/jtd-20-1792.

Comron Hassanzadeh<sup>1</sup>, Timothy Sita<sup>2</sup>, Rohan Savoor<sup>2</sup>, et al.

**BACKGROUND:** Consolidation durvalumab improved overall survival (OS) in locally advanced non-small cell lung cancer (LA-NSCLC) treated with chemoradiotherapy (CRT) in the PACIFIC trial; however, pneumonitis was increased with durvalumab. We sought to examine real-world outcomes with the PACIFIC paradigm, especially factors associated with pneumonitis, using a multi-institutional review. **METHODS:** Patients with LA-NSCLC treated with CRT followed by durvalumab from January 2017-February 2019 were identified at 2 institutions. We characterized demographics, tumor factors, radiotherapy, and duration of durvalumab. We examined pneumonitis outcomes including re-challenge success, with secondary endpoints of progression-free survival (PFS) and OS. **RESULTS:** Thirty-four patients were included with median follow-up of 12 months (range, 3 to 20 months); 94% had stage III disease. The cumulative grade >2 pneumonitis rate was 26.5% with 2 patients developing grade 3 pneumonitis and no grade 4/5 events. Median time to pneumonitis after RT was 2.4 months (range, 0 to 4.9 months). Pneumonitis management included median prednisone dose of 60 mg for median taper of 6 weeks with durvalumab held for median of 4.5 weeks (range, 2 to 8 weeks); 70% of pneumonitis patients received durvalumab re-challenge, with pneumonitis recurring in 14% of patients. 3-month and 6-month pneumonitis-free-survival were 76.9% and 73.6%, respectively; 9- and 12-month OS were 96% (75.1-99.8%), 86.6% (63.5-95.5%), respectively; 9- and 12-month PFS were 68% (47.5-82.5%), 48.7% (25.3-68.3%). Pneumonitis development did not significantly impact PFS or OS (P>0.05). **CONCLUSIONS:** Among LA-NSCLC patients treated with CRT followed by consolidation durvalumab, more than 25% developed symptomatic pneumonitis. In this small case series, pneumonitis did not appear to negatively impact survival, and durvalumab re-challenge appeared feasible after pneumonitis treatment with steroids.

**Rural-urban differences in health-related quality of life: patterns for cancer survivors compared to other older adults** Qual Life Res. 2020 Nov 2. doi: 10.1007/s11136-020-02683-3. Online ahead of print.

Jennifer L Moss<sup>1,2</sup>, Casey N Pinto<sup>3</sup>, Scherezade K Mama<sup>4</sup>, Maria Rincon<sup>5</sup>, Erin E Kent<sup>6</sup>, Mandi Yu<sup>7</sup>, Kathleen A Cronin<sup>7</sup>

**PURPOSE:** Health-related quality of life (HRQOL) among older cancer survivors can be impaired by factors such as treatment, comorbidities, and social challenges. These HRQOL impairments may be especially pronounced in rural areas, where older adults have higher cancer burden and more comorbidities and risk factors for poor health. This study aimed to assess rural-urban differences in HRQOL for older cancer survivors and controls. **METHODS:** Data came from Surveillance, Epidemiology, and End Results-Medicare Health Outcomes Survey (SEER-MHOS), which links cancer incidence from 18 U.S. population-based cancer registries to survey data for Medicare Advantage Organization enrollees (1998-2014). HRQOL measures were 8 standardized subscales and 2 global summary measures. We matched (2:1) controls to breast, colorectal, lung, and prostate cancer survivors, creating an analytic dataset of 271,640 participants (ages 65+). HRQOL measures were analyzed with linear regression models including multiplicative interaction terms (rurality by cancer status), controlling for sociodemographics, cohort, and multimorbidities. **RESULTS:** HRQOL scores were higher in urban than rural areas (e.g., global physical component summary score for breast cancer survivors: urban mean = 38.7, standard error [SE] = 0.08; rural mean = 37.9, SE = 0.32; p < 0.05), and were generally lower among cancer survivors compared to controls. Rural cancer survivors had particularly poor vitality

(colorectal:  $p = 0.05$ ), social functioning (lung:  $p = 0.05$ ), role limitation-physical (prostate:  $p < 0.01$ ), role limitation-emotional (prostate:  $p < 0.01$ ), and global mental component summary (prostate:  $p = 0.02$ ). **CONCLUSION:** Supportive interventions are needed to increase physical, social, and emotional HRQOL among older cancer survivors in rural areas. These interventions could target cancer-related stigma (particularly for lung and prostate cancers) and/or access to screening, treatment, and ancillary healthcare resources.

[Nurse-led, screening-triggered, early specialised palliative care intervention programme for patients with advanced lung cancer: study protocol for a multicentre randomised controlled trial](#)

BMJ Open. 2020 Nov 26;10(11):e037759. doi: 10.1136/bmjopen-2020-037759. Daisuke Fujisawa 1 2, Shigeki Umemura 3, Ayumi Okizaki 4 5 6, et al.

**INTRODUCTION:** It has been suggested that palliative care integrated into standard cancer treatment from the early phase of the disease can improve the quality of life of patients with cancer. In this paper, we present the protocol for a multicentre randomised controlled trial to examine the effectiveness of a nurse-led, screening-triggered, early specialised palliative care intervention programme for patients with advanced lung cancer. **METHODS AND ANALYSIS:** A total of 206 patients will be randomised (1:1) to the intervention group or the control group (usual care). The intervention, triggered with a brief self-administered screening tool, comprises comprehensive need assessments, counselling and service coordination by advanced-level nurses. The primary outcome is the Trial Outcome Index of the Functional Assessment of Cancer Therapy (FACT) at 12 weeks. The secondary outcomes include participants' quality of life (FACT-Lung), depression (Patient Health Questionnaire-9), anxiety (Generalized Anxiety Disorder-7), illness perception (Prognosis and Treatment Perceptions Questionnaire), medical service use and survival. A mixed-method approach is expected to provide an insight about how this intervention works. **ETHICS AND DISSEMINATION:** This study has been approved by the Institutional Review Board of the National Cancer Center Japan (approval number: 2016-235). The findings will be disseminated through peer-reviewed publications and conference presentations and will be reflected on to the national healthcare policy.

[The Sickness Behavior Inventory-Revised: Sickness behavior and its associations with depression and inflammation in patients with metastatic lung cancer](#)

Palliat Support Care. 2020 Nov 23;1-10. doi: 10.1017/S1478951520001169. Online ahead of print. Daniel C McFarland 1, Leah E Walsh 2, Rebecca Saracino 1, Christian J Nelson 1, William Breitbart 1, Barry Rosenfeld 2

**BACKGROUND:** Inflammation may contribute to the high prevalence of depressive symptoms seen in lung cancer. "Sickness behavior" is a cluster of symptoms induced by inflammation that are similar but distinct from depressive symptoms. The Sickness Behavior Inventory-Revised (SBI-R) was developed to measure sickness behavior. We hypothesized that the SBI-R would demonstrate adequate psychometric properties in association with inflammation. **METHOD:** Participants with stage IV lung cancer ( $n = 92$ ) were evaluated for sickness behavior using the SBI-R. Concomitant assessments were made of depression (Patient Hospital Questionnaire-9, Hospital Anxiety and Depression Scale) and inflammation [C-reactive protein (CRP)]. Classical test theory (CTT) was applied and multivariate models were created to explain SBI-R associations with depression and inflammation. Factor Analysis was also used to identify the underlying factor structure of the hypothesized construct of sickness behavior. A longitudinal analysis was conducted for a subset of participants. **RESULTS:** The sample mean for the 12-item SBI-R was 8.3 (6.7) with a range from 0 to 33. The SBI-R demonstrated adequate internal consistency with a Cronbach's coefficient of 0.85, which did not increase by more than 0.01 with any single-item removal. This analysis examined factor loadings onto a single factor extracted using the principle components method. Eleven items had factor loadings that exceeded 0.40. SBI-R total scores were significantly correlated with depressive symptoms ( $r = 0.78$ ,  $p < 0.001$ ) and CRP ( $r = 0.47$ ,  $p < 0.001$ ). Multivariate analyses revealed

that inflammation and depressive symptoms explained 67% of SBI-R variance. **SIGNIFICANCE OF RESULTS:** The SBI-R demonstrated adequate reliability and construct validity in this patient population with metastatic lung cancer. The observed findings suggest that the SBI-R can meaningfully capture the presence of sickness behavior and may facilitate a greater understanding of inflammatory depression.

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## COMPLEMENTARY & ALTERNATIVE THERAPY

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[The effects of traditional Chinese medicine combined with chemotherapy on immune function and quality of life in patients with non-small cell lung cancer: A protocol for systematic review and meta-analysis](#) *Medicine* (Baltimore). 2020 Nov 6;99(45):e22859. doi: 10.1097/MD.00000000000022859.

Li-Na Zhao 1 , Yin-Qing Yang 2 , Wen-Wen Wang 1 , Qian Li 1 , Hua Xiao 1

**BACKGROUND:** This article will evaluate the effects of traditional Chinese medicine (TCM) combined with chemotherapy on the immune function and quality of life of patients with non-small cell lung cancer (NSCLC), and evaluate the published side effects. **METHODS:** The systematic review and meta-analysis will be conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. The databases we will search include: PubMed, EMBASE, Cochrane Library, Web of Science, China National Knowledge Infrastructure, China Biomedicine, Wan fang Data, and Technology Periodical Database. The search date is from inception to June 30, 2020. There are no restrictions on the document language. The literatures included in this study are randomized controlled trials. The main results include ratio of CD3, CD4, CD8, CD4/CD8, NK cells, the level of IgA, IgG, IgM, and Karnofsky performance status score. The secondary result is to evaluate various side effects during treatment. We will use the Cochrane Collaboration tool to evaluate each study and use Review Manager software (RevMan, version 5.3) to merge and analyze the data. The 2 researchers will independently cross-screen the literature, extract data, and evaluate the quality. If there are differences, we will resolve them through discussion or consultation with a third reviewer. **RESULTS:** The results of this study will provide high-quality evidence for the effect of TCM combined with chemotherapy on the immune function and quality of life of patients with NSCLC. **CONCLUSION:** This article will comprehensively evaluate the effects of TCM combined with chemotherapy on the immune function and quality of life of patients with NSCLC and provide evidence-based evidence for clinical practice.

[Efficacy and safety of TCM combined with chemotherapy for SCLC: a systematic review and meta-analysis](#) *J Cancer Res Clin Oncol*. 2020 Nov;146(11):2913-2935. doi: 10.1007/s00432-020-03353-0.

Epub 2020 Aug 14. Shuntai Chen 1 2 , Yanju Bao 3 , Jing Xu 4 , et al.

**BACKGROUND:** Chemotherapy is the standard treatment for small cell lung cancer (SCLC), but chemotherapy resistance and adverse reactions remain major problems. Although Traditional Chinese Medicine (TCM) is widely applied for patients with SCLC in China, the evidence of TCM in the treatment for SCLC is limited. **PURPOSE:** To evaluate the efficacy and safety of TCM combined with chemotherapy for patients with SCLC. **METHOD:** We conducted a systematic search of PubMed, EMBASE, the Chinese National Knowledge Infrastructure, the VIP Information Database, and the Wanfang Database for randomized-controlled trials (RCTs) that are relevant. The included studies were reviewed by two investigators, with relevant data extracted independently. The effect estimate of interest was the relative risk (RR) or mean difference with 95% confidence intervals (95% CIs). **RESULTS:** 22 RCTs involving 1887 patients were included in this study. Compared with patients treated with chemotherapy alone, those with Chinese herbal medicine and chemotherapy (TCM-C) had better therapeutic effects (RR = 1.295, 95% CI 1.205-1.391, P < 0.001), KPS scores (RR = 1.310, 95% CI 1.210-1.418, P < 0.001), 1-year survival rate (RR = 1.282, 95% CI 1.129-1.456, P < 0.001), 3-year survival rate (RR = 2.109, 95% CI 1.514-2.939, P < 0.001), and 5-year survival rate (RR = 2.373, 95% CI 1.227-4.587, P = 0.01). The incidence of gastrointestinal reaction (RR of = 0.786, 95% CI 0.709-0.870, P

< 0.000) and bone marrow depression (RR = 0.837, 95% CI 0.726-0.965, P = 0.014) in TCM-C group were lower than that in the C group. **CONCLUSION:** The systematic review indicated that TCM combined with chemotherapy may improve therapeutic effect, quality of life, and prolong survival time. More large-scale and higher quality RCTs are warranted to support our findings.

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## MISCELLANEOUS WORKS

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### [An Assessment of Distress Levels of Patients Undergoing Lung Cancer Treatment and Surveillance During the COVID-19 Pandemic](#) J Nurse Pract. 2020 Nov 21. doi: 10.1016/j.nurpra.2020.10.020.

Denise Albano, Melissa Feraca, Barbara Nemesure

**BACKGROUND:** According to the Centers for Disease Control and Prevention, COVID-19 has affected more than 5,119,711 patients with more than 163,651 confirmed deaths reported. The mass media coverage and widespread eruption of illnesses have been associated with adverse mental health outcomes.<sup>1</sup> Cancer patients represent an already-compromised population with elevated levels of anxiety and distress; the introduction of the COVID-19 pandemic places this vulnerable group at an even higher risk for mental health consequences. The purpose of this quality improvement initiative was to identify lung cancer patients in our care who demonstrated increased levels of anxiety and distress directly related to the COVID-19 pandemic and to facilitate the acquisition of appropriate care to address their mental health needs. This initiative was designed to aid in the reduction of stress and anxiety in an already burdened population. **METHODS:** The sample included 441 patients undergoing treatment for or surveillance of lung cancer who were screened from April 2020 to July 2020 through the Lung Cancer Evaluation Center. Using the National Comprehensive Cancer Network (NCCN) Distress Thermometer, patients were called and asked a series of questions regarding their distress levels in relation to the COVID-19 pandemic. The NCCN tool uses a numeric scale from 0 to 10 to quantify level of distress, with 0 representing no distress and 10 indicating severe distress. Any patient scoring a 6 or greater was referred to the cancer center social worker. The social worker evaluated the patients' needs and formulated a plan. Any patient who reported a distress level between 3 and 5 was counseled by the nurse practitioner to evaluate further needs. Patients reported reasons for distress as fear of delayed testing, contracting the virus, and changes in their lifestyle (not seeing family, isolation, etc.). **RESULTS:** We found that screening all patients during the pandemic yielded a higher than normal percentage of individuals who were in need of some level of mental health services. Cancer patients, particularly lung cancer patients, have increased fear due to the respiratory symptoms of COVID-19. After completion of this quality improvement initiative, we have incorporated distress assessment and triage protocols into our practice for all patients. **IMPORTANCE AND IMPLICATIONS:** Patients with underlying medical conditions including cancer know that they are at increased risk of complications from the COVID-19 virus. This may cause them increased anxiety, distress, and fear. Screening this population with phone calls can effectively identify patients at risk, and with the implementation of this initiative, we can ensure that those who feel isolated or experience heightened levels of distress receive the appropriate care they need.

### [Potential Drug Interactions of Repurposed COVID-19 Drugs with Lung Cancer Pharmacotherapies](#) Arch Med Res. 2020 Nov 17;S0188-4409(20)31189-9. doi:

10.1016/j.arcmed.2020.11.006. Online ahead of print. Gayathri Baburaj 1, Levin Thomas 1, Mahadev Rao 2

Lung cancer patients are at heightened risk for developing COVID-19 infection as well as complications due to multiple risk factors such as underlying malignancy, anti-cancer treatment induced immunosuppression, additional comorbidities and history of smoking. Recent literatures have reported a significant proportion of lung cancer patients coinfecting with COVID-19. Chloroquine, hydroxychloroquine, lopinavir/ritonavir, ribavirin, oseltamivir, remdesivir, favipiravir, and umifenovir



represent the major repurposed drugs used as potential experimental agents for COVID-19 whereas azithromycin, dexamethasone, tocilizumab, sarilumab, famotidine and ceftriaxone are some of the supporting agents that are under investigation for COVID-19 management. The rationale of this review is to identify potential drug-drug interactions (DDIs) occurring in lung cancer patients receiving lung cancer medications and repurposed COVID-19 drugs using Micromedex and additional literatures. This review has identified several potential DDIs that could occur with the concomitant treatments of COVID-19 repurposed drugs and lung cancer medications. This information may be utilized by the healthcare professionals for screening and identifying potential DDIs with adverse outcomes, based on their severity and documentation levels and consequently design prophylactic and management strategies for their prevention. Identification, reporting and management of DDIs and dissemination of related information should be a major consideration in the delivery of lung cancer care during this ongoing COVID-19 pandemic for better patient outcomes and updating guidelines for safer prescribing practices in this coinfecting condition.

### **Time to surgery in thoracic cancers and prioritization during COVID-19: a systematic review**

J Thorac Dis. 2020 Nov;12(11):6640-6654. doi: 10.21037/jtd-20-2400.

Scott C Fligor 1 , Savas T Tsikis 1 , Sophie Wang 1 , Ana Sofia Ore 1 , Benjamin G Allar 1 , Ashlyn E Whitlock 1 , Rodrigo Calvillo-Ortiz 1 , Kevin Arndt 1 , Mark P Callery 1 , Sidhu P Gangadharan 1

**BACKGROUND:** Coronavirus disease 2019 (COVID-19) has overwhelmed hospital resources worldwide, requiring widespread cancellation of non-emergency operations, including lung and esophageal cancer operations. In the United States, while hospitals begin to increase surgical volume and tackle the backlog of cases, the specter of a "second wave," with a potential vaccine months to years away, highlights the ongoing need to triage cases based upon the risk of surgical delay. We synthesize the available literature on time to surgery and its impact on outcomes along with a critical appraisal of the released triage guidelines in the United States.

**METHODS:** We performed a systematic literature review using PubMed according to preferred reporting items for systematic reviews and meta-analyses guidelines evaluating relevant literature from the past 15 years. **RESULTS:** Out of 679 screened abstracts, 12 studies investigating time to surgery in lung cancer were included. In stage I-II lung cancer, delayed resection beyond 6 to 8 weeks is consistently associated with lower survival. No identified evidence justifies a 2 cm cutoff for immediate versus delayed surgery. For stage IIIa lung cancer, time to surgery greater than 6 weeks after neoadjuvant therapy is similarly associated with worse survival. For esophageal cancer, 254 abstracts were screened and 23 studies were included. Minimal literature addresses primary esophagectomy, but time to surgery over 8 weeks is associated with lower survival. In the neoadjuvant setting, longer time to surgery is associated with increased pathologic complete response, but also decreased survival. The optimal window for esophagectomy following neoadjuvant therapy is 6 to 8 weeks. **CONCLUSIONS:** In the setting of the COVID-19 pandemic, timely resection of lung and esophageal cancer should be prioritized whenever possible based upon local resources and disease-burden.

### **Impact of COVID-19 on Cancer Care: How the Pandemic Is Delaying Cancer Diagnosis and Treatment for American Seniors**

JCO Clin Cancer Inform. 2020 Nov;4:1059-1071. doi: 10.1200/CCI.20.00134. Debra Patt 1 , Lucio Gordan 2 , Michael Diaz 2 , Ted Okon 3 , Lance Grady 4 , Merrill Harmison 4 , Nathan Markward 4 , Milena Sullivan 4 , Jing Peng 4 , Anan Zhou 4

**PURPOSE:** While the immediate care and access disruptions associated with the COVID-19 pandemic have received growing attention in certain areas, the full range of gaps in cancer screenings and treatment is not yet well understood or well documented throughout the country comprehensively. **METHODS:** This study used a large medical claims clearinghouse database representing 5%-7% of the Medicare fee-for-service population to characterize changes in the utilization of cancer care services and gain insight

into the impact of COVID-19 on the US cancer population, including identification of new patients, gaps in access to care, and disruption of treatment journeys. **RESULTS:** In March-July 2020, in comparison with the baseline period of March-July 2019, there is a substantial decrease in cancer screenings, visits, therapy, and surgeries, with variation by cancer type and site of service. At the peak of the pandemic in April, screenings for breast, colon, prostate, and lung cancers were lower by 85%, 75%, 74%, and 56%, respectively. Significant utilization reductions were observed in April for hospital outpatient evaluation and management (E&M) visits (-74%), new patient E&M visits (-70%), and established patient E&M visits (-60%). A decrease in billing frequency was observed for the top physician-administered oncology products, dropping in both April (-26%) and July (-31%). Mastectomies were reduced consistently in April through July, with colectomies similarly reduced in April and May and prostatectomies dipping in April and July. **CONCLUSION:** The current impact of the COVID-19 pandemic on cancer care in the United States has resulted in decreases and delays in identifying new cancers and delivery of treatment. These problems, if unmitigated, will increase cancer morbidity and mortality for years to come.

[Smoking-Related Social Interactions as Experienced by Persons Who Smoked Long-term](#) Clin Nurse Spec. Nov/Dec 2020;34(6):282-289. doi: 10.1097/NUR.0000000000000555.

Claire Burke Draucker 1, Susan M Rawl, Emilee Vode, Matthew Fields, Candice Elkins, Olivia Morgan, Sara R Perez, Lucy Straber, Lisa Carter-Harris

**PURPOSE/AIMS:** Smoking-related stigma is manifested in the everyday social interactions of persons who smoke and can result in low self-esteem, diminished self-efficacy, and resistance to smoking cessation. The purpose of this study was to describe smoking-related social interactions as experienced by persons with a history of long-term smoking. **DESIGN:** This study used a qualitative descriptive approach. **METHODS:** This study is part of a larger study designed to identify factors that influence lung cancer screening participation. Data were drawn from 39 qualitative interviews with persons from the parent study. All descriptions about smoking-related social interactions found in the narratives were extracted, coded, categorized, and summarized with content analytic techniques. **RESULTS:** Seven different types of social interactions were identified: (a) being looked down on for smoking, (b) being humiliated for smoking in public, (c) being banished while smoking, (d) being blamed for one's health problems, (e) not "really" being blamed for smoking, (f) being told "just quit," and (g) being worried about hurting others. **CONCLUSIONS:** Clinical nurse specialists should promote antismoking campaigns that are not stigmatizing, discuss health risks of smoking in a respectful manner, provide evidence-based cessation resources, improve communication with persons who smoke, and address stigma in programs to improve screening for smoking-related illnesses.

[Exceptional Survival Among Kentucky Stage IV Non-small Cell Lung Cancer Patients: Appalachian Versus Non-Appalachian Populations](#) J Rural Health. 2020 Nov 18. doi:

10.1111/jrh.12537. Online ahead of print. Vira Pravosud 1, Nathan L Vanderford 2 3, Bin Huang 4 3, Thomas C Tucker 1 3, Susanne M Arnold 5 3

**PURPOSE:** To determine differences in exceptional survival (ES)-survival of 5 years or more past diagnosis-between stage IV non-small cell lung cancer (NSCLC) patients residing in the Appalachian versus non-Appalachian regions of Kentucky. **METHODS:** This was a population-based, retrospective case-control study of Kentucky patients, diagnosed with stage IV NSCLC between January 1, 2000, and December 31, 2011. The data were drawn from the Kentucky Cancer Registry. **FINDINGS:** Findings from the multivariable logistic regression revealed no significant differences in the odds of ES between patients who resided in Appalachian versus non-Appalachian Kentucky. Being female and undergoing surgery only as the first course of treatment were associated with higher odds of ES. Increasing age, unspecified histology, having poorly differentiated or undifferentiated carcinomas, and receiving radiation therapy only as the first course of treatment were associated with decreased odds of ES. **CONCLUSION:**

Differences in the odds of ES among stage IV NSCLC patients were not related to residence in Appalachian versus non-Appalachian Kentucky. ES was associated with other nongenetic and treatment factors that warrant further investigations.

[Coronavirus Disease 2019 Infection in a Patient Population with Lung Cancer: Incidence, Presentation, and Alternative Diagnostic Considerations](#) JTO Clin Res Rep. 2021 Jan;2(1):100124. doi: 10.1016/j.jtocrr.2020.100124. Epub 2020 Nov 12. Andrew J Piper-Vallillo 1 2 , Meghan J Mooradian 1 , Catherine B Meador 1 , et al.

**INTRODUCTION:** Lung cancer is associated with severe coronavirus disease 2019 (COVID-19) infections. Symptom overlap between COVID-19 and lung cancer may complicate diagnostic evaluation. We aimed to investigate the incidence, symptoms, differential diagnosis, and outcomes of COVID-19 in patients with lung cancer. **METHODS:** To determine an at-risk population for COVID-19, we retrospectively identified patients with lung cancer receiving longitudinal care within a single institution in the 12 months (April 1, 2019 to March 31, 2020) immediately preceding the COVID-19 pandemic, including an "active therapy population" treated within the last 60 days of this period. Among patients subsequently referred for COVID-19 testing, we compared symptoms, laboratory values, radiographic findings, and outcomes of positive versus negative patients. **RESULTS:** Between April 1, 2019 and March 31, 2020, a total of 696 patients received longitudinal care, including 406 (58%) in the active therapy population. Among 55 patients referred for COVID-19 testing, 24 (44%) were positive for COVID-19, representing a cumulative incidence of 3.4% (longitudinal population) and 1.5% (active therapy population). Compared with patients who were COVID-19 negative, those who were COVID-19 positive were more likely to have a supplemental oxygen requirement (11% versus 54%,  $p = 0.005$ ) and to have typical COVID-19 pneumonia imaging findings (5 versus 56%,  $p = 0.001$ ). Otherwise, there were no marked differences in presenting symptoms. Among patients who were COVID-19 negative, alternative etiologies included treatment-related toxicity (26%), atypical pneumonia (22%), and disease progression (22%). A total of 16 patients positive for COVID-19 (67%) required hospitalization, and seven (29%) died from COVID-related complications. **CONCLUSIONS:** COVID-19 was infrequent in this lung cancer population, but these patients experienced high rates of morbidity and mortality. Oncologists should maintain a low threshold for COVID-19 testing in patients with lung cancer presenting with acute symptoms.