



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

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

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#### [SHR-A1403, a novel c-mesenchymal-epithelial transition factor \(c-Met\) antibody-drug conjugate, overcomes AZD9291 resistance in non-small cell lung cancer cells overexpressing c-Met.](#)

Tong M1,2, Gao M1,2, Xu Y1,2, Fu L1,2, Li Y1,2, Bao X1,2, Fu H1,2, Quan H1,2, Lou L1,2. *Cancer Sci.* 2019 Nov;110(11):3584-3594. doi: 10.1111/cas.14180. Epub 2019 Sep 9.

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) have been used as the first-line treatment of non-small cell lung cancers (NSCLC) harboring EGFR-activating mutations, but acquired resistance is ubiquitous and needs to be solved urgently. Here, we introduce an effective approach for overcoming resistance to the EGFR-TKI, AZD9291, in NSCLC cells using SHR-A1403, a novel c-mesenchymal-epithelial transition factor (c-Met)-targeting antibody-drug conjugate (ADC) consisting of an anti-c-Met monoclonal antibody (c-Met mAb) conjugated to a microtubule inhibitor. Resistant cells were established by exposing HCC827 to increasing concentrations of EGFR-TKI. c-Met was found to be overexpressed in most resistant cells. AZD9291 resistance was partially restored by combination of AZD9291 and crizotinib only in resistant cells overexpressing phospho-c-Met, which synergistically inhibited c-Met-mediated phosphorylation of the downstream targets ERK1/2 and AKT. In resistant cells overexpressing c-Met, neither crizotinib nor c-Met mAb was able to overcome AZD9291 resistance. In contrast, SHR-A1403 strongly inhibited proliferation of AZD9291-resistant HCC827 overexpressing c-Met, regardless of the levels of c-Met phosphorylation. SHR-A1403 bound to resistant cells overexpressing c-Met was internalized into cells and released associated microtubule inhibitor, resulting in cell-killing activity that was dependent on c-Met expression levels only, irrespective of the involvement of c-Met or EGFR signaling in AZD9291 resistance. Consistent with its activity in vitro, SHR-A1403 significantly inhibited the growth of AZD9291-resistant HCC827 tumors and caused tumor regression in vivo. Thus, our findings show that SHR-A1403 efficiently overcomes AZD9291 resistance in cells overexpressing c-Met, and further indicate that c-Met expression level is a biomarker predictive of SHR-A1403 efficacy.

[A utility approach to individualized optimal dose selection using biomarkers.](#) Li P1, Taylor JMG1, Kong S2, Jolly S3, Schipper MJ1,3. *Biom J.* 2019 Nov 6. doi: 10.1002/bimj.201900030. [Epub ahead of print]

In many settings, including oncology, increasing the dose of treatment results in both increased efficacy and toxicity. With the increasing availability of validated biomarkers and prediction models, there is the potential for individualized dosing based on patient specific factors. We consider the setting where there is an existing dataset of patients treated with heterogeneous doses and including binary efficacy and toxicity outcomes and patient factors such as clinical features and biomarkers. The goal is to analyze the data to estimate an optimal dose for each (future) patient based on their clinical features and biomarkers. We propose an optimal individualized dose finding rule by maximizing utility functions for individual patients while limiting the rate of toxicity. The utility is defined as a weighted combination of efficacy and toxicity probabilities. This approach maximizes overall efficacy at a prespecified constraint on overall toxicity. We model the binary efficacy and toxicity outcomes using logistic regression with dose, biomarkers and dose-biomarker interactions. To incorporate the large number of potential parameters, we use the LASSO method. We additionally constrain the dose effect to be non-negative for both efficacy and toxicity for all patients. Simulation studies show that the utility approach combined with any of the modeling methods can improve efficacy without increasing toxicity relative to fixed dosing. The proposed methods are illustrated using a dataset of patients with lung cancer treated with radiation therapy.

[Initial Results from Mobile Low-Dose Computerized Tomographic Lung Cancer Screening Unit: Improved Outcomes for Underserved Populations.](#) Raghavan D1, Wheeler M2, Doege D2, Doty JD 2nd2, Levy H2, Dungan KA2, Davis LM2, Robinson JM2, Kim ES2, Mileham KF2, Oliver J2, Carrizosa D. *Oncologist.* 2019 Nov 26. pii: theoncologist.2019-0802. doi: 10.1634/theoncologist.2019-0802. [Epub ahead of print]

**INTRODUCTION:** The National Lung Screening Trial (NLST) demonstrated that screening high-risk patients with low-dose computed tomography (CT) of the chest reduces lung cancer mortality compared with screening with chest x-ray. Uninsured and Medicaid patients usually lack access to this hospital-based screening test because of geographic and socioeconomic factors. We hypothesized that a mobile screening unit would improve access and confer the benefits demonstrated by the NLST to this underserved group, which is most at risk of lung cancer deaths. **PATIENTS AND METHODS:** We created a mobile unit by building a Samsung BodyTom portable 32-slice low-dose CT scanner into a 35-foot coach; it delivers high-quality images for both soft tissue and bone and includes a waiting area and high-speed wireless internet connection for fast image transfer. The unit was extensively tested to show robustness and stability of mobile equipment. This project was designed to screen uninsured and underinsured patients, otherwise with eligibility criteria identical to that of the National Lung Screening Trial, with the only difference being exclusion of patients eligible for Medicare (which provides financial coverage for CT-based lung cancer screening). **RESULTS:** We screened 550 patients (20% black, 3% Hispanic, 70% rural) with a male-to-female ratio of 1.1:1, median age 61 years (range, 55-64), and found 12 lung cancers at initial screen (2.2%), including 6 at stage I-II (58% of total lung cancers early stage) and 38 Lung-RADS 4 (highly suspicious) lesions that are being followed closely. Incidental findings included nonlung cancers and coronary artery disease. **DISCUSSION:** In this initial pilot study, using the first mobile low-dose whole body CT screening unit in the U.S., the initial cancer detection rate is comparable to that reported in the NLST, despite excluding patients over the age of 64 years who have Medicare coverage, but with marked improvement of screening rates specifically in underserved sociodemographic, racial, and ethnic groups and with better outcomes than conventionally found in the underserved and at lower cost per case. **IMPLICATIONS FOR PRACTICE:** This study shows clearly

that a mobile low-dose CT scanning unit allows effective lung cancer screening for underserved populations, such as impoverished African Americans, Hispanics, Native Americans, or isolated rural groups, and has a pick-up rate of 1% for early stage disease. If confirmed in a planned randomized trial, this will be policy changing, as these groups usually present with advanced disease; this approach will produce better survival data at lower cost per case.

[A Prospective Randomized Comparative Study of Three Guided Bronchoscopic Approaches for Investigating Pulmonary Nodules: The PRECISION-1 Study.](#) Yarmus L1, Akulian J2, Wahidi M3, et al. *Chest*. 2019 Nov 1. pii: S0012-3692(19)34119-4. doi: 10.1016/j.chest.2019.10.016. [Epub ahead of print]

**BACKGROUND:** The capability of bronchoscopy in the diagnosis of peripheral pulmonary nodules (PPNs) remains limited. Despite decades of effort, evidence suggests that the diagnostic accuracy for electromagnetic navigational bronchoscopy (EMN) and radial endobronchial ultrasound (EBUS) approach only 50%. New developments in robotic bronchoscopy (RB) may offer improvements in the assessment of PPNs. **METHODS:** A prospective single-blinded randomized controlled comparative study to assess success in localization and puncture of PPNs, using an ultrathin bronchoscope with radial EBUS (UTB-rEBUS) vs EMN vs RB in a human cadaver model of PPNs < 2 cm, was performed. The primary end point was the ability to successfully localize and puncture the target nodule, verified by cone-beam CT comparing RB and EMN. Secondary end points included needle to target position "miss" distance, and UTB-rEBUS comparisons. **RESULTS:** Sixty procedures were performed to target 20 PPNs over the study period. Implanted PPNs were distributed across all lobes, with 80% located within the lung periphery. The target PPN mean diameter was  $16.5 \pm 1.5$  mm, with 50% noted to have a CT bronchus sign. The rate of successful PPN localization and puncture was superior when using RB, compared with EMN (80% vs 45%;  $P = .02$ ). Among unsuccessful needle passes, the median needle to target "miss" distance was significantly different when comparing UTB-rEBUS, EMN, and RB ( $P = .0014$ ). **CONCLUSIONS:** In a cadaver model, use of RB significantly increased the ability to localize and successfully puncture small PPNs when compared with existing technologies. This study demonstrates the potential of RB to precisely reach, localize, and puncture small nodules in the periphery of the lung.

[Cost-effectiveness of lung MRI in lung cancer screening.](#) Allen BD1, Schiebler ML2, Sommer G3, Kauczor HU4,5, Biederer J4,5,6,7, Kruser TJ8, Carr JC9, Hazen G10. *Eur Radiol*. 2019 Nov 20. doi: 10.1007/s00330-019-06453-9. [Epub ahead of print]

**OBJECTIVES:** Recent studies with lung MRI (MRI) have shown high sensitivity (Sn) and specificity (Sp) for lung nodule detection and characterization relative to low-dose CT (LDCT). Using this background data, we sought to compare the potential screening performance of MRI vs. LDCT using a Markov model of lung cancer screening. **METHODS:** We created a Markov cohort model of lung cancer screening which incorporated lung cancer incidence, progression, and mortality based on gender, age, and smoking burden. Sensitivity (Sn) and Sp for LDCT were taken from the MISCAN Lung Microsimulation and Sn/Sp for MRI was estimated from a published substudy of the German Lung Cancer Screening and Intervention Trial. Screening, work-up, and treatment costs were estimated from published data. Screening with MRI and LDCT was simulated for a cohort of male and female smokers (2 packs per day; 36 pack/years of smoking history) starting at age 60. We calculated the screening performance and cost-effectiveness of MRI screening and performed a sensitivity analysis on MRI Sn/Sp and cost. **RESULTS:** There was no difference in life expectancy between MRI and LDCT screening (males 13.28 vs. 13.29 life-years; females 14.22 vs. 14.22 life-years). MRI had a favorable cost-effectiveness ratio of \$258,169 in men and \$403,888 in women driven by fewer false-positive screens. On sensitivity analysis, MRI remained cost effective at screening costs < \$396 dollars and  $Sp > 81\%$ . **CONCLUSIONS:** In this Markov model of lung cancer screening, MRI has a near-equivalent life expectancy benefit and has

superior cost-effectiveness relative to LDCT. **KEY POINTS:** • In this Markov model of lung cancer screening, there is no difference in mortality between yearly screening with MRI and low-dose CT. • Compared to low-dose CT, screening with MRI led to a reduction in false-positive studies from 26 to 2.8% in men and 26 to 2.6% in women. • Due to similar life-expectancy and reduced false-positive rate, we found a favorable cost-effectiveness.

[Impact of coexisting gene mutations in EGFR-mutated non-small cell lung cancer before treatment on EGFR T790M mutation status after EGFR-TKIs.](#) Takeda M1, Sakai K2, Hayashi H3, Tanaka K3, Haratani K3, Takahama T3, Kato R3, Yonesaka K3, Nishio K2, Nakagawa K3. Lung Cancer. 2019 Nov 3;139:28-34. doi: 10.1016/j.lungcan.2019.10.028. [Epub ahead of print]

**OBJECTIVES:** The T790M secondary mutation of epidermal growth factor receptor gene (EGFR) is the most common mechanism of acquired resistance to first- or second-generation EGFR tyrosine kinase inhibitors (TKIs). We investigated the association between gene mutation profile in EGFR mutation-positive non-small cell lung cancer (NSCLC) before EGFR-TKI treatment and T790M status after EGFR-TKI treatment. **MATERIALS AND METHODS:** A total of 57 EGFR mutation-positive NSCLC patients who had undergone a repeat biopsy (tissue or liquid) after failure of treatment with a first- or second-generation EGFR-TKI and who had sufficient tumor tissue available from before treatment for genetic analysis was enrolled. The gene mutation profile of tumor tissue obtained before EGFR-TKI treatment was evaluated by next-generation sequencing with a comprehensive cancer gene panel (409 genes). The number of potentially damaging nonsynonymous mutations was predicted with PolyPhen-2 software. **RESULTS:** Progression-free survival during EGFR-TKI treatment did not differ significantly between patients who developed T790M-mediated resistance and those who developed T790M-independent resistance. The predicted number of damaging nonsynonymous mutations in pretreatment tumor tissue was significantly lower in patients who developed T790M-mediated resistance than in those with T790M-independent resistance ( $P = 0.049$ ). **CONCLUSIONS:** Coexisting mutations in tumor tissue before EGFR-TKI treatment may contribute to the emergence of cell clones responsible for development of T790M-dependent or T790M-independent TKI resistance in patients with EGFR-mutated NSCLC. Multiplex genomic testing of pretreatment tumor tissue may thus provide a means of identifying patients likely to develop T790M-mediated TKI resistance and therefore inform treatment selection.

[What Exactly Is Shared Decision-Making? A Qualitative Study of Shared Decision-Making in Lung Cancer Screening.](#) Melzer AC1,2, Golden SE3, Ono SS3,4, Datta S5, Crothers K6,7, Slatore CG3,8,9. J Gen Intern Med. 2019 Nov 19. doi: 10.1007/s11606-019-05516-3. [Epub ahead of print]

**BACKGROUND:** Shared decision-making (SDM) is widely recommended and required by the Centers or Medicare and Medicaid for patients considering lung cancer screening (LCS). **OBJECTIVE:** We examined clinicians' communication practices and perceived barriers of SDM for LCS at three medical centers with established screening programs. **DESIGN:** Multicenter qualitative study of clinicians participating in LCS. **APPROACH:** We performed semi-structured interviews, which were transcribed and analyzed using directed content analysis, guided by a theoretical model of patient-clinician communication. **PARTICIPANTS:** We interviewed 24 clinicians including LCS coordinators (2), pulmonologists (3), and primary care providers (17), 4 of whom worked for the LCS program, a thoracic surgeon, and a radiologist. **RESULTS:** All clinicians agreed with the goal of SDM, to ensure the screening decision was congruent with the patient's values. The depth and type of information presented by each clinician role varied considerably. LCS coordinators presented detailed information including numeric estimates of benefit and harm. Most PCPs explained the process more generally, focusing on logistics and the high rate of nodule detection. No clinician explicitly elicited values or communication preferences. Many PCPs tailored the conversation based on their implicit understanding of patients' values and preferences, gained from past experiences. PCPs reported that time, lack of detailed personal



knowledge of LCS, and patient preferences were barriers to SDM. Many clinicians perceived that a significant proportion of patients were not interested in specific percentages and preferred to receive a clinician recommendation. **CONCLUSIONS:** Our results suggest that clinicians support the goal of SDM for LCS decisions but PCPs may not perform some of its elements. The lack of completion of some elements, such as PCPs' lack of in-depth information exchange, may reflect perceived patient preferences for communication. As LCS is implemented, further research is needed to support a personalized, patient-centered approach to produce better outcomes.

**Video-Based Education in Lung Cancer Screening.** Alban J1, Alban LF2, Clayburn A3, Khanal A4, Feldman L5. *J Cancer Educ.* 2019 Nov 15. doi: 10.1007/s13187-019-01629-9. [Epub ahead of print] Lung cancer (LC) is the leading cause of cancer mortality in the USA; the American Cancer Society (ACS) estimates upwards of 220,000 new cases will be diagnosed this year. Recently, the Center for Medicare/Medicaid Services (CMS) agreed to cover LC screening with low-dose computed tomography (CT) for patients; however, CMS requires prior documentation of a shared decision-making (SDM) visit between the patient and the referring clinician to inform them about risks of screening. LC screening programs have begun to use YouTube for patient recruitment, education, and marketing of screening. The objective of this study is to shed light on the role of YouTube in lung cancer screening in terms of guidelines, screening options, target population, steps after screening, and risks and benefits of screening. We searched YouTube.com™ to identify videos dealing with lung screening using the keywords: lung cancer screening. Videos without sound, uploaded before 2009, longer than 20 min, duplicate videos, and videos in a language other than English were excluded. This method yielded 123 videos that fit criteria. Videos were coded for inclusion of LC screening process, risks and benefits of screening, screening guidelines, risk factors for LC, and treatment options after LC diagnosis. One hundred twenty-three videos had a cumulative 261,261 views across all videos. A total of 38.7% of the videos included no mention of United States Preventive Services Task Force (USPSTF) or CMS guidelines for LC screening. Only 30% included any mention of the risks associated with screening: 14% mentioned false positives, 12% radiation, and 4% anxiety associated with screening. Ninety-two percent of all videos sampled were intended for patients, and the majority of videos were created by medical institutions (66%) and news channels (17%). Lung cancer screening videos on YouTube's platform have garnered a substantial amount of views. While all videos sampled highlighted the benefits of LC screening, the majority fail to discuss the risks associated with the screening process. Most videos were produced for marketing purposes rather than educational and therefore should not be used as a substitute for SDM visits.

**State-level variations in the utilization of lung cancer screening among fee-for-service Medicare beneficiaries: an analysis of the 2015-2017 Physician and Other Supplier data.** Liu B1, Dharmarajan K2, Henschke CI3, Taioli E4. *Chest.* 2019 Nov 21. pii: S0012-3692(19)34223-0. doi: 10.1016/j.chest.2019.11.005. [Epub ahead of print]

**BACKGROUND:** Lung cancer screen (LCS) is an important secondary prevention measure to reduce lung cancer mortality. We aim to assess state-level variations in LCS among the US elderly during the first three years since Medicare began its LCS reimbursement policy in 2015. **METHODS:** This ecological study examined the relationships between LCS utilization density, defined as the number of low-dose computed tomography (LDCT) or shared decision making and counseling (SDMC) per 1000 fee-for-service (FFS) Medicare beneficiaries derived from the Medicare Provider Utilization and Payment Data: Physician and Other Supplier Public Use File, and state-level factors from several publicly available data sources, using Kruskal-Wallis tests and cluster analysis. **RESULTS:** In 2017, the median utilization density per 1000 FFS beneficiaries was 3.32 for LDCT and 0.46 for SDMC, which was 24 and 13 times the 2015 level, respectively. From 2015 to 2017, the total number of unique providers billed for LCS increased from 222 to 3444 for LDCT and from 20 to 523 for SDMC. Higher utilizations for both LDCT

and SDMC tended to concentrate in the northeastern and upper Midwest states than southwest states. The cluster of states with high utilization density was not those with the most lung cancer mortality and/or smoking prevalence. **CONCLUSIONS:** We found a steady increase in LCS utilization since Medicare began its reimbursement policy. The utilization and its growth varied across the US states and differed between LDCT and SDMC, indicating large growth potentials for LCS and for states with high lung cancer mortality and smoking prevalence.

## CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

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### NSCLC - SURGERY

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#### [Are segmentectomy and lobectomy comparable in terms of curative intent for early stage non-small cell lung cancer?](#) Mimae T1, Okada M2. Gen Thorac Cardiovasc Surg. 2019 Nov 6. doi:

10.1007/s11748-019-01219-y. [Epub ahead of print]

In 1995, Ginsberg et al. compared lobectomy with limited resection including segmentectomy and wide-wedge resection for stage I lung cancer in a randomized controlled trial and found that limited resection should not be applied to otherwise healthy patients with clinical stage IA lung cancer who can tolerate lobectomy. However, recent advances in diagnostic technology have improved the precision of detecting early-stage and small lung cancers. Therefore, whether radical segmentectomy, anatomical segmentectomy with hilar and mediastinal lymph node dissection (that is more valuable than wedge resection in terms of oncological aspects) and lobectomy are comparable in terms of curative intent for patients with early-stage non-small cell lung cancer (NSCLC) remains controversial. The role of segmentectomy differs according to tumor or patient characteristics. High resolution computed tomography findings of tumor size, location, and the presence or ratio of a ground glass opacity (GGO) component and the maximum of standardized uptake value on fluorine-18-2-deoxy-D-glucose positron emission tomography are important for selecting surgical procedures because the malignant potential of even early-stage NSCLC is variable. The ongoing JCOG0802/WJOG4607L, JCOG1211, and CALGB140503 trials will disclose the influence of segmentectomy for patients with early-staged NSCLCs that are small peripheral tumors based on preoperative high-resolution computed tomography findings about preserved pulmonary function and long-term prognosis. Segmentectomy is a key surgical procedure that general thoracic surgeons will need to master considering that it can be converted to lobectomy if the surgical margin is insufficient or lymph node metastasis is intraoperatively confirmed.

#### [The Society of Thoracic Surgeons Composite Score Rating for Pulmonary Resection for Lung Cancer.](#) Broderick SR1, Grau-Sepulveda M2, Kosinski AS2, et al. Ann Thorac Surg. 2019 Nov 2. pii:

S0003-4975(19)31604-2. doi: 10.1016/j.athoracsur.2019.08.114. [Epub ahead of print]

**BACKGROUND:** The Society of Thoracic Surgeons (STS) General Thoracic Surgery Database (GTSD) has developed composite quality measures for lobectomy and esophagectomy. We sought to develop a composite measure including all resections for lung cancer. **METHODS:** The STS lung cancer composite score is based on two outcomes: risk-adjusted mortality and morbidity. General Thoracic Surgery Database (GTSD) data were included from 1/2015 - 12/2017. "Star ratings" were created for centers with  $\geq 30$  cases using 95% Bayesian credible intervals. The Bayesian model was performed with and without inclusion of minimally invasive approach to assess the impact of approach on the composite measure.

**RESULTS:** The study population included 38,461 patients from 256 centers. Overall operative mortality was 1.3% (495/38,461); Major complication rate was 7.9% (3,045/38,461). Median nodes examined was 10 (IQR 5-16); Median nodal stations sampled was 4 (IQR 3-5). Positive resection margins were identified in 3.7% (1,420/38,461). 214 centers with  $\geq 30$  cases were assigned star ratings. There were 7 one-star, 194 two-star and 13 three-star programs. 70.6% of resections were performed through a

minimally invasive approach. Inclusion of minimally invasive approach, which was adjusted for in previous models, altered the star ratings for 3% (6/214) of programs. **CONCLUSIONS:** Participants in the STS GTSD perform lung cancer resection with low morbidity and mortality. Lymph node data suggest participants are meeting contemporary staging standards. There is wide variability among participants in application of minimally invasive approaches. Risk adjustment for approach alters ratings in 3% of participants.

### [Optimal Surgical Timing after Neoadjuvant Therapy for Stage IIIa Non-Small Cell Lung Cancer.](#)

Rice JD1, Heidel J1, Trivedi JR1, van Berkel VH2. *Ann Thorac Surg.* 2019 Nov 19. pii: S0003-4975(19)31705-9. doi: 10.1016/j.athoracsur.2019.09.076. [Epub ahead of print]

**BACKGROUND:** Patients with clinically/pathologically diagnosed stage IIIa non-small cell lung cancer (NSCLC) considered for surgery are recommended to undergo neoadjuvant chemotherapy with/without radiation. Timing of operation after therapy is not standardized. We investigate timing of intervention after neoadjuvant therapy and impact on outcomes in this demographic. **METHODS:** The National Cancer Database was queried for patients with clinical/pathological Stage IIIa NSCLC between 2010-2015. Patients were then divided into short (<77 days), mid (77-114 days) and long-delay (>114 days) groups based on interquartile values. These groups were then compared for age, race, gender, insurance type, Charlson-Deyo Score, length of stay, readmission rate and overall survival based on timing of operation. **RESULTS:** There were 31357 patients with clinical/pathological Stage IIIa NSCLC. 5946 patients underwent surgical intervention. Preoperatively, 3593 patients underwent chemoradiotherapy, 2185 underwent chemotherapy only and 168 patients received radiation alone. The short, mid and long delay groups were clinically and statistically similar in age, gender, insurance type, comorbidity index, treating facility type and distance from home. Long delay groups had larger tumor size compared to other groups. Postoperative length of stay, rates of 30-day readmission as well as 30- and 90-day mortality were similar across all groups. Cox modeling demonstrated a significant difference in survival when patients underwent earlier operative intervention compared to late and when patients received chemoradiation compared to chemotherapy alone. Short, mid and long delay groups 1-year survival was 82%, 83% and 80% and 3-year survival was 59%, 58% and 52% respectively (p=0.0003). **CONCLUSIONS:** The delay in surgical resection of Stage IIIa NSCLC is not associated increased early mortality, however it is associated with worse 3-year post-resection survival.

### [Postoperative outcomes of robotic-assisted lobectomy in obese patients with non-small-cell lung cancer.](#)

Casiraghi M1, Sedda G1, Diotti C1, Mariolo AV1, Galetta D1, Tessitore A1, Maisonneuve P2, Spaggiari L1,3. *Interact Cardiovasc Thorac Surg.* 2019 Nov 22. pii: ivz273. doi: 10.1093/icvts/ivz273. [Epub ahead of print]

**OBJECTIVES:** The aim of this study was to assess the postoperative outcomes of robotic-assisted lobectomy in obese patients to determine the impact of the robotic approach on a high-risk population who were candidates for major pulmonary resection for non-small-cell lung cancer (NSCLC). **METHODS:** Between January 2007 and August 2018, we retrospectively reviewed the medical records of 224 obese patients (body mass index  $\geq 30$ ) who underwent pulmonary lobectomy at our institution via robotic-assisted thoracic surgery (RATS, n = 51) or lateral muscle-sparing thoracotomy (n = 173). **RESULTS:** Forty-two patients were individually matched with those who had the same pathological tumour stage and similar comorbidities and presurgical treatment. The median operative time was significantly longer in the RATS group compared to that in the thoracotomy group (200 vs 158 min; P = 0.003), whereas the length of stay was significantly better for the RATS group (5 vs 6 days; P = 0.047). Postoperative complications were significantly more frequent after open lobectomy than in the RATS group (42.9% vs 16.7%; P = 0.027). After a median follow-up of 4.4 years, the 5-year overall survival rate was 67.6% [95% confidence interval (CI) 45.7-82.2] for the RATS group, and 66.1% (95%

CI 46.8-79.9) for the open surgery group (log-rank  $P = 0.54$ ). The 5-year cumulative incidence of cancer-related deaths was 24.8% (95% CI 9.7-43.5) for the RATS group and 23.6% (95% CI 10.8-39.2) for the open surgery group (Gray's test,  $P = 0.69$ ). **CONCLUSIONS:** RATS is feasible and safe for obese patients with NSCLC with advantages compared to open surgery in terms of early postoperative outcomes. In addition, the long-term survival rate was comparable to that of the open approach.

### [Comparison of Long-term Survival of Patients With Early-Stage Non-Small Cell Lung Cancer After Surgery vs Stereotactic Body Radiotherapy.](#)

Chi A1, Fang W2, Sun Y1, Wen S3. JAMA Netw Open. 2019 Nov 1;2(11):e1915724. doi: 10.1001/jamanetworkopen.2019.15724.

**IMPORTANCE:** Previous comparisons of surgery and stereotactic body radiotherapy (SBRT) for early-stage (ES) non-small cell lung cancer (NSCLC) did not account for the extent of regional lymph node examination (LNE) during surgery. **OBJECTIVE:** To compare long-term overall survival (OS) of patients with ES NSCLC after surgery vs SBRT when the extent of regional LNE in patients undergoing surgery is thoroughly considered. **DESIGN, SETTING, AND PARTICIPANTS:** Cohort study with survival comparisons using the multivariable Cox proportional hazards model and after propensity score matching. Data from the National Cancer Database were analyzed from October 28, 2018, through April 18, 2019. Patients with ES NSCLC diagnosed between January 1, 2004, and December 31, 2015, who underwent any curative-intent surgery or SBRT were included. **MAIN OUTCOMES AND MEASURES:** Long-term OS. **RESULTS:** Of 104 709 total patients, 91 330 underwent surgery (42 508 [46.5%] male; median [interquartile range] age, 68 [61-75] years) and 13 379 received SBRT (6065 [45.3%] male; median [interquartile range] age, 75 [68-81] years). Surgery, especially lobectomy (hazard ratio [HR], 0.53; 95% CI, 0.50-0.56), and regional LNE, especially when more than 10 lymph nodes were examined (HR, 0.73; 95% CI, 0.69-0.77), were associated with better long-term OS ( $P < .001$ ). Pneumonectomy was not associated with reduced mortality risk when 0 nodes were examined (HR for stage T1, 1.43; 95% CI, 0.67-3.06;  $P = .35$ ; HR for stage T2-T3, 0.62; 95% CI, 0.34-1.13;  $P = .12$ ) or when more than 15 nodes were examined for stage T1 disease in patients younger than 80 years (HR, 0.77; 95% CI, 0.54-1.09;  $P = .14$ ) or when patients aged 80 years or older received regional LNE of any extent (>15 nodes examined: HR for stage T1, 0.65; 95% CI, 0.16-2.64;  $P = .54$ ; HR for stage T2-T3, 0.90; 95% CI, 0.50-1.60;  $P = .71$ ). Less extensive surgery was not associated with improved OS when 0 nodes were examined in patients aged 80 years or older with stage T2 to T3 tumors (HR for lobectomy, 0.90; 95% CI, 0.65-1.25;  $P = .53$ ) and in selected operable patients older than 75 years with stage T1 tumors (HR for lobectomy, 1.07; 95% CI, 0.57-2.00;  $P = .84$ ). **CONCLUSIONS AND RELEVANCE:** This study found that, overall, surgery coupled with regional LNE of appropriate extent was associated with the best long-term OS in patients with ES NSCLC.

### [A Minimally Invasive Approach to Lobectomy After Induction Therapy Does Not Compromise Survival.](#)

Jeffrey Yang CF1, Nwosu A2, Mayne NR2, Wang YY3, Raman V2, Meyerhoff RR2, D'Amico TA2, Berry MF3. Ann Thorac Surg. 2019 Nov 13. pii: S0003-4975(19)31691-1. doi: 10.1016/j.athoracsur.2019.09.065. [Epub ahead of print]

**BACKGROUND:** The objective of this study was to evaluate the impact of a VATS approach on outcomes in patients who underwent lobectomy after induction therapy. **METHODS:** Outcomes of patients with T2-T4, N0, M0 and T1-T4, N1-N2, M0 non-small-cell lung cancer (NSCLC) who received induction chemotherapy or chemoradiation followed by lobectomy in the National Cancer Data Base (NCDB) (2010-2014) were assessed using Kaplan-Meier, propensity score-matched, multivariable logistic regression and Cox proportional hazards analyses. **RESULTS:** In the NCDB, 2,887 lobectomy patients met inclusion criteria (VATS 676 [23%], Thoracotomy 2,211 [77%]). Of the VATS cases, patients who underwent induction chemoradiation were more likely to undergo conversion (aOR 1.70,  $p = 0.05$ ). Compared to an open approach, VATS was associated with decreased length of stay (median: 5



days vs 6 days,  $P < 0.001$ ) and no significant differences in 30-day mortality (VATS [1.5% (n=10)] vs open [2.6% (n=58)];  $P=0.13$ ) and 90-day mortality (VATS [3.7% (n=25)] vs open [5.6% (n=124)];  $P=0.14$ ). There were no significant differences in 5-year survival between the VATS and open groups in both the entire cohort (VATS [50.3%] vs open [52.3%];  $P=0.83$ ) and in a propensity score-matched analysis of 876 patients; furthermore, a VATS approach was also not associated with worse survival in multivariable analysis (HR = 1.02; 95% CI [0.86, 1.20];  $P = 0.83$ ). **CONCLUSIONS:** In this national analysis, a VATS approach for lobectomy in patients who received induction therapy for locally advanced NSCLC was not associated with worse short-term or long-term outcomes when compared to an open approach.

**The association of nodal upstaging with surgical approach and its impact on long-term survival after resection of non-small-cell lung cancer.**

Hennon MW<sup>1,2</sup>, DeGraaff LH<sup>2</sup>, Groman A<sup>3</sup>, Demmy TL<sup>1,2</sup>, Yendamuri S<sup>1,2</sup>. Eur J Cardiothorac Surg. 2019 Nov 25. pii: ezz320. doi: 10.1093/ejcts/ezz320. [Epub ahead of print]

**OBJECTIVES:** Proponents of open thoracotomy (OPEN) and robot-assisted thoracic surgery (RATS) claim its oncological superiority over video-assisted thoracic surgery (VATS) in terms of the accuracy of lymph node staging. **METHODS:** The National Cancer Database was queried for patients with non-small-cell lung cancer (NSCLC) undergoing lobectomy without neoadjuvant therapy from 2010 to 2014. Nodal upstaging rates were compared using a surgical approach. Overall survival adjusted for confounding variables was examined using the Cox proportional hazards model. **RESULTS:** A total of 64 676 patients fulfilled the selection criteria. The number of patients who underwent lobectomy by RATS, VATS and OPEN approaches was 5470 (8.5%), 17 545 (27.1%) and 41 661 (64.4%), respectively. The mean number of lymph nodes examined for each of these approaches was 10.9, 11.3 and 10 ( $P < 0.01$ ) and upstaging rates were 11.2%, 11.7% and 12.6% ( $P < 0.01$ ), respectively. For patients with clinical stage I disease (N = 46 826; RATS = 4338, VATS = 13 416 and OPEN = 29 072), the mean lymph nodes examined were 10.6, 10.8 and 9.4 ( $P < 0.01$ ), and upstaging rates were 10.8%, 11.1% and 12.1% ( $P < 0.01$ ), respectively. A multivariable analysis suggested an association with improved survival with RATS and VATS compared with OPEN surgery [hazard ratio (HR) = 0.89 and 0.89, respectively;  $P < 0.01$ ] for patients with all stages. In stage I disease, VATS but not RATS was associated with increased overall survival compared with the OPEN approach (HR = 0.81;  $P < 0.01$ ). **CONCLUSIONS:** RATS lobectomy is not superior to VATS lobectomy with respect to lymph node yield or upstaging of NSCLC. Increased nodal upstaging by the OPEN approach does not confer a survival advantage in any stage of NSCLC and may be associated with decreased overall survival.

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

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**First-line PD-1/PD-L1 inhibitor plus chemotherapy vs chemotherapy alone for negative or < 1% PD-L1-expressing metastatic non-small-cell lung cancers.**

Landre T<sup>1</sup>, Des Guetz G<sup>2</sup>, Chouahnia K<sup>3</sup>, Taleb C<sup>4</sup>, Vergnenègre A<sup>5</sup>, Chouaïd C<sup>6</sup>. J Cancer Res Clin Oncol. 2019 Nov 4. doi: 10.1007/s00432-019-03070-3. [Epub ahead of print]

**AIMS:** Single-agent anti-PD-1/PD-L1 clinical efficacy against < 1% PD-L1-expressing non-small-cell lung cancers (NSCLCs) is controversial. **METHODS:** This meta-analysis examined randomized-trial data comparing first-line PD-1/PD-L1-inhibitor + chemotherapy (CT) vs CT alone for advanced < 1% PD-L1 NSCLCs. Outcome measures included overall survival (OS), progression-free survival (PFS) and objective response rate (ORR). **RESULTS:** IMpower (atezolizumab + CT), Keynote (pembrolizumab + CT) and CheckMate (nivolumab + CT) trials included 2037 NSCLCs (1246 PD-L1-negative; 791 < 1% PD-L1 expression). Anti-PD-1/PD-L1 + CT was significantly associated (hazard ratio [95% confidence interval]) with prolonged OS (0.75 [0.63-0.89];  $p = 0.0008$ ) and PFS (0.72 [0.65-0.80];

$p < 0.0001$ ), and higher ORR (odds ratio 2.06 [1.50-2.83];  $p < 0.0001$ ). **CONCLUSIONS:** First-line anti-PD-1/PD-L1 + CT combination appears superior to CT alone for advanced,  $< 1\%$  PD-L1-expressing NSCLCs for OS, PFS and ORR.

**Population Pharmacokinetics of Nivolumab in Combination With Ipilimumab in Patients With Advanced Malignancies.** Zhang J1, Sanghavi K1, Shen J1, Zhao X1, Feng Y1, Statkevich P1, Sheng J1, Roy A1, Zhu L1. CPT Pharmacometrics Syst Pharmacol. 2019 Nov 10. doi: 10.1002/psp4.12476. [Epub ahead of print]

Nivolumab is a fully human monoclonal antibody that inhibits programmed cell death-1 activation. To assess covariate effects on nivolumab clearance (CL), a population pharmacokinetics model was developed using data from 6,468 patients with colorectal cancer, hepatocellular carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, or small cell lung cancer who received nivolumab as monotherapy or in combination with ipilimumab or chemotherapy across 25 clinical studies. Nivolumab CL was similar across the tumor types examined; CL was higher for ipilimumab 1 mg/kg every 6 weeks (by 17%) and 3 mg/kg every 3 weeks (by 29%) vs. nivolumab monotherapy. Nivolumab CL over time was partially explained by time-varying covariates. A greater decrease in nivolumab time-varying CL was associated with increased albumin and body weight and a responder status. Our findings support the observed association between nivolumab CL and disease severity.

**Compartmental analysis of T cell clonal dynamics as a function of pathologic response to neoadjuvant PD-1 blockade in resectable non-small cell lung cancer.** Zhang J1, Ji Z1, Caushi JX2, El Asmar M2, et al. Clin Cancer Res. 2019 Nov 21. pii: clincanres.2931.2019. doi: 10.1158/1078-0432.CCR-19-2931. [Epub ahead of print]

**PURPOSE:** Neoadjuvant PD-1 blockade is a promising treatment for resectable non-small cell lung cancer (NSCLC), yet immunological mechanisms contributing to tumor regression and biomarkers of response are unknown. Using paired tumor/blood samples from a phase 2 clinical trial (NCT02259621), we explored whether the peripheral T cell clonotypic dynamics can serve as a biomarker for response to neoadjuvant PD-1 blockade. **EXPERIMENTAL DESIGN:** T cell receptor (TCR) sequencing was performed on serial peripheral blood, tumor and normal lung samples from resectable NSCLC patients treated with neoadjuvant PD-1 blockade. We explored the temporal dynamics of the T cell repertoire in the peripheral and tumoral compartments in response to neoadjuvant PD-1 blockade by using the TCR as a molecular barcode. **RESULTS:** Higher intratumoral TCR clonality was associated with reduced percent residual tumor at the time of surgery, and the TCR repertoire of tumors with major pathologic response (MPR;  $< 10\%$  residual tumor after neoadjuvant therapy) had a higher clonality and greater sharing of tumor infiltrating clonotypes with the peripheral blood relative to tumors without MPR. Additionally, the post-treatment tumor bed of patients with MPR was enriched with T cell clones that had peripherally expanded between weeks 2-4 after anti-PD-1 initiation and the intratumoral space occupied by these clonotypes was inversely correlated with percent residual tumor. **CONCLUSIONS:** Our study suggests that exchange of T cell clones between tumor and blood represents a key correlate of pathologic response to neoadjuvant immunotherapy, and shows that the periphery may be a previously underappreciated originating compartment for effective anti-tumor immunity.

**Lesion-Level Response Dynamics to Programmed Cell Death Protein (PD-1) Blockade.** Osorio JC1, Arbour KC1,2, Le DT3, et al. J Clin Oncol. 2019 Nov 1;JCO1900709. doi: 10.1200/JCO.19.00709. [Epub ahead of print]

**PURPOSE:** Response to programmed cell death protein 1 (PD-1) blockade is often conceptualized as resulting from reinvigoration of tumor-infiltrating lymphocytes. However, recruited antitumor immunity from the periphery may also be an important contributor to response. A detailed assessment of the

response dynamics of individual metastasis could provide insight to the systemic and local features that mediate response and resistance to immunotherapy. **MATERIALS AND METHODS:** Patients with metastatic non-small-cell lung cancer (NSCLC) or mismatch repair deficiency (MMRD) carcinoma treated with PD-1 monotherapy were evaluated independently. Absolute and percent change of each target lesion were quantified at each computed tomography scan using RECIST. Patterns of progression were predefined as systemic or mixed and were correlated with clinical outcomes. **RESULTS:** A total of 761 individual lesions from 214 patients with NSCLC and 290 lesions from 78 patients with MMRD carcinoma were examined. Individual target lesion responses aligned with best overall response of each patient (85% NSCLC and 93% MMRD lesions responded in patients with partial response/complete response). In responding patients, timing of response was uniform (73% NSCLC and 76% MMRD lesions responded synchronously), and deeper responses were associated with prolonged progression-free survival and overall survival. By contrast, at progression, mixed progression was common (45% of NSCLC and 53% of MMRD) and associated with improved survival compared with those who experienced systemic progression (NSCLC hazard ratio [HR], 0.58; P = .001; MMRD HR, 0.40; P = .07). Organ sites had differential responses, with lymph node and liver metastasis among the most and least responsive, respectively. **CONCLUSION:** Temporal-spatial patterns of response across individual metastases tend to be uniform, favoring the role of peripheral, clonally directed antitumor immunity as a key mediator of response to PD-1 blockade. In contrast, progression is more heterogeneous, potentially revealing the clinical importance of local features and intertumoral heterogeneity.

[Comparisons between tumor burden and other prognostic factors that influence survival of patients with non-small cell lung cancer treated with immune checkpoint inhibitors.](#) Sakata Y1, Kawamura K1, Ichikado K1, et al. *Thorac Cancer*. 2019 Dec;10(12):2259-2266. doi: 10.1111/1759-7714.13214. Epub 2019 Nov 3.

**BACKGROUND:** The use of baseline tumor burden (TB) as a prognostic factor for non-small cell lung cancer (NSCLC) patients treated with immune checkpoint inhibitors (ICIs) and associations between TB and other prognostic biomarkers remain unclear. In this study, we investigated the association between TB and survival in NSCLC patients treated with ICIs in comparison with other biomarkers. **METHODS:** We retrospectively evaluated 83 NSCLC patients with ICIs administered between February 2016 and December 2018. TB was measured as the sum of the unidimensional diameters of up to five target lesions. **RESULTS:** The median observation period was 14.2 months. A total of 42 patients died during the follow-up. Univariate Cox regression analysis showed that baseline TB was associated with OS. Cox regression analysis adjusted for Eastern Cooperative Oncology Group performance status (ECOG PS) alone or with addition of programmed cell death ligand 1 expression and treatment line showed that TB was a prognostic factor for OS. Using time-dependent receiver operating characteristic curve analysis, the optimal TB cutoff for predicting OS was 12 cm, and patients were divided into a high TB group (n = 21) and a low TB group (n = 62). The low TB group achieved significantly longer OS than the high TB group (median OS: 18.5 months, [95% CI = 11.7-not reached] vs. 2.3 months [95% CI = 1.3-2.9], P < 0.001). **CONCLUSION:** TB is a useful, clinically measurable prognostic factor of survival in NSCLC patients treated with ICIs.

[Final Overall Survival, Other Efficacy and Safety Results from ASCEND-3: Phase II Study of Ceritinib in ALKi-Naïve Patients With ALK-Rearranged Non-Small-Cell Lung Cancer.](#) Nishio M1, Felip E2, Orlov S3, et al. *J Thorac Oncol*. 2019 Nov 25. pii: S1556-0864(19)33660-3. doi: 10.1016/j.jtho.2019.11.006. [Epub ahead of print]

**INTRODUCTION:** The phase II, single-arm ASCEND-3 study assessed efficacy and safety of ceritinib in anaplastic lymphoma kinase (ALK) inhibitor (ALKi)-naïve patients with ALK-rearranged non-small-cell lung cancer (NSCLC) who had received ≤ 3 prior lines of chemotherapy. Here, we report the final

efficacy and safety results. **METHODS:** Eligible patients (including those with asymptomatic or neurologically stable brain metastases [BM]) received oral ceritinib 750 mg/day (fasted). Primary endpoint: investigator-assessed overall response rate (ORR). Secondary endpoints: Blinded Independent Review Committee (BIRC)-assessed ORR; investigator- and BIRC-assessed overall intracranial response rate, duration of response (DOR), time to response, disease control rate, and progression-free survival (PFS); overall survival (OS); and safety. Exploratory endpoints: patient-reported outcomes.

**RESULTS:** Of the 124 patients enrolled, 122 (98.4%) had received prior antineoplastic medications (31 patients [25.0%],  $\geq 3$  regimens), and 49 (39.5%) had baseline BM. Median follow-up time (data cutoff: January 22, 2018): 52.1 months (range, 48.4–60.1). Investigator-assessed ORR was 67.7% (95% CI, 58.8 to 75.9) and median PFS was 16.6 months (95% CI, 11.0 to 23.2). Median OS was 51.3 months (95% CI, 42.7 to 55.3). Most common adverse events (AEs [all grades],  $\geq 60\%$  of patients, all-causality): diarrhea (85.5%), nausea (78.2%), and vomiting (71.8%). Overall, 18 patients (14.5%) had an AE leading to treatment discontinuation. Health-related quality of life was maintained during ceritinib treatment.

**CONCLUSION:** Ceritinib demonstrated prolonged and clinically meaningful OS, PFS, and DOR in chemotherapy pretreated ( $\leq 3$  lines), ALKi-naïve patients with ALK+ NSCLC. The safety profile is consistent with that of previously reported studies.

**[Pemetrexed Plus Platinum for Patients With Advanced Non-small Cell Lung Cancer and Interstitial Lung Disease.](#)** Fujita T1, Kuroki T2, Hayama N2, Shiraishi Y2, Amano H2, Nakamura M2, Hirano S3, Tabeta H2, Nakamura S2. *In Vivo*. 2019 Nov-Dec;33(6):2059-2064. doi: 10.21873/invivo.11704.

**BACKGROUND/AIM:** Pemetrexed plus platinum followed by pemetrexed maintenance has been one of the standard first-line treatments in advanced nonsquamous non-small cell lung cancer (NSCLC), but little is known regarding its safety and efficacy for patients with interstitial lung disease (ILD).

**PATIENTS AND METHODS:** The medical records of 24 patients with advanced nonsquamous NSCLC and preexisting ILD who received pemetrexed and platinum doublet therapy with and without pemetrexed maintenance in the first-line setting between December 2009 and June 2016, were retrospectively reviewed. **RESULTS:** The median progression-free survival time was 4.7 months, and the median overall survival time was 9.5 months. Of the 24 patients analyzed, six received pemetrexed maintenance.

Acute exacerbation of ILD (AE-ILD) occurred in five (20.8 %) of 24 patients, including two fatal cases.

**CONCLUSION:** The treatment with pemetrexed plus platinum has a high risk of AE-ILD in patients with advanced nonsquamous NSCLC and preexisting ILD.

**[Brigatinib in Crizotinib-Refractory ALK+ Non-Small Cell Lung Cancer: 2-Year Follow-up on Systemic and Intracranial Outcomes in the Phase 2 ALTA Trial.](#)** Huber RM1, Hansen KH2, Paz-Ares Rodríguez L3, et al. *J Thorac Oncol*. 2019 Nov 19. pii: S1556-0864(19)33645-7. doi: 10.1016/j.jtho.2019.11.004. [Epub ahead of print]

**INTRODUCTION:** We report updated data from a phase 2 randomized study evaluating brigatinib in crizotinib-refractory anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC).

**METHODS:** Patients were randomized 1:1 to oral brigatinib 90 mg qd (arm A) or 180 mg qd with 7-day lead-in at 90 mg (B), stratified by central nervous system (CNS) metastases and best response to crizotinib. Primary endpoint was investigator-assessed confirmed objective response rate (cORR) per Response Evaluation Criteria In Solid Tumors v1.1. Secondary endpoints included independent review committee (IRC)-assessed progression-free survival (PFS), intracranial PFS (iPFS) and overall survival (OS). Exploratory analyses included CNS vs ex-CNS target lesion response and correlation of depth of response with PFS and OS. **RESULTS:** Among 222 randomized patients (A/B: n=112/110), 59 (27%) remained on brigatinib at analysis (median follow-up: 19.6/24.3 months in A/B). At baseline, 71%/67% had brain lesions. Investigator-assessed cORR was 46%/56%. Median IRC-assessed PFS was 9.2 months



(95% confidence interval, 7.4-12.8)/16.7 months (11.6-21.4). Median OS was 29.5 months (18.2-not reached [NR])/34.1 months (27.7-NR). IRC-confirmed intracranial ORR (iORR) in patients with measurable baseline brain lesions was 50% (13/26)/67% (12/18); median duration of intracranial response (iDOR) was 9.4/16.6 months. IRC-assessed iPFS was 12.8/18.4 months. Across arms, median IRC-assessed PFS was 1.9, 5.5, 11.1, 16.7, and 15.6 months for patients with no, 1%-25%, 26%-50%, 51%-75%, and 76%-100% target lesion shrinkage, respectively. No new safety findings were observed with longer follow-up. **CONCLUSIONS:** Brigatinib (180 mg qd with lead-in) continues to demonstrate robust PFS, long iPFS and iDOR, and high iORR in crizotinib-refractory patients. Depth of response may be an important endpoint to capture in future targeted therapy trials.

**Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC.** Ramalingam SS1, Vansteenkiste J1, Planchard D1, et al. N Engl J Med. 2019 Nov 21. doi: 10.1056/NEJMoa1913662. [Epub ahead of print]

**BACKGROUND:** Osimertinib is a third-generation, irreversible tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR-TKI) that selectively inhibits both EGFR-TKI-sensitizing and EGFR T790M resistance mutations. A phase 3 trial compared first-line osimertinib with other EGFR-TKIs in patients with EGFR mutation-positive advanced non-small-cell lung cancer (NSCLC). The trial showed longer progression-free survival with osimertinib than with the comparator EGFR-TKIs (hazard ratio for disease progression or death, 0.46). Data from the final analysis of overall survival have not been reported. **METHODS:** In this trial, we randomly assigned 556 patients with previously untreated advanced NSCLC with an EGFR mutation (exon 19 deletion or L858R allele) in a 1:1 ratio to receive either osimertinib (80 mg once daily) or one of two other EGFR-TKIs (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily, with patients receiving these drugs combined in a single comparator group). Overall survival was a secondary end point. **RESULTS:** The median overall survival was 38.6 months (95% confidence interval [CI], 34.5 to 41.8) in the osimertinib group and 31.8 months (95% CI, 26.6 to 36.0) in the comparator group (hazard ratio for death, 0.80; 95.05% CI, 0.64 to 1.00; P = 0.046). At 3 years, 79 of 279 patients (28%) in the osimertinib group and 26 of 277 (9%) in the comparator group were continuing to receive a trial regimen; the median exposure was 20.7 months and 11.5 months, respectively. Adverse events of grade 3 or higher were reported in 42% of the patients in the osimertinib group and in 47% of those in the comparator group. **CONCLUSIONS:** Among patients with previously untreated advanced NSCLC with an EGFR mutation, those who received osimertinib had longer overall survival than those who received a comparator EGFR-TKI. The safety profile for osimertinib was similar to that of the comparator EGFR-TKIs, despite a longer duration of exposure in the osimertinib group. (Funded by AstraZeneca; FLAURA ClinicalTrials.gov number, NCT02296125.).

**ALK Mutation Status Before and After Alectinib Treatment in Locally Advanced or Metastatic ALK-positive NSCLC: Pooled Analysis of Two Prospective Trials.** Noé J1, Lovejoy A2, Ignatius Ou SH3, Yaung SJ2, Bordogna W1, Klass DM2, Cummings CA4, Shaw AT5. J Thorac Oncol. 2019 Nov 8. pii: S1556-0864(19)33633-0. doi: 10.1016/j.jtho.2019.10.015. [Epub ahead of print]

**BACKGROUND:** The effectiveness of ALK inhibitors can be limited by the development of ALK resistance mutations. This exploratory analysis assessed the efficacy of alectinib in patients with non-small-cell lung cancer (NSCLC) and ALK point mutations using pooled data from two single-arm phase II studies. **METHODS:** Studies NP28673 and NP28761 enrolled adults with locally advanced/metastatic ALK-positive NSCLC who had progressed on crizotinib. ALK mutation analysis was conducted on cell-free DNA (cfDNA) from 187 patients post-crizotinib/pre-alectinib, and from 49 of these patients who subsequently progressed on alectinib. **RESULTS:** Baseline characteristics were generally balanced across patient subgroups. At baseline, 34 distinct ALK mutations were identified in 48/187 patients (25.7%). Median investigator-assessed progression-free survival was longer in patients without ALK single-

nucleotide variants (n = 138) versus those with (n = 48): 10.2 months (95% confidence interval [CI], 8.1-14.3) versus 5.6 months (95% CI, 4.5-10.9), respectively. Sixteen out of 32 patients (50%) with ALK resistance mutations to crizotinib achieved an investigator-assessed response to alectinib (all partial responses); most of these ALK mutations were known to be sensitive to alectinib. Analysis of plasma samples taken post-progression on alectinib revealed that 26/49 (53%) samples harbored 16 distinct ALK mutations, with known alectinib-resistance mutations, I1171 T/N/S, G1202R, and V1180L, observed in 15/49 (31%) tumors. **CONCLUSION:** Alectinib appears clinically active against ALK rearrangements and mutations, as well as several ALK variants that can cause resistance to crizotinib. The use of cfDNA in plasma samples may be an alternative non-invasive method for monitoring resistance mutations during therapy.

[The ACTIVE study protocol: apatinib or placebo plus gefitinib as first-line treatment for patients with EGFR-mutant advanced non-small cell lung cancer \(CTONG1706\).](#) Zhang Z1,2, Luo F1,2, et al. *Cancer Commun (Lond)*. 2019 Nov 7;39(1):69. doi: 10.1186/s40880-019-0414-4.

**BACKGROUND:** Gefitinib, as the first epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) approved for the treatment of advanced non-small cell lung cancer (NSCLC), has been proved to significantly improve the progression-free survival (PFS) in the first-line setting but suffers from resistance 7-10 months after treatment initiation. Apatinib (YN968D1), a potent vascular endothelial growth factor receptor (VEGFR) 2-TKI, specifically binds to VEGFR2 and leads to anti-angiogenic and anti-neoplastic effect. Concurrent inhibition of VEGFR and EGFR pathways represents a rational approach to improve treatment responses and delay the onset of treatment resistance in EGFR-mutant NSCLC. This ACTIVE study aims to assess the combination of apatinib and gefitinib as a new treatment approach for EGFR-mutant NSCLC as a first-line setting. **METHODS:** This multicenter, randomized, double-blind, placebo-controlled phase III study (NCT02824458) has been designed to assess the efficacy and safety of apatinib or placebo combined with gefitinib as a first-line treatment for patients with EGFR-mutant advanced NSCLC. A total of 310 patients with EGFR-mutation (19del or 21L858R), pathological stage IIIB to IV non-squamous NSCLC were to be enrolled. The primary endpoint is investigator assessment of PFS, and the secondary endpoints include independent radiological central (IRC)-confirmed PFS, overall survival (OS), objective response rate (ORR), disease control rate (DCR), time to progressive disease (TTPD), duration of response (DoR), quality of life (QoL) and safety. The patients are randomized in a 1:1 ratio to receive gefitinib (250 mg, p.o. q.d.) plus apatinib (500 mg, p.o. q.d.) or gefitinib plus placebo, given until disease progression or intolerable adverse events. Exploratory biomarker analysis will be performed. This study is being conducted across China and comprises of 30 participating centers. Enrollment commenced in August 2017 and finished in December 2018, most of the patients are in the follow-up period. **ANTICIPATED OUTCOMES AND SIGNIFICANCE:** The present study will be the first to evaluate the efficacy and safety profile of the combination of apatinib plus gefitinib as a first-line therapy for patients with EGFR-positive advanced non-squamous NSCLC. Importantly, this trial will provide comprehensive evidence on the treatment of EGFR-TKIs combined with antiangiogenic therapy. Trial registration [Clinicaltrials.gov](https://clinicaltrials.gov) NCT02824458. Registered 23 June 2016.

[Outcomes of first-line pembrolizumab monotherapy for PD-L1-positive \(TPS ≥50%\) metastatic NSCLC at US oncology practices.](#) Velcheti V1, Chandwani S2, Chen X2, Pietanza MC2, Piperdi B2, Burke T2. *Immunotherapy*. 2019 Nov 27. doi: 10.2217/imt-2019-0177. [Epub ahead of print]

**AIM:** To determine real-world outcomes with first-line pembrolizumab monotherapy for metastatic non-small-cell lung cancer with PD-L1 tumor expression ≥50%. **METHODS:** This retrospective study included adults with ECOG 0-1 initiating first-line pembrolizumab monotherapy on/after 24 October 2016 (EHR cohort) or from 1 December 2016 through 30 November 2017 (spotlight cohort) with ≥6-month follow-up. We estimated Kaplan-Meier overall survival (OS, both cohorts), and, for spotlight, real-

world progression-free survival (rwPFS) by Kaplan-Meier and real-world tumor response (rwTR).

**RESULTS:** For 423 patients in the EHR cohort and 188 in spotlight, median OS was 18.9 months (95% CI: 14.9-25.5) and 19.1 months (12.6-not reached), respectively. For spotlight, median rwPFS was 6.8 months (5.3-8.1); rwTR of complete/partial response was 48% (41-56%). **CONCLUSION:** Observed OS, rwPFS and rwTR were consistent with clinical trial findings.

### **Differential Efficacy of Anti-VEGF Antibodies Based on Sex and Race in a Diverse Cohort of Advanced Nonsquamous Non-Small Cell Lung Cancer.**

Sukrithan V1, Barbaro A2, Chergui A3, Ko B1, Lin J4, Cheng H1, Goel S1. Am J Clin Oncol. 2019 Nov 18. doi: 10.1097/COC.0000000000000628. [Epub ahead of print]

**OBJECTIVES:** Bevacizumab with chemotherapy improved overall survival (OS) in the E4599 trial in metastatic nonsquamous non-small cell lung cancer (NS-NSCLC). A meta-analysis demonstrated an OS benefit with bevacizumab only in a subset of nonwhite patients. We explored the efficacy of antivascular endothelial growth factor antibodies (AVA) in a diverse cohort. **MATERIALS AND METHODS:** Patients with advanced (stage IIIB/IV, American Joint Committee Cancer 7th edition) recurrent or metastatic NS-NSCLC diagnosed January 2006 to December 2017 at a single medical center were included. Survival analysis was performed with log-rank testing of the Kaplan-Meier estimator. Univariate models were constructed, and significant variables, age, sex, race were incorporated into a multivariate Cox proportional hazard model. Data analysis was performed on SAS. **RESULTS:** A total of 171 patients, 80 were treated with AVA and 91 were untreated. Median age: 63 years, 55% females, 19% non-Hispanic whites, 44% blacks and 32% Hispanic whites; median 40 pack-years of smoking; 11.7% had sensitizing epidermal growth factor receptor mutations. Patients who received AVA had a survival benefit (26.6 vs. 19 mo, P=0.025). Adjusting for age, sex, race/ethnicity, epidermal growth factor receptor mutations, Eastern Cooperative Oncology Group performance status and number of metastases; AVA therapy was associated with improved OS (adjusted hazard ratio=0.62; P=0.049). In a subgroup analysis, females had survival benefit with AVA (median survival: 29.1 vs. 14.2 mo, log-rank P=0.02) which was significant in the adjusted model (adjusted hazard ratio=0.52; P=0.049). **CONCLUSIONS:** In a diverse cohort of patients with advanced NS-NSCLC, a survival benefit was confirmed with AVA. The greatest magnitude of benefit was in blacks and non-Hispanic whites. A significant survival benefit was limited to female patients.

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## **NSCLC - RADIOTHERAPY**

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**Plasma D-Dimer Levels are Elevated in Radiation Oncology Patients.** Louneva N1, Maity A1, Kennedy AR1. Radiat Res. 2019 Nov 1. doi: 10.1667/RR15429.1. [Epub ahead of print]

D-dimer plasma levels were evaluated to determine whether they are altered by radiation. D-dimer levels were measured in radiation oncology patients, who were diagnosed with prostate, breast or lung cancer, or leukemia, as well as in healthy subjects serving as controls. Blood samples from radiotherapy patients were taken at three different time points: pre-, on- and post-radiotherapy. For the patients, considered together, differences between the D-dimer levels at these three time points compared to controls were statistically significant. Compared to the pre-radiotherapy measurements, radiation exposure was associated with a significant increase in the D-dimer levels at the on- and post-radiotherapy time points. At the post-radiotherapy time point, D-dimer levels in the patients were not significantly reduced compared to the on-radiotherapy levels, indicating that the risk for developing disseminated intravascular coagulation (DIC) may be increased in some radiation oncology patients. Of particular concern are the post-radiotherapy results observed for the D-dimer levels in the leukemia patients, in which the average fold increase in the D-dimer levels was 5.43 (compared to the pre-radiotherapy levels). These results suggest that leukemia patients might benefit from frequent assessment of their D-dimer levels after their

total-body irradiation-conditioning regimen to detect early signs of DIC development. It is hoped that the results described here will lead to heightened awareness in the radiation oncology community that the risk of DIC development is greatly increased in some of these patients.

[\*\*A Pilot Study of Atezolizumab plus Hypofractionated Image-guided Radiotherapy for the Treatment of Advanced Non-Small Cell Lung Cancer.\*\*](#) Qin A1, Rengan R2, Lee S3, et al. *Int J Radiat Oncol Biol Phys.* 2019 Nov 19. pii: S0360-3016(19)34007-6. doi: 10.1016/j.ijrobp.2019.10.047. [Epub ahead of print]

**INTRODUCTION:** Preclinical data and subset analyses from immunotherapy clinical trials indicate that prior radiotherapy was associated with better progression-free survival (PFS) and overall survival (OS) when combined with immune checkpoint inhibitors in patients with non-small cell lung cancer (NSCLC). We present a prospective study of hypofractionated, image-guided radiation therapy (HIGRT) to a single site of metastatic disease concurrently with atezolizumab in patients with metastatic NSCLC.

**METHODS:** Patients meeting eligibility criteria received atezolizumab 1200mg IV every 3 weeks with concurrent 3- or 5-fraction HIGRT starting no later than the second cycle. The 3-fraction regimen employed a minimum of 8 Gy per fraction compared to 6 Gy for the 5-fraction regimen. Imaging was obtained every 12 weeks to assess response. **RESULTS:** From October 2015 to February 2017, 12 patients enrolled in the study (median age 64, range 55-77). The best response by RECIST criteria was partial response in 3 and stable disease in 3, for a disease control rate (DCR) of 50%. Five patients had a grade 3 immune-related adverse event (irAE), including choreoretinitis (n =1), pneumonitis (n=1), transaminitis (n=1), fatigue (n =1) and peripheral neuropathy (n=1). The median PFS was 2.3 months and the median OS was 6.9 months (range: 0.4-not reached). There was no clear association between peripheral blood T-cell repertoire characteristics at baseline, PD-L1, or tumor mutations and response or outcome. One long-term survivor exhibited oligoclonal T cell populations in a baseline tumor biopsy that were consistently detected in peripheral blood over the entire course of the study. **CONCLUSIONS:** HIGRT plus atezolizumab resulted in ORR of 25% and DCR of 50% in this pilot study. The incidence of grade 3 AEs was similar to that of atezolizumab alone. Though a pilot study with limited sample size, the results generated hypotheses worthy of further investigation.

[\*\*Cost-Effectiveness Analysis of Upfront SBRT for Oligometastatic Stage IV Non-Small Cell Lung Cancer Based on Mutational Status.\*\*](#) Kim H1, Vargo JA1, Ling DC1, Beriwal S1, Smith KJ2. *Am J Clin Oncol.* 2019 Nov;42(11):837-844. doi: 10.1097/COC.0000000000000608.

**OBJECTIVES:** Current National Comprehensive Cancer Network (NCCN) guidelines support systemic therapy based on mutational status in stage IV non-small cell lung cancer (NSCLC), with stereotactic body radiation therapy (SBRT) reserved for oligoprogression. We aimed to evaluate the cost-effectiveness of the routine addition of SBRT to upfront therapy in stage IV NSCLC by mutational subgroup.

**MATERIALS AND METHODS:** A Markov state transition model was constructed to perform a cost-effectiveness analysis comparing SBRT plus maintenance therapy with maintenance therapy alone for oligometastatic NSCLC. Three hypothetical cohorts were analyzed: epidermal growth factor receptor or anaplastic lymphoma kinase mutation-positive, programmed death ligand-1 expressing, and mutation-negative group. Clinical parameters were obtained largely from clinical trial data, and cost data were based on 2018 Medicare reimbursement. Strategies were compared using the incremental cost-effectiveness ratio with effectiveness in quality-adjusted life years (QALYs) and evaluated with a willingness to pay threshold of \$100,000 per QALY gained. **RESULTS:** SBRT plus maintenance therapy was not cost-effective at a \$100,000/QALY gained threshold, assuming the same survival for both treatments, resulting in an incremental cost effectiveness ratio of \$564,186 and \$299,248 per QALY gained for the epidermal growth factor receptor or anaplastic lymphoma kinase positive and programmed death ligand-1 positive cohorts, respectively. Results were most sensitive to the cost of maintenance



therapy. A large overall survival gain with SBRT could potentially result in upfront SBRT becoming cost-effective. For the mutation-negative cohort, upfront SBRT was nearly cost-effective, costing \$128,424 per QALY gained. **CONCLUSION:** Adding SBRT to maintenance therapy is not a cost-effective strategy for oligometastatic NSCLC compared with maintenance therapy alone for mutation-positive groups. However, this should be validated via randomized trials.

[Intrafraction 4D-cone beam CT acquired during volumetric arc radiotherapy delivery: kV parameter optimization and 4D motion accuracy for lung stereotactic body radiotherapy \(SBRT\) patients.](#) Liang J1, Lack D2, Zhou J3, Liu Q1, Grills I1, Yan D1. J Appl Clin Med Phys. 2019 Nov 1. doi: 10.1002/acm2.12755. [Epub ahead of print]

**PURPOSE:** Elekta XVI 5.0 allows for four-dimensional cone beam computed tomography (4D CBCT) image acquisition during treatment delivery to monitor intrafraction motion. These images can have poorer image quality due to undersampling of kV projections and treatment beam MV scatter effects. We determine if a universal intrafraction preset can be used for stereotactic body radiotherapy (SBRT) lung patients and validate the accuracy of target motion characterized by XVI intrafraction 4D CBCT.

**METHODS:** The most critical parameter within the intrafraction preset is the nominal AcquisitionInterval, which controls kV imaging acquisition frequency. An optimal value was determined by maximizing the kV frame number acquired up to 1000 frames, typical of pretreatment 4D CBCT. CIRS motion phantom intrafraction phase images for 16 SBRT beams were obtained. Mean target position, time-weighted standard deviation, and amplitude for these images as well as target motion for three SBRT lung patients were compared to respective pretreatment 4D CBCTs. Evaluation of intrafraction 4D CBCT reconstruction revealed inclusion of MV only images acquired to remove MV scatter effects. A workaround to remove these images was developed. **RESULTS:** AcquisitionInterval of 0.1°/frame was optimal. The number of kV frames acquired was 567-1116 and showed strong linear correlation with beam monitor unit (MUs). Phantom target motion accuracy was excellent with average differences in target position, standard deviation and amplitude range of  $\leq 0.5$  mm. Target tracking for SBRT patients also showed good agreement. Evaluation of phase sorting wave forms showed that inclusion of MV only images significantly impacts intrafraction image reconstruction for patients and use of workaround is necessary. **CONCLUSIONS:** A universal intrafraction imaging preset can be used safely for SBRT lung patients. The number of kV projections with MV delivery parameters varies; however images with fewer kV projections still provided accurate target position information. Impact of the reconstruction workaround was significant and is mandated for all 4D CBCT intrafraction imaging performed at our institution.

[Salvage Therapy for Locoregional Recurrence After Stereotactic Ablative Radiotherapy for Early-Stage Non-Small Cell Lung Cancer.](#) Brooks ED1, Verma V2, Senan S3, et al. J Thorac Oncol. 2019 Nov 8. pii: S1556-0864(19)33634-2. doi: 10.1016/j.jtho.2019.10.016. [Epub ahead of print]

Although isolated local (LRs) and regional recurrences (RRs) constitute a minority of post-stereotactic ablative radiotherapy (SABR) relapses, their management is becoming increasingly important as the use of SABR continues to expand. However, few evidence-based strategies are available to guide treatment of these potentially curable recurrences. On behalf of the Advanced Radiation Technology Committee (ART) of the International Association for the Study of Lung Cancer (IASLC), this article was written to address management of recurrent disease. Topics discussed include diagnosis and workup, including the roles of volumetric and functional imaging as well as histopathologic methods; clinical outcomes after salvage therapy; patterns of recurrence after salvage therapy; and management options. Our main conclusions are that survival for patients with adequately salvaged LR is similar to that for patients after primary SABR without recurrence, and survival for those with salvaged RRs (regardless of nodal burden or location) is similar to that of patients with de novo stage III disease. Although more than half of

patients who undergo salvage do not develop a second relapse, the predominant pattern of second failure is distant, especially for RRs. Management requires rigorous multidisciplinary coordination. Isolated LR's can be managed with resection and nodal dissection, repeat SABR, thermal ablation, or systemic therapies. RRs can be treated with combined chemoradiotherapy, radiation or chemotherapy alone, or supportive services. Finally, regular and structured follow-up is recommended after post-SABR salvage therapy.

### [Pathological Correlation of Cellular Imaging using Apparent Diffusion Coefficient \(ADC\) quantification in patients with Brain Metastases following Gamma Knife Radiosurgery.](#)

Borghei-Razavi H1, Sharma M1, Emch T2, et al. World Neurosurg. 2019 Nov 13. pii: S1878-8750(19)32873-6. doi: 10.1016/j.wneu.2019.11.037. [Epub ahead of print]

**INTRODUCTION:** The aim of our study was to evaluate the role of apparent diffusion coefficient (ADC) in differentiating Radiation necrosis (RN) from recurrent tumor following Gamma Knife radiosurgery (GKRS) for brain metastases (BM). **METHOD:** Forty-one patients with BM who underwent surgical intervention following GKRS at Cleveland Clinic (2006 -2017) were included in this retrospective study. The ADC values of the growing lesions and the contralateral hemisphere were calculated using Agfa IMPAX software©. These values were correlated to the percentage of RN identified on pathological evaluation of the surgical specimen. **RESULTS:** The median age of the patients was 59 years (range: 25-86) and lung cancer (63.4%) was the most common malignancy. Median initial (pre-GK) target volume of the lesions was 5.4 cc [Range: 0.135-45.6] and median GKRS dose was 18.0 Gy. Surgical resection or biopsy was performed at a median of 176 days following GKRS. Two variables were statistically significant predictors of predominate RN (75-100%) in the surgical specimen: i) ADC of the lesion on the pre-resection MRI, and ii) initial pre-GK target volume. ADC > 1.5 x10<sup>-3</sup> mm<sup>2</sup>/s within the lesion on MRI predicted significant RN on pathological evaluation of the lesion (p < 0.05). Similarly, when the target volume before GK was large (> 10 cc), the risk of identifying significant necrosis in the pathological specimen was elevated (p < 0.05). **CONCLUSION:** Our data suggest that combination of lesion ADC on MRI prior to surgical intervention and the initial target volume can predict RN with reasonable accuracy.

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## SMALL CELL LUNG CANCER - SCLC

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### [YAP1 promotes multidrug resistance of small cell lung cancer by CD74-related signaling pathways.](#)

Song Y1, Sun Y2, Lei Y3, Yang K4, Tang R1. Cancer Med. 2019 Nov 6. doi: 10.1002/cam4.2668. [Epub ahead of print]

**BACKGROUND:** Our previous research found that YAP1 may have a role in multidrug resistance (MDR) in small cell lung cancer (SCLC). However, its underlying mechanism is unknown. **METHODS:** In this study, we investigated the expression of YAP1 using immunohistochemical staining and assessed the relationship between the expression of YAP1 and overall survival in patients with SCLC. We established H69 stable cell lines that overexpressed constitutively active YAP1 and H446 stable cell lines that dominate negative YAP1. We conducted CCK-8, flow cytometric analysis, and in vivo chemosensitivity experiments to evaluate the function of YAP1 in drug sensitivity apoptosis in vitro and in vivo. **RESULTS:** The results indicated that patients with high YAP1 expression have shorter survival rates and more advanced disease stage than those with low YAP1 expression. YAP1 may induce MDR by inhibiting the apoptosis of SCLC. YAP1 induced MDR when YAP1 was hyperactivated, and drug sensitivity increased when YAP1 was inhibited in vitro and in vivo. CD74 was significantly correlated with YAP1 in SCLC samples. Inhibition of CD74 using ISO-1 increased drug sensitivity significantly. **CONCLUSIONS:** The expression of YAP1 is significantly correlated with overall survival and disease stage in patients with SCLC. YAP1 may play an important role in these patients. We were the first to

report that YAP1 can induce MDR in SCLC in vitro and in vivo. CD74 may be involved in YAP1-induced MDR.

[Geriatric Nutritional Risk Index as a prognostic marker in patients with extensive-stage disease small cell lung cancer: Results from a randomized controlled trial.](#) Lee GW1, Go SI2, Kim DW3, Kim HG2, Kim JH4, An HJ5, Jang JS6, Kim BS7, Hahn S8, Heo DS3. Thorac Cancer. 2019 Nov 10. doi: 10.1111/1759-7714.13229. [Epub ahead of print]

**BACKGROUND:** Clinical impact of the Geriatric Nutritional Risk Index (GNRI) in patients with extensive-stage disease small cell lung cancer (ED-SCLC) have not previously been reported. **METHODS:** This study analyzed 352 patients enrolled in a previous randomized phase III trial comparing the efficacy of irinotecan plus cisplatin with that of etoposide plus cisplatin as the first-line therapy for ED-SCLC. GNRI values were calculated using serum albumin levels and actual and ideal bodyweights. Patients with a GNRI > 98, 92-98, and <92 were grouped into no, low, and moderate/major risk groups, respectively. **RESULTS:** The objective response rates were 63.2%, 52.6%, and 49.2% in the no, low, and moderate/major risk groups, respectively (P = 0.024). The median progression-free survival (PFS) was shorter in patients with a lower GNRI than in those with a higher GNRI (no vs. low vs. moderate/major risk group; 6.5 vs. 5.8 vs. 5.9 months, respectively; P = 0.028). There were significant differences in median overall survival (OS) according to GNRI (no vs. low vs. moderate/major risk group; 13.2 vs. 10.3 vs. 8.4 months, respectively; P < 0.001). Multivariate analysis revealed that being in the moderate/major risk group was an independent poor prognostic factor for PFS (hazard ratio [HR]: 1.300, 95% confidence interval [CI]: 1.012-1.670; P = 0.040) and OS (HR: 1.539; 95% CI: 1.069-2.216; P = 0.020). **CONCLUSIONS:** This prospective study shows that a low GNRI value was associated with a poor prognosis, and it supports the relationship between systemic inflammation, nutritional status, and clinical outcomes in patients with ED-SCLC. **Key points SIGNIFICANT FINDINGS OF THE STUDY:** The lower GNRI group had a low response rate to chemotherapy for ED-SCLC. The HRs for PFS and OS were 1.300 and 1.539 in the patients with GNRI < 92.

[Final report of a prospective randomized study on thoracic radiotherapy target volume for limited-stage small cell lung cancer with radiation dosimetric analyses.](#) Hu X1, Bao Y2, Xu YJ1, et al. Cancer. 2019 Nov 12. doi: 10.1002/cncr.32586. [Epub ahead of print]

**BACKGROUND:** The thoracic radiotherapy (TRT) target volume for limited-stage small-cell lung cancer (SCLC) has been controversial for decades. In this report, the final results of a prospective randomized trial on the TRT target volume before and after induction chemotherapy are presented. **METHODS:** After 2 cycles of etoposide and cisplatin, patients arm were randomized to receive TRT to the postchemotherapy or prechemotherapy tumor volume in a study arm and a control arm. Involved-field radiotherapy was received in both arms. TRT consisted of 1.5 grays (Gy) twice daily in 30 fractions to up to a total dose of 45 Gy. Lymph node regions were contoured, and intentional and incidental radiation doses were recorded. **RESULTS:** The study was halted early because of slow accrual. Between 2002 and 2017, 159 and 150 patients were randomized to the study arm or the control arm, respectively; and 21.4% and 19.1% of patients, respectively, were staged using positron emission tomography/computed tomography (P = .31). With a median follow-up of 54.1 months (range, 19.9-165.0 months) in survivors, the 3-year local/regional progression-free probability was 58.2% and 65.5% in the study and control arms, respectively (P = .44), and the absolute difference was -7.3% (95% CI, -18.2%, 3.7%). In the study and control arms, the median overall survival was 21.9 months and 26.6 months, respectively, and the 5-year overall survival rate was 22.8% and 28.1%, respectively (P = .26). Grade 3 esophagitis was observed in 5.9% of patients in the study arm versus 15.5% of those in the control arm (P = .01). The isolated out-of-field failure rate was 2.6% in the study arm versus 4.1% in the control arm (P = .46), and all such failures were located in the supraclavicular fossa or contralateral hilum. The regions 7, 3P, 4L, 6, 4R, 5, and 2L

received incidental radiation doses >30 Gy. **CONCLUSIONS:** TRT could be limited to the postchemotherapy tumor volume, and involved-field radiotherapy could be routinely applied for limited-stage SCLC.

**Prognostic value of tumor cavitation in extensive-stage small-cell lung cancer patients treated with anlotinib.** Chen D1, Xu J1, Zhao Y1, Chu T1, Zhong H1, Han B2, Zhong R3. *J Cancer Res Clin Oncol.* 2019 Nov 6. doi: 10.1007/s00432-019-03064-1. [Epub ahead of print]

**PURPOSE:** Anlotinib is a novel multi-target tyrosine kinase inhibitor (TKI) for tumor angiogenesis and tumor cell proliferation. The efficacy of anlotinib as a third-line or beyond therapy for SCLC was confirmed in the ALTER1202 trial. For lung cancer patients treated with antiangiogenesis agents, the phenomenon of cavitation is commonly seen in the lung target lesions. The impact of tumor cavitation on survival in lung cancer patients treated with vascular-targeted therapy remains controversial. Our retrospective study was to investigate the prognostic value of tumor cavitation in extensive-stage SCLC patients treated with anlotinib. **METHODS:** A total of 73 extensive-stage SCLC patients confirmed by histopathology from January 2018 to January 2019 were retrospectively analyzed. All patients received anlotinib therapy at Shanghai Chest Hospital. We defined tumor cavitation of the lung target lesions as that part of solid component was changed to air-filled area according to chest CT. Progression-free survival (PFS) was calculated from the beginning of anlotinib therapy to the disease progression or the last follow-up visit. **RESULTS:** Eleven (15.0%) patients had tumor cavitation during anlotinib therapy. The ORR of the 73 patients was 15.1%. Multivariate logistic regression analysis showed that tumor cavitation during anlotinib therapy was not associated with gender ( $P = 0.630$ ), age ( $P = 0.190$ ), smoking status ( $P = 0.165$ ), anatomy type ( $P = 0.641$ ), and the line of anlotinib therapy ( $P = 0.302$ ). The median PFS of all patients was 2.6 months (95%CI 2.1-3.2). According to the univariate analysis, the median PFS in patients with and without tumor cavitation was 5.0 months and 2.2 months, respectively, and the difference was statistically significant ( $P = 0.041$ ). According to the multivariate analysis, tumor cavitation was an independent factor for PFS after adjusting gender, age, smoking status, anatomy type, the line of anlotinib therapy, tumor cavitation, and response to anlotinib (adjusted HR 0.316, 95%CI 0.142-0.702;  $P = 0.005$ ). **CONCLUSIONS:** In 73 extensive-stage SCLC patients treated with anlotinib, no demographic/clinical characteristic was related to tumor cavitation, and tumor cavitation was an independent factor in predicting better PFS.

**Efficacy of Second-line Chemotherapy in Patients With Sensitive Relapsed Small-cell Lung Cancer.** Wakuda K1, Miyawaki T2, Miyawaki E2, et al. *In Vivo.* 2019 Nov-Dec;33(6):2229-2234. doi: 10.21873/invivo.11727.

**BACKGROUND/AIM:** To evaluate treatment efficacy of cisplatin, etoposide, and irinotecan combined therapy (PEI), platinum-rechallenge chemotherapy (Pt-Re) and amrubicin monotherapy (AMR) for patients with sensitive relapsed small cell lung cancer (SCLC). **PATIENTS AND METHODS:** We defined sensitive relapse as treatment-free interval (TFI)  $\geq 90$  days. We retrospectively collected patients' data from medical records between September 2002 and December 2016. Patients with sensitive relapsed SCLC who received second-line chemotherapy were separated into those treated with PEI, with Pt-Re, or with AMR. **RESULTS:** Seventy-one patients (16 PEI group, 27 Pt-Re group, and 28 AMR group) were assessable for efficacy. No significant differences in patient characteristics were found among the three groups. The median overall survival (MST) was 29.3 months in the PEI group, 24.6 months in the Pt-Re group, and 20.6 months in the AMR group ( $p=0.042$ ). **CONCLUSION:** A significant difference was observed in the overall survival of patients treated with PEI, Pt-Re and AMR and the MST of PEI was the longest.



[The Epidemiology of Depressive Symptoms in the Last Year of Life](#). Kozlov E1, Dong X1, Kelley AS2,3, Ankuda CK2. J Am Geriatr Soc. 2019 Nov 5. doi: 10.1111/jgs.16197. [Epub ahead of print]

**BACKGROUND/OBJECTIVE:** Depression impacts quality of life at all life stages, but the epidemiology of depression in the last year of life is unknown. This study's objectives were to document the epidemiology of depressive symptoms in the year prior to death and to assess how the trajectory of depressive symptoms varies by sociodemographic and clinical factors. **DESIGN:** Observational, cross-sectional, cohort study using the Health and Retirement Study. **SETTING:** Population-based survey. **PARTICIPANTS:** A total of 3274 individuals who died within 12 months after assessment. **MEASURES:** Primary outcome: eight-item Center for Epidemiologic Studies Depression Scale (CESD-8). Covariates included sociodemographics, self-reported illnesses, and activity of daily living (ADL) limitations. **RESULTS:** Average CESD-8 score increased over the last year of life, with 59.3% screening positive for depression in the last month before death. Depression symptoms increased gradually from 12 to 4 months before death (increase of 0.05 points/month; 95% confidence interval [CI] = 0.01-0.08 points/month) and then escalated from 4 to 1 months before death (increase of 0.29 points/month; 95% CI = 0.16-0.39 points/month). Women, younger adults, and nonwhite adults all demonstrated higher rates of depressive symptoms. Individuals with cancer reported escalating rates of depressive symptoms at the end of life, while individuals with lung disease and ADL impairment demonstrated persistently high rates throughout the year before death. **CONCLUSIONS:** This study revealed high rates of depressive symptoms in the last year of life as well as differences in the burden of depressive symptoms. A public health approach must be taken to screen for and appropriately treat symptoms of depression across the lifespan.

[Physical Activity and Exercise in Lung Cancer Care: Will Promises Be Fulfilled?](#) Avancini A1, Sartori G2,3, Gkoutakos A4, et al. Oncologist. 2019 Nov 26. pii: theoncologist.2019-0463. doi: 10.1634/theoncologist.2019-0463. [Epub ahead of print]

Lung cancer remains the leading cause of cancer-related death worldwide. Affected patients frequently experience debilitating disease-related symptoms, including dyspnea, cough, fatigue, anxiety, depression, insomnia, and pain, despite the progresses achieved in term of treatment efficacy. Physical activity and exercise are nonpharmacological interventions that have been shown to improve fatigue, quality of life, cardiorespiratory fitness, pulmonary function, muscle mass and strength, and psychological status in patients with lung cancer. Moreover, physical fitness levels, especially cardiorespiratory endurance and muscular strength, are demonstrated to be independent predictors of survival. Nevertheless, patients with lung cancer frequently present insufficient levels of physical activity and exercise, and these may contribute to quality of life impairment, reduction in functional capacity with skeletal muscle atrophy or weakness, and worsening of symptoms, particularly dyspnea. The molecular bases underlying the potential impact of exercise on the fitness and treatment outcome of patients with lung cancer are still elusive. Counteracting specific cancer cells' acquired capabilities (hallmarks of cancer), together with preventing treatment-induced adverse events, represent main candidate mechanisms. To date, the potential impact of physical activity and exercise in lung cancer remains to be fully appreciated, and no specific exercise guidelines for patients with lung cancer are available. In this article, we perform an in-depth review of the evidence supporting physical activity and exercise in lung cancer and suggest that integrating this kind of intervention within the framework of a global, multidimensional approach, taking into account also nutritional and psychological aspects, might be the most effective strategy. **IMPLICATIONS FOR PRACTICE:** Although growing evidence supports the safety and efficacy of exercise in lung cancer, both after surgery and during and after medical treatments, most patients are insufficiently active or sedentary. Engaging in exercise programs is particularly arduous for patients with lung cancer, mainly because of a

series of physical and psychosocial disease-related barriers (including the smoking stigma). A continuous collaboration among oncologists and cancer exercise specialists is urgently needed in order to develop tailored programs based on patients' needs, preferences, and physical and psychological status. In this regard, benefit of exercise appears to be potentially enhanced when administered as a multidimensional, comprehensive approach to patients' well-being.

**[Development of an app for lung cancer survivors \(iEXHALE\) to increase exercise activity and improve symptoms of fatigue, breathlessness and depression.](#)** Henshall C1, Davey Z1.

Psychooncology. 2019 Nov 26. doi: 10.1002/pon.5252. [Epub ahead of print]

**OBJECTIVE:** Exercise-based self-management interventions are recommended for lung cancer survivors and can provide physical, psychosocial and emotional relief. Mobile health technologies can encourage self-management; however, currently, no cancer-related app addresses exercise-specific needs of lung cancer survivors. This paper details the design, development and testing of an exercise app for lung cancer survivors (iEXHALE), which aims to increase exercise activity and improve symptoms.

**METHODS:** The research had two stages: (1) focus groups with healthcare professionals, patients and family members (n=21) and (2) app development and usability study with lung cancer survivors (n=6). The Capability, Opportunity, Motivation-Behaviour model was used as a theoretical framework; data were thematically analysed. **RESULTS:** Focus group findings identified many helpful exercises for managing lung cancer survivors' symptoms. These findings, alongside relevant literature, informed iEXHALE's content and design. The usability study found that lung cancer survivors valued iEXHALE's self-management capabilities but identified potential modifications including improved self-monitoring diaries and navigation. **CONCLUSIONS:** iEXHALE's development has been theoretically and empirically informed, showing value as a self-management tool. Next, we will test its effectiveness, acceptability and cost-effectiveness.

**[Nature of Discussions About Systemic Therapy Discontinuation or Hospice among Patients, Families, and Palliative Care Clinicians during Care for Incurable Cancer: A Qualitative Study.](#)**

Traeger L1,2, Rapoport C1, Wright E1, El-Jawahri A3,2, Greer JA1,2, Park ER4,2, Jackson VA5,2, Temel JS3,2. J Palliat Med. 2019 Nov 13. doi: 10.1089/jpm.2019.0402. [Epub ahead of print]

**BACKGROUND:** Patient/clinician communication is critical to quality cancer care at the end-of-life (EOL). Yet discussions about systemic therapy discontinuation or hospice as a care option are commonly deferred. Real-time communication about these complex topics has not been evaluated. Palliative care visits may provide useful insight into how communication about EOL care occurs over time. Objective: To explore the nature of discussions about systemic therapy discontinuation and hospice among patients, families, and palliative care clinicians during care for incurable cancer. **DESIGN:** Qualitative study of palliative care visits. **SETTING/SUBJECTS:** We audiorecorded visits of patients and families who participated in a palliative care trial from diagnosis of incurable lung or noncolorectal gastrointestinal cancer through the course of cancer care (n = 30). Measurements: We used thematic analysis to characterize communication patterns in the context of clinical events. **RESULTS:** Content and tenor of discussions shifted in relation to patient health status. In the absence of acute medical deterioration, discussions addressed hospice broadly as an EOL care option. Candid exchanges between patients and families and their clinicians supported increasing depth and specificity of EOL care communication. As clinicians identified that patients were not tolerating treatment, the clinicians encouraged contemplation about quality-of-life implications of continuing treatment or the possibility that treatment might harm more than help, in anticipation of change in health status. **CONCLUSIONS:** Longitudinal relationships with palliative care clinicians functioned through multiple pathways to support patients and families in making complex EOL care decisions. Results inform models and interventions of communication at the EOL.

### [Educational Attainment and Quality of Life among Older Adults before a Lung Cancer Diagnosis.](#)

Schwartz RM1,2,3, Bevilacqua KG1, Alpert N2,3, Liu B2,3, Dharmarajan KV4, Ornstein KA5, Taioli E2,3. *J Palliat Med.* 2019 Nov 8. doi: 10.1089/jpm.2019.0283. [Epub ahead of print]

**BACKGROUND:** Demographic and contextual factors are associated with quality of life (QoL) in older adults and prediagnosis QoL among older adults has important implications for supportive care in older cancer patients. Objective: To examine whether lower educational attainment is associated with poorer QoL among community dwelling older adults just before their diagnosis of lung cancer in a nationally representative sample. **DESIGN:** This study used the Surveillance, Epidemiology, and End Results (SEER)-Medicare Health Outcomes Survey (MHOS) dataset, which provides cancer registry data linked with survey data for Medicare Advantage enrollees. Subjects: Adults 65 years and older at time of diagnosis with first or only primary lung cancer and with at least one survey before their cancer diagnosis. **MEASUREMENTS:** Level of education attained was categorized as less than high school (<HS) or at least a high school diploma (≥HS). QoL was calculated based on individual subscale scores from the 36-item Short Form Health Survey (SF-36) until 2006 (Veteran's RAND 12-Item Survey [VR-12] after 2006). Demographic covariates as well as number of comorbidities were adjusted for in multivariable models. **RESULTS:** Higher education was positively associated with prediagnosis mental and physical QoL. Other factors associated with lower QoL were Medicaid status and number of comorbidities. **CONCLUSIONS:** Particular attention should focus on identifying and addressing QoL needs among vulnerable older adults to bolster QoL to mitigate its potential impact on prognosis following a lung cancer diagnosis.

### [Psychosocial interventions for informal caregivers of lung cancer patients: A systematic review.](#)

Kedia SK1, Collins A1, Dillon PJ2, Akkus C1, Ward KD1, Jackson BM3. *Psychooncology.* 2019 Nov 8. doi: 10.1002/pon.5271. [Epub ahead of print]

**OBJECTIVE:** Caregivers of patients with lung cancer often face physical, emotional, and financial distress, which not only negatively affects the caregivers' mental health and quality of life but may also impact patients' well-being. The purpose of this systematic review is to examine the content, delivery, and efficacy of psychosocial interventions targeting caregivers of lung cancer patients. **METHODS:** Studies included in this systematic review assessed psychosocial interventions for caregivers of lung cancer patients that were published in English between January 2009 and December 2017. These interventions focused on burden, mental health, quality of life, self-efficacy, and/or coping as outcome measures. CINAHL, PubMed, PsycInfo, Science Direct, and Web of Science databases were searched using the terms (lung cancer OR lung neoplasms OR thoracic cancer) AND (caregiver OR caregiving) AND (intervention OR program) to systematically review the relevant literature on this topic. **RESULTS:** From the 22 studies included in this systematic review, interventions were classified into four categories: communication-based interventions, coping skills training interventions, multicomponent interventions, and stress reduction interventions. The majority of the interventions (especially communication-based and multicomponent) led to improvement, albeit not always statistically significant, in one or more outcomes; however, the most frequently reported improvements included, burden, distress, anxiety, depression, overall quality of life, self-efficacy, and coping abilities. **CONCLUSIONS:** The unmet needs of informal caregivers of lung cancer patients have a significant impact on their mental health and quality of life, but this burden can be alleviated by psychosocial interventions that offer appropriate support, education, and resources.

[Distinct Stress Profiles Among Oncology Patients Undergoing Chemotherapy.](#) Langford DJ1, Cooper B2, Paul S2, Humphreys J3, Hammer MJ4, Levine J5, Conley YP6, Wright F7, Dunn LB8, Miaskowski

C2. J Pain Symptom Manage. 2019 Nov 8. pii: S0885-3924(19)30642-6. doi: 10.1016/j.jpainsymman.2019.10.025. [Epub ahead of print]

**CONTEXT:** Cancer and its treatment are inherently stressful and stress impacts important patient outcomes. Patients vary considerably in their response to stress. Understanding this variability requires a patient-centered multidimensional approach. **OBJECTIVES:** The objectives of this study were to identify and characterize patient subgroups with distinct multidimensional stress profiles (stress appraisal, exposure, and adaptation) during cancer treatment. **METHODS:** Among 957 patients undergoing chemotherapy for breast, gastrointestinal, gynecological, or lung cancer, latent profile analysis was performed to identify patient subgroups using concurrent evaluations of global (Perceived Stress Scale) and cancer-specific (Impact of Events Scale-Revised) stress, lifetime stress exposure (Life Stressor Checklist-Revised), and resilience (Connor-Davidson Resilience Scale-10). **RESULTS:** Three latent classes were identified: "Normative" (54.3%; intermediate global stress and resilience, lower cancer-related stress, lowest life stress); "Stressed" (39.9%; highest global and cancer-specific stress scores, lowest resilience, most life stress); and "Resilient" (5.7%; lowest global stress, cancer-specific stress comparable to Normative class, highest resilience, intermediate life stress). Characteristics that distinguished the Stressed from the Normative class included: younger age, female gender, lower socioeconomic status, unmarried/partnered, living alone, poorer functional status, and higher comorbidity burden. Compared to Stressed patients, Resilient patients were more likely to be partnered, not live alone, and had a higher functional status. No demographic or clinical characteristics differentiated Normative from Resilient patients. Exposure to specific life stressors differed significantly among the classes. **CONCLUSION:** A subset of patients warrants intensive psychosocial intervention to reduce stress and improve adaptation to cancer. Intervention efforts may be informed by further study of Resilient patients.

**[Impact of an Animation Education Program on Promoting Compliance With Active Respiratory Rehabilitation in Postsurgical Lung Cancer Patients: A Randomized Clinical Trial.](#)** Li J1, Davies M, Ye M, Li Y, Huang L, Li L. Cancer Nurs. 2019 Nov 8. doi: 10.1097/NCC.0000000000000758. [Epub ahead of print]

**BACKGROUND:** Non-small cell lung cancer is the most common type of lung cancer. Lung resection is proven to be the most effective curative treatment for early-stage non-small cell lung cancer (stages I-IIIa). Studies show evidence-based pulmonary rehabilitation is critical for improving exercise capacity and pulmonary function, reducing burden of cancer-related symptoms, and facilitating quality of life following a lung resection. **OBJECTIVE:** To explore the effectiveness of an animation education program to promote respiratory rehabilitation outcomes for postsurgical lung cancer patients.

**INTERVENTIONS/METHODS:** Eighty lung cancer patients who had undergone lung resection were equally randomized to 2 groups with 40 participants in each group. The intervention group received animation education. The control group received traditional face-to-face education. The training-related knowledge and exercise compliance were evaluated at baseline, 3 days after education, and the day of discharge, along with related pulmonary functional indicators. **RESULTS:** Eighty of 99 eligible participants were enrolled (80.8%). Mean scores of training-related knowledge and exercise compliance in the intervention group were higher than those of the control group. Occurrences of postoperative pulmonary complications and the indwelling time of thoracic drainage tube were lower, and 6-minute walk distance was longer compared with the control group. No statistical differences in other pulmonary functional indicators were found. **CONCLUSIONS:** Educational animation is effective for promoting training-related knowledge and exercise compliance with active respiratory rehabilitation in postsurgical lung cancer patients. **IMPLICATIONS FOR PRACTICE:** Oncology nurses can implement animation as an innovative educational method for improving cancer patients' uptake and compliance on health education.



### [The Oldest Old: A National Analysis of Outcomes for Patients 90 Years or Older With Lung](#)

[Cancer](#). Yang CJ1, Brown AB2, Deng JZ1, Lui NS1, Backhus LM3, Shrager JB1, D'Amico TA2, Berry MF4. *Ann Thorac Surg*. 2019 Nov 12. pii: S0003-4975(19)31582-6. doi: 10.1016/j.athoracsur.2019.09.027. [Epub ahead of print]

**BACKGROUND:** Most clinicians will encounter patients 90 years or older with non-small cell lung cancer (NSCLC), but evidence that informs treatment decisions for this extremely elderly population is lacking. This study evaluated outcomes associated with treatment strategies for this nonagenarian population. **METHODS:** Treatment and overall survival for patients 90 years and older with NSCLC in the National Cancer Data Base (2004-2014) were evaluated using logistic regression, the Kaplan-Meier method, and multivariable Cox proportional hazard models. **RESULTS:** The majority (n = 4152, 57.6%) of the 7205 patients 90 years or older with stage I-IV NSCLC did not receive any therapy. For the entire cohort, receiving treatment was associated with significantly better survival when compared with no therapy (5-year survival, 9.3% [95% confidence interval [CI], 8.0%-10.7%] vs 1.7% [95% CI, 1.2%-2.2%]; multivariable adjusted hazard ratio, 0.53; P < .001). Stage I patients had the most pronounced survival benefit with treatment (median survival, 27.4 months vs 10.0 months with no treatment; P < .001). Among this subset of patients with stage I disease (n = 1430), only 12.7% (n = 182) had surgery and 33% (n = 471) had no therapy. In these stage I patients surgery was associated with significantly better 5-year survival (33.7% [95% CI, 25.4%-42.1%]) than nonoperative therapy (17.1% [95% CI, 13.7%-20.8%]) and no therapy (6.2% [95% CI, 3.8%-9.4%]). **CONCLUSIONS:** Therapy for nonagenarians with NSCLC is associated with a significant survival benefit but is not used in most patients. Treatment should not be withheld for these "oldest old" patients based on their age alone but should be considered based on stage and patient preferences in a multidisciplinary setting.

### [Neuropsychological Symptoms and Intrusive Thoughts Are Associated With Worse Trajectories of Chemotherapy-Induced Nausea](#)

Singh K1, Paul SM2, Kober KM2, Conley YP3, Wright F4, Levine JD5, Joseph PV6, Miaskowski C7. *J Pain Symptom Manage*. 2019 Nov 2. pii: S0885-3924(19)30640-2. doi: 10.1016/j.jpainsymman.2019.10.023. [Epub ahead of print]

**CONTEXT:** Although chemotherapy-induced vomiting is well controlled with evidence-based antiemetic regimens, chemotherapy-induced nausea (CIN) remains a significant clinical problem. **OBJECTIVES:** Study purposes, in a sample of outpatients with breast, gastrointestinal, gynecological, or lung cancer who received two cycles of chemotherapy (CTX, n = 1251), were to evaluate for interindividual differences in the severity of CIN and to determine which demographic, clinical, symptom, and stress characteristics are associated with higher initial levels as well as with the trajectories of CIN. **METHODS:** Patients were recruited during their first or second cycle of CTX. Patients completed self-report questionnaires a total of six times over two cycles of CTX. Hierarchical linear modeling was used to evaluate for interindividual differences in and characteristics associated with the severity of CIN. **RESULTS:** Across the two cycles of CTX, higher levels of sleep disturbance, depression, and morning fatigue, as well as higher levels of intrusive thoughts, were associated with higher initial levels of CIN. In addition, lower functional status scores and shorter cycle lengths were associated with higher initial levels of CIN, and younger age and higher emetogenicity of the CTX regimen were associated with both higher initial levels as well as worse trajectories of CIN severity. **CONCLUSION:** These findings suggest that common symptoms associated with cancer and its treatment are associated with increased severity of CIN. Targeted interventions for these symptoms may reduce the burden of unrelieved CIN.

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## COMPLEMENTARY & ALTERNATIVE THERAPY

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[Huaier extract suppresses non-small cell lung cancer progression through activating NLRP3-dependent pyroptosis.](#) Xie J1, Zhuan B2, Wang H3, Wang Y2, Wang X3, Yuan Q3, Yang Z3. *Anat Rec (Hoboken)*. 2019 Nov 6. doi: 10.1002/ar.24307. [Epub ahead of print]

Recent studies have reported the anticancer activity of huaier extract in various human malignancies. However, little is known about the effect of huaier extract in non-small cell lung cancer (NSCLC) and its underlying mechanism. The current study aimed to investigate whether huaier extract affects the progression of NSCLC. mRNA and proteins expression of pyroptotic-related genes (NLRP3, caspase-1, IL-1 $\beta$ , and IL-18) in NSCLC tissues and cells were, respectively, detected by qRT-PCR and western blot. The effects of huaier extract on NSCLC cell viability and cytotoxicity were evaluated by CCK-8 assay, colony formation assay, and LDH detection kit. Besides, we established a xenograft model to assess the antitumor effect of huaier extract on tumor growth in vivo. Our results showed that the expression of pyroptotic-related genes was downregulated in NSCLC tissues and cell lines. Huaier extract pretreatment inhibited cell viability and the percentage of colony formation of H520 and H358 cells, and upregulated the expression of pyroptotic-related genes. Mechanistically, huaier extract exhibited antitumor effect in NSCLC via inducing NLRP3-dependent pyroptosis in vitro and in vivo. In conclusion, our finding confirmed that huaier extract played an antitumor role in NSCLC progression through promoting pyroptotic cell death, which provided a new potential strategy for NSCLC clinical treatment.

[Compound Kushen Injection as an Adjunctive Therapy for the Treatment of Non-Small-Cell Lung Cancer: A Meta-Analysis of Randomized Controlled Trials.](#)

Pu L1,2, Chen WH1, Cao LX1, Wu KJ3,4, Chen SL1, Lin JH1, Li CL1, Wang SQ1, Zhu MM1, Zhang YM1. *Evid Based Complement Alternat Med*. 2019 Nov 6;2019:7241927. doi: 10.1155/2019/7241927. eCollection 2019.

**OBJECTIVES:** To evaluate the efficacy and safety of compound Kushen injection (CKI) combined with chemo treatment (chemo) for non-small-cell lung cancer (NSCLC). **METHODS:** We systematically searched the literature published in seven databases, including Embase, PubMed, central, MEDLINE, CNKI, Wanfang, and VIP, from their inception to April 2019 for all randomized controlled trials (RCTs) comparing CKI plus chemo with chemo alone in patients with NSCLC. Our main end point was clinical efficiency and the secondary outcomes were Karnofsky performance score (KPS), immune function, and adverse events. The Cochrane risk of bias tool was applied for quality assessment. **RESULTS:** 10 studies involving 1019 participants were included. The clinical response rate (relative risk (RR) = 1.21, 95% confidence interval (CI): 1.06 to 1.37; P=0.003), KPS (RR = 2.18, 95% CI: 1.49 to 3.17; P < 0.0001), immune function (mean differences (MD) = 0.82, 95% CI: 0.12 to 1.52; P=0.02) and adverse effects (RR = 0.67, 95% CI: 0.60 to 0.74; P < 0.00001) in the CKI plus chemo group showed significant differences when compared with chemo alone. **CONCLUSIONS:** CKI combined with chemo can improve clinical efficiency, KPS, and immune function and reduce adverse reactions in patients with NSCLC when compared with chemo alone. However, more rigorously designed RCTs are needed to validate this benefit, as some of the included RCTs are of low methodological quality.

[Effect of acupuncture on lung cancer-related fatigue: study protocol for a multi-center randomized controlled trial.](#) Wang Z1,2, Li S3, Wu L2, Qi Q1,2, Liu H2, Jin X4, Tian J5, Zhang M6, Ma X2, Sun D5, Xu S7, Wu H8. *Trials*. 2019 Nov 9;20(1):625. doi: 10.1186/s13063-019-3701-0.

**BACKGROUND:** Fatigue is one of the primary symptoms in lung cancer, with a prevalence of 88.0% in survivors of cancer, and an even higher prevalence post resection surgery. Effective fatigue control after lung cancer surgery is important for patient recovery and quality of life. Some studies have shown that acupuncture might be effective in treating cancer-related fatigue; however, randomized controlled trials (RCTs) of suitable sample size are limited. **METHOD/DESIGN:** This is a multi-center, patient-blinded RCT. A total of 320 eligible patients will be recruited in four centers and randomly assigned to either the

acupuncture group or the sham acupuncture group in a 1:1 ratio. Treatment will be given twice per week for 12 sessions. Treatment will be given at acupoints GV20, GV29, CV12, CV6, CV4, and bilateral LI4, LR3, SP6, ST36. The primary outcome will be assessed using the Chinese version of The Brief Fatigue Inventory. The secondary outcomes will be measured using The European Organization for Research and The Treatment of Cancer Quality of Life Questionnaire, and the Hamilton Rating Scale for Depression. The primary outcome will be assessed at all main points (baseline, the 3rd week, the 6th week, and at follow up time points) and the secondary outcomes will be assessed at baseline and the 6th week. Intention-to-treat analysis will be used in this RCT. **DISCUSSION:** This trial protocol provides an example of the clinical application acupuncture treatment in the management of lung cancer-related fatigue. If the acupuncture treatment protocol confirms that acupuncture is an effective and safe option for lung cancer-related fatigue, it can be adopted as a standardized treatment.

[Traditional Chinese Medicine Prolongs Progression-Free Survival and Enhances Therapeutic Effects in Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor \(EGFR-TKI\)Treated Non-Small-Cell Lung Cancer \(NSCLC\) Patients Harboring EGFR Mutations.](#) Tang M1, Wang S1, Zhao B1, Wang W2, Zhu Y3, Hu L4, Zhang X5, Xiong S6. *Med Sci Monit.* 2019 Nov 9;25:8430-8437. doi: 10.12659/MSM.917251.

**BACKGROUND:** Lung cancer is the most common cause of cancer-associated deaths worldwide. This study aimed to investigate the efficacy and safety of Traditional Chinese Medicine combining EGFR-TKIs in treatment of NSCLC patients harboring EGFR mutations. **MATERIAL AND METHODS:** This study involved 153 advanced-stage NSCLC patients harboring EGFR mutations. Patients were divided into a Control group (administered EGFR-TKI, n=61) and an Experimental group (administered Traditional Chinese Medicine combining EGFR and TKI, n=92). Progression-free survival (PFS) was evaluated for exon 19 deletion and/or 21 deletion patients. Disease control rate (DCR) was assessed to observe therapeutic effects. Adverse effects, including rashes, diarrhea, ALT/AST increase, dental ulcers, and onychia lateralis, were also evaluated. **RESULTS:** TCM combining EGFR-TKI (90.11%) demonstrated no DCR improvement compared to single EGFR-TKI (83.33%) ( $p>0.05$ ). Median PFS (mPFS) of TCM combining EGFR-TKI (13 months) was significantly longer compared to that in the single EGFR-TKI group (8.8 months) ( $p=0.001$ ). For 19DEL mutant NSCLC, the mPFS (11 months) in TCM combining EGFR-TKI was significantly longer compared to single EGFR-TKI (8.5 months) ( $p=0.007$ ). The mPFS of L858 mutant NSCLC patients in EGFR-TKI combining CTM (14 months) was significantly longer compared to single EGFR-TKI (9.5 months) ( $p=0.015$ ). TCM combining EGFR-TKI was more inclined to prolong mPFS of NSCLC with exon 21 deletion. TCM combining EGFR-TKI illustrated no additional adverse effects in NSCLC patients ( $p=0.956$ ). **CONCLUSIONS:** Application of Traditional Chinese Medicine prolonged progression-free survival and enhanced therapeutic effect in NSCLC patients harboring EGFR mutations receiving EGFR-TKI treatment. Meanwhile, adjunctive Chinese medicine combining EGFR-TKI in NSCLC with EGFR mutations caused no adverse effects.

[The efficacy and safety of Kyung-Ok-Ko on cancer-related fatigue in lung cancer patients: Study protocol for a randomized, patients-assessor blind, placebo-controlled, parallel-group, single-center trial.](#) Kim K1,2, Kong M3, Lee SH4, Lee BJ1,2. *Medicine (Baltimore).* 2019 Nov;98(44):e17717. doi: 10.1097/MD.00000000000017717.

**BACKGROUND:** Cancer-related fatigue (CRF) is a major symptom experienced by lung cancer patients receiving chemotherapy and radiation therapy. Since CRF has a multidimensional influence on cancer patients, they may experience physical weakening, a decline in cognitive function, and depression from emotional consequences. Kyung-Ok-Ko is used for improving fatigue or weak physical constitution. It is known to be effective in immune activation, reducing fatigue, and enhancing cognitive function. Although Kyung-Ok-Ko is clinically used for the treatment of CRF, its efficacy and safety against CRF in lung

cancer patients are yet to be studied. Therefore, we aimed to investigate the efficacy and safety of Kyung-Ok-Ko. **METHODS:** This is a randomized, placebo-controlled, patients-assessor blind, parallel-group, single-center clinical trial. Lung cancer patients with CRF, after termination of chemo or radiation therapies, are randomized in a 1:1 ratio to receive either Kyung-Ok-Ko or placebo for 6 weeks. The primary outcome is Brief Fatigue Inventory (BFI). The secondary outcomes include Visual Analog Fatigue Scale (VAFS), Functional Assessment of Cancer Therapy (FACIT) Fatigue scale, Hospital Anxiety Depression Scale (HADS), Montreal Cognitive Assessment Korean version (MoCA-K), and Korean pattern identification questionnaire. Adverse events are evaluated by Common Terminology Criteria for Adverse Events (CTCAE). All outcomes and adverse events are assessed at the baseline, mid-treatment, post-treatment, and at 1-month follow-up. **DISCUSSION:** This study investigates whether Kyung-Ok-Ko can alleviate CRF in lung cancer patients. The results of this study will provide clinical evidence for the application of Kyung-Ok-Ko in the treatment of CRF in lung cancer patients.

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## MISCELLANEOUS WORKS

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### [Disparities in Receiving Guideline-Concordant Treatment for Lung Cancer in the United States.](#)

Blom EF1, Ten Haaf K2, Arenberg DA3, de Koning HJ2. Ann Am Thorac Soc. 2019 Nov 1. doi: 10.1513/AnnalsATS.201901-094OC. [Epub ahead of print]

**RATIONALE:** The level of adherence to lung cancer treatment guidelines in the United States is unclear. Also, it is unclear whether previously identified disparities by racial/ethnic group and by age persist across all clinical subgroups. **OBJECTIVES:** To assess the level of adherence to the minimal lung cancer treatment recommended by the National Comprehensive Cancer Network guidelines (guideline-concordant treatment) in the United States, and to assess the persistence of disparities by racial/ethnic group and by age across all clinical subgroups. **METHODS:** We evaluated whether 441,812 lung cancer cases in the National Cancer Database diagnosed between 2010-2014 received guideline-concordant treatment. Multivariable logistic regression models were used to assess possible disparities in receiving guideline-concordant treatment by racial/ethnic group and by age across all clinical subgroups, and whether these persist after adjusting for patient, tumor, and health care provider characteristics. **RESULTS:** Overall, 62.1% of subjects received guideline-concordant treatment (range across clinical subgroups: 50.4%-76.3%). However, 21.6% received no treatment (range: 10.3%-31.4%) and 16.3% received less intensive treatment than recommended (range: 6.4%-21.6%). Among the most common less intensive treatments for all subgroups was conventionally fractionated radiotherapy only (range: 2.5%-16.0%), as was chemotherapy only for non-metastatic subgroups (range: 1.2% to 13.7%), and conventionally fractionated radiotherapy & chemotherapy for localized non-small cell lung cancer (5.9%). Guideline-concordant treatment was less likely with increasing age despite adjusting for relevant covariates (age  $\geq 80$  compared to  $< 50$ : adjusted odds ratio [aOR]=0.12, 95% confidence interval [95% CI]=0.12-0.13). This disparity was present in all clinical subgroups. Also, non-Hispanic Blacks were less likely to receive guideline-concordant treatment than non-Hispanic Whites (aOR=0.78, 95% CI=0.76-0.80). This disparity was present in all clinical subgroups, although statistically non-significant for extensive disease small cell lung cancer. **CONCLUSIONS:** Between 2010-2014, many lung cancer patients in the United States received no treatment or less intensive treatment than recommended. Particularly, elderly lung cancer patients and non-Hispanic Blacks are less likely to receive guideline-concordant treatment. Patterns of care among those receiving less intensive treatment than recommended suggest room for improved uptake of treatments such as Stereotactic Body Radiation Therapy among localized non-small cell lung cancer.

### [Hispanics/Latinos in the Bronx Have Improved Survival in Non-Small Cell Lung Cancer](#)

[Compared with Non-Hispanic Whites.](#) Klugman M1, Xue X2, Ginsberg M2, Cheng H3, Rohan T2,



Hosgood HD 3rd2. J Racial Ethn Health Disparities. 2019 Nov 11. doi: 10.1007/s40615-019-00660-2. [Epub ahead of print]

**BACKGROUND:** Hispanics/Latinos are a growing yet understudied population in the United States (US). Despite lower socioeconomic status, Hispanics/Latinos tend to have similar or better health outcomes than Non-Hispanic Whites (NHWs). This phenomenon has not been conclusively studied for lung cancer. **METHODS:** Using a cohort of patients at Montefiore Medical Center (MMC) in the Bronx, NY, we examined factors related to lung cancer survival by race/ethnicity with an emphasis on Hispanics/Latinos. Subjects were diagnosed with non-small cell lung cancer (NSCLC) between 2004 and 2017. Demographic and clinical data were obtained from MMC's clinical systems and tumor-related information from MMC/Einstein's Cancer Registry. Survival was assessed using Cox proportional hazards modeling adjusted for clinical and sociodemographic factors including smoking. Factors related to survival within each major racial/ethnic group were examined. **RESULTS:** Hispanics/Latinos experienced decreased risk of death relative to NHWs [hazard ratio (HR) = 0.70, 95% confidence interval (95%CI) 0.57-0.86] overall and by sex (males: HR = 0.78, 95%CI 0.59-1.03, females: HR = 0.61, 95%CI 0.44-0.86). Decreased risk among Hispanics/Latinos relative to NHWs was evident in never-smokers (HR = 0.55, 95%CI 0.29-1.01), ever-smokers (HR = 0.72, 95%CI 0.57-0.90), younger subjects (HR = 0.73, 95%CI 0.54-0.99), and older subjects (HR = 0.72, 95%CI 0.53-0.97). Surgery was associated with improved survival in Hispanics/Latinos (HR = 0.60, 95%CI 0.43-0.85), and smoking with worse survival (HR = 1.56, 95%CI 1.02-2.39). Survival did not differ between Non-Hispanic Blacks and NHWs. **CONCLUSIONS:** In a poor urban community, Hispanics/Latinos experience improved survival from NSCLC compared to NHWs, which is not entirely explained by smoking. Future research should investigate the drivers of this benefit and differences in survival by Hispanic/Latino origin.

[Factors associated with utilization of high cost agents for the treatment of metastatic non-small cell lung cancer.](#) Bradley CJ1, Eguchi M2, Perrailon MC3. J Natl Cancer Inst. 2019 Nov 9. pii: djz223. doi: 10.1093/jnci/djz223. [Epub ahead of print]

**BACKGROUND:** Antineoplastic agents approved in recent decades are a marked advancement in cancer treatment but come at considerable cost. These drugs may widen survival disparities between patients who receive these agents and those who do not. We examine factors associated with the utilization of high cost antineoplastic agents for the treatment of metastatic non-small cell lung cancer (mNSCLC). **METHODS:** We conducted a retrospective observational study using 2007-2015 SEER-Medicare data supplemented with the Area Health Resource File. Patients were aged 66 years or older enrolled in fee-for-service Medicare Part D, were diagnosed with a first primary diagnosis of mNSCLC, and received an antineoplastic agent. High cost agents were defined as agents costing \$5000 or more per month. Independent variables include race/ethnicity, urban or rural residency, census tract poverty, and treatment facility type (e.g., National Cancer Institute (NCI) designation). **RESULTS:** Patients who lived in areas of high poverty were 4 percentage points less likely to receive high cost agents (two-sided  $p < 0.001$ ). Patients who were not treated at a NCI designated center were 10 percentage points less likely to receive these agents (two-sided  $p < 0.001$ ). A 27 percentage point increase in the likelihood of receiving a high cost agent was observed in 2015 compared to 2007, highlighting the rapid change in practice patterns (two-sided  $p < 0.001$ ). **CONCLUSION:** Potential policy and care delivery solutions involve outreach and support to community physicians who treat patients in remote areas. We estimate that widespread use of these agents conservatively cost approximately \$3 billion per year for metastatic non-small cell lung cancer alone.

[Understanding Lung Cancer Resources and Barriers Among Worksites With Mostly Male Employees in Eight Rural Kentucky Counties: A Focus Group Discussion.](#) Knight JR1, Williamson

LH1, Armstrong DK1, Westbrook EA2. Am J Mens Health. 2019 Nov-Dec;13(6):1557988319882585. doi: 10.1177/1557988319882585.

Kentucky has the highest cancer incidence and mortality rates in the United States, and lung cancer is Kentucky's leading cause of cancer deaths. Males in Kentucky have higher lung incidence and mortality rates than females. Through support from the SelfMade Health Network, Kentucky developed a Regional Resource Lead Organization that collaboratively developed a multi-component worksite intervention on lung cancer among male populations. The intervention targets eight Kentucky counties. The first component and focus of this manuscript included focus group meetings with organizational representatives in each county that provide health, educational, and social services to men and worksites. The focus groups discussed four distinct areas: (a) lung cancer-related resources and services in each county; (b) perceived ways men in worksites learn about and access health-related services; (c) identification of potential challenges and barriers to reaching men in worksites; and (d) creation of linkages and potential partnerships between community organizations and worksites. Forty-five organizational representatives participated in the eight focus groups. Most resources and services discussed were related to tobacco treatment. Employers were the most commonly perceived way men learn about and access health-related services, while attitudes and behaviors were the most commonly perceived barriers preventing men from accessing services. The most common potential linkages and partnerships across all areas were community organizations and groups, employers, health-care providers, and mass media. Partnering with employers may provide an opportunity to reach males with lung cancer prevention and control resources and services.

[Including the patient voice in the development and implementation of patient-reported outcomes in cancer clinical trials.](#) Addario B1, Geissler J2, Horn MK3, Krebs LU4, Maskens D5, Oliver K6, Plate A7, Schwartz E8, Willmarth N9. Health Expect. 2019 Nov 13. doi: 10.1111/hex.12997. [Epub ahead of print]

**CONTEXT:** Patient-reported outcomes (PROs) are used in parallel with clinical evidence to inform decisions made by industry, clinicians, regulators, health technology assessment bodies and other health-care decision-makers. In addition, PRO data can also guide shared decision making and individual patient choice. Yet, the quality of many PROs in cancer clinical trials is suboptimal and requires improvement to add value to health care and policy decision making. **OBJECTIVE:** To show how the integration of the patient and/or patient advocate at all stages of PRO development can help to realize the full potential of PROs. **METHODS:** We examined the literature to show that the patient voice is often absent from the planning and implementation of PROs in cancer clinical trials. Good practice examples from the literature were combined with guideline recommendations, training or educational resources, and our own experience to create detailed practical steps for the inclusion of patients and/or patient advocates throughout PRO development. **RESULTS:** Patient or patient advocates can play an active role in shaping PROs that are meaningful to the patient. They can contribute to content, choice of medium and implementation in a way that may support PRO completion and minimize missing data. Patients and their advocates can work to ensure PRO findings are disseminated appropriately in a way that is accessible to patients. **CONCLUSION:** This practical guidance aims to optimize PRO development and implementation in clinical trials, resulting in robust, relevant data that reflect the patient experience and that support decisions made by all stakeholders involved in research and health care.

[Lung Cancer in the Young.](#) Galvez-Nino M1, Ruiz R2, Pinto JA3, Roque K2, Mantilla R2, Raez LE4, Mas L2. Lung. 2019 Nov 26. doi: 10.1007/s00408-019-00294-5. [Epub ahead of print]

**INTRODUCTION:** Median age at diagnosis of lung cancer is 70 years. Its presentation in patients 40 or younger is uncommon and it has been proposed that maybe it is a different disease due to its clinical characteristics and genetic makeup. There are a limited number of studies in this population and they

report different clinic-pathological characteristics in comparison with older patients. **METHODS:** We described the incidence of lung cancer patients diagnosed at age 40 or younger at the Instituto Nacional de Enfermedades Neoplásicas (INEN), Lima-Peru; from 2009 to 2017 and evaluated the characteristic of NSCLC. Epidemiologic and clinic-pathological data was collected from clinical files. Analysis was carried out using SPSSv19 software. **RESULTS:** We identified 3823 patients with lung cancer seen at INEN during the study period. Among these, 166 (4.3%) patients were 40 years or younger, and 137/166 (82.5%) were NSCLC. Median age at diagnosis was 36 years (range 14-40 years) and 59.1% of patients were female. A smoking history was present in 14.4% of patients. Frequent symptoms at diagnosis were cough (62.0%), chest pain (51.8%) and dyspnea (40.9%). Adenocarcinoma was the most common histological type (63.3%). Most patients had advanced disease at diagnosis (84.7%). The median overall survival was 8.2 months. **CONCLUSIONS:** The proportion of young patients with lung cancer in our population is higher than that reported in the most recent literature. Lung cancer in the young is mostly sporadic, more frequent in women, usually adenocarcinoma type and it presents with advanced disease, resulting in a very poor survival.

**Trends in cancer incidence among American Indians and Alaska Natives and Non-Hispanic Whites in the United States, 1999-2015.** Gopalani SV1, Janitz AE1, Martinez SA1, Gutman P2, Khan S2, Campbell JE1. *Epidemiology*. 2019 Nov 14. doi: 10.1097/EDE.0000000000001140. [Epub ahead of print]

**BACKGROUND:** Female breast, prostate, lung, and colorectal cancers are the leading incident cancers among American Indian and Alaska Native (AI/AN) and non-Hispanic White (NHW) persons in the US. To understand racial differences, we assessed incidence rates, analyzed trends, and examined geographic variation in incidence by Indian Health Service (IHS) regions. **METHODS:** To assess differences in incidence, we used age-adjusted incidence rates to calculate rate ratios (RRs) and 95% confidence intervals (CIs). Using joinpoint regression, we analyzed incidence trends over time for the four leading cancers from 1999 to 2015. **RESULTS:** For all four cancers, overall and age-specific incidence rates were lower among AI/ANs than NHWs. By IHS regions, incidence rates for lung cancer were higher among AI/ANs than NHWs in Alaska (RR: 1.46; 95% CI: 1.37, 1.56), Northern (RR: 1.29; 95% CI: 1.25, 1.33) and Southern (RR: 1.06; 95% CI: 1.03, 1.09) Plains. Similarly, colorectal cancer incidence rates were higher in AI/ANs than NHWs in Alaska (RR: 2.29; 95% CI: 2.14, 2.45) as well as Northern (RR: 1.04; 95% CI: 1.00, 1.09) and Southern (RR: 1.11; 95% CI: 1.07, 1.15) Plains. Also, AI/AN women in Alaska had a higher incidence rate for breast cancer than NHW women (RR: 1.05; 95% CI: 1.05, 1.20). From 1999 to 2015, incidence rates for all four cancers decreased in NHWs, but only rates for prostate (average annual percent change [AAPC]: -4.70) and colorectal (AAPC: -1.80) cancers decreased considerably in AI/ANs. **CONCLUSION:** Findings from this study highlight the racial and regional differences in cancer incidence.