



Caring Ambassadors Lung Cancer Program Literature Review, November 2021

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SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

[Comorbidity Profiles and Lung Cancer Screening among Older Adults: U.S. Behavioral Risk Factor Surveillance System 2017-2019](#) Ann Am Thorac Soc. 2021 Nov;18(11):1886-1893. doi:

10.1513/AnnalsATS.202010-1276OC. Shailesh Advani¹, Dongyu Zhang³, Martin Tammemagi⁴, et al.

RATIONALE: Although lung cancer screening (LCS) with low-dose computed tomography (LDCT) is now recommended for those meeting standard risk factor-based eligibility criteria, the role of comorbidity in the uptake of LCS with LDCT in an older real-world U.S. population is not well established.

Objectives: To examine the relationships between comorbidity, functional status, and LCS utilization in the United States. **METHODS:** Using population-based data from the 2017-2019 Behavioral Risk Factor Surveillance System, we examined the association of comorbid conditions and functional limitations regarding activities of daily living with LCS utilization among participants that met the LCS criteria based on the U.S. Preventive Service Taskforce guidelines. We employed multivariable weighted logistic regression models to evaluate these associations, both overall and within subgroups defined by age (<65 yr vs. ≥65 yr), sex, and smoking history. **RESULTS:** Of 11,214 participants who met the eligibility criteria for LCS, 1,731 (16%) underwent LCS with LDCT. The majority were White (90%), male (55%), former smokers (52%), and living with at least one chronic comorbid condition (77%). More than 28% had three or more comorbid conditions, and approximately 40% of participants reported having some form of functional limitations. In the multivariable models, the likelihood of undergoing LCS with LDCT within the past year was positively associated with higher amount of comorbidity (≥5 vs. 0: adjusted odds ratio, 2.34; 95% confidence interval [CI], 1.22-4.48) but not with functional limitations (≥3 vs. 0: adjusted odds ratio, 1.00; 95% CI, 0.66-1.50). **CONCLUSIONS:** The presence of comorbid conditions is associated with a higher likelihood of undergoing LCS with LDCT. Because poor health status may diminish the benefits of screening, future research is needed to precisely characterize the health status of LCS-eligible individuals.

[Estimating the population health impact of a multi-cancer early detection genomic blood test to complement existing screening in the US and UK](#) Br J Cancer. 2021 Nov;125(10):1432-1442. doi:

10.1038/s41416-021-01498-4. Epub 2021 Aug 23. Allan Hackshaw 1 , Sarah S Cohen 2 , Heidi Reichert 3 , Anuraag R Kansal 4 , Karen C Chung 4 , Joshua J Ofman 4

BACKGROUND: Multi-cancer early detection (MCED) next-generation-sequencing blood tests represent a potential paradigm shift in screening. **METHODS:** We estimated the impact of screening in the US and UK. We used country-specific parameters for uptake, and test-specific sensitivity and false-positive rates for current screening: breast, colorectal, cervical and lung (US only) cancers. For the MCED test, we used cancer-specific sensitivities by stage. Outcomes included the true-positive:false-positive (TP:FP) ratio; and the cost of diagnostic investigations among screen positives, per cancer detected (Diagcost). Outcomes were estimated for recommended screening only, and then when giving the MCED test to anyone without cancer detected by current screening plus similarly aged adults ineligible for recommended screening. **RESULTS:** In the US, current screening detects an estimated 189,498 breast, cervical, colorectal and lung cancers. An MCED test with 25-100% uptake detects an additional 105,526-422,105 cancers (multiple types). The estimated TP:FP (Diagcost) was 1.43 (\$89,042) with current screening but only 1:1.8 (\$7060) using an MCED test. For the UK the corresponding estimates were 1:18 (£10,452) for current screening, and 1:1.6 (£2175) using an MCED test. **CONCLUSIONS:** Adding an MCED blood test to recommended screening can potentially be an efficient strategy. Ongoing randomised studies are required for full efficacy and cost-effectiveness evaluations.

[Lung cancer staging, the established role of bronchoscopy](#) Curr Opin Pulm Med. 2021 Nov 1. doi: 10.1097/MCP.0000000000000843. Online ahead of print. Tanya Marshall 1 , Satish Kalanjeri, Francisco Aecio Almeida

PURPOSE: OF REVIEW: Lung cancer is the leading cause of cancer-related deaths worldwide. In the absence of distant metastases, accurate mediastinal nodal staging determines treatment approaches to achieve most favourable outcomes for patients. Mediastinal staging differentiates N0/N1 disease from N2/N3 in surgical candidates. Likewise, presence of nodal involvement in nonsurgical candidates who are being considered for stereotactic body radiation therapy is also critical. This review article seeks to discuss the current options available for mediastinal staging in nonsmall cell lung cancer (NSCLC), particularly the role of bronchoscopy. **RECENT FINDINGS:** Although several techniques are available to stage the mediastinum, bronchoscopy with EBUS-TBNA with or without EUS-FNA appears to be superior in most clinical situations based on its ability to concomitantly diagnose and stage at once, safety, accessibility to the widest array of lymph node stations, cost and low risk of complications. However, training and experience are required to achieve consistent diagnostic accuracy with EBUS-TBNA. **SUMMARY:** EBUS-TBNA with or without EUS-FNA is considered the modality of choice in the diagnosis and staging of NSCLC in both surgical and nonsurgical candidates.

[Comparative clinical outcomes for patients with advanced NSCLC harboring EGFR exon 20 insertion mutations and common EGFR mutations](#) Lung Cancer. 2021 Nov 6;162:154-161. doi: 10.1016/j.lungcan.2021.10.020. Online ahead of print. Lyudmila Bazhenova 1 , Anna Minchom 2 , Santiago Viteri 3 , et al.

INTRODUCTION: Real-world clinical outcomes in patients with advanced NSCLC harboring EGFR exon 20 insertion (exon20ins) mutations have not been extensively studied. We conducted a retrospective cohort study to assess the clinical outcomes of EGFR exon20ins compared with common EGFR (cEGFR) mutations. **METHODS:** Adults with advanced NSCLC harboring any EGFR mutations in the NSCLC Flatiron registry (2011 through May 2020) were included. To compare the relative prognosis (prognostic value) of exon20ins vs cEGFR, real-world overall survival (rwOS) was the primary endpoint. Separately, to compare the relative response to tyrosine kinase inhibitor (TKI) treatment (predictive value), real-world progression-free survival (rwPFS) was the primary endpoint. **RESULTS:** For the prognostic value analysis, 3014 patients with EGFR mutant NSCLC (cEGFR, n = 2833; EGFR exon20ins, n = 181) were

eligible. The median (95% CI) rWOS was 16.2 (11.04-19.38) months in the EGFR exon20ins cohort vs 25.5 (24.48-27.04) months in the cEGFR cohort (adjusted HR, 1.75 [1.45-2.13]; $p < 0.0001$); 5-year rWOS was 8% and 19%, respectively. For the predictive value analysis, 2825 patients received TKI treatment and were eligible (cEGFR, $n = 2749$; EGFR exon20ins, $n = 76$). The median (95% CI) rWPFS from start of the first TKI was 2.9 (2.14-3.91) months in the EGFR exon20ins cohort vs 10.5 (10.05-10.94) months in the cEGFR cohort (adjusted HR, 2.69 [2.05-3.54]; $p < 0001$). Among patients with EGFR exon20ins, the most common prescribed first-line therapy was platinum-based chemotherapy (61.3%) followed by EGFR TKIs (21.5%); second-line treatments were varied, with no clear standard of care. **CONCLUSIONS:** Patients with EGFR exon20ins have poor prognosis and receive little benefit from EGFR TKI treatment. More effective therapies are needed in this difficult-to-treat population.

[Patient-centered Reporting in Radiology: A Single-site Survey Study of Lung Cancer Screening](#)

Results J Thorac Imaging. 2021 Nov 1;36(6):367-372. doi: 10.1097/RTI.0000000000000591. Spencer K Barrett 1 , James Patrie 1 , Andrea B Kitts 2 , Michael Hanley 1 , Christina M Swanson 1 , Hans Vitzthum von Eckstaedt 1 , Arun Krishnaraj 1

PURPOSE: This study aimed to assess whether patients preferred traditional or patient-friendly radiology reports and, secondarily, whether one reporting style led to a subjective improvement in patients' understanding of their imaging results and next steps in their clinical care. **MATERIALS AND METHODS:** This randomized study included patients who had previously enrolled in an institutional comprehensive lung cancer screening program. Three hundred patients were randomly selected from the program database to receive both traditional and patient-centered radiology reports. Randomization also occurred at both the risk level of the fictitious test results (low, intermediate, or high) and the order in which the reports were read by each participant. Participants completed a survey providing demographic information and indicating which report style was preferred and which report style led to a better understanding of screening results and future options. In addition, each report style was rated (from 1 to 5) for clarity, understandability, attractiveness, and helpfulness. **RESULTS:** A total of 46 responses for report preference data and 41 responses for attribute rating data were obtained. Overall, participants demonstrate a preference for patient-friendly reports (65.2%) over traditional reports (21.7%). On a 5-point scale, average ratings for patient-friendly reports were higher than traditional reports by 1.2 ($P < 0.001$) for clarity, 1.5 ($P < 0.001$) for understandability, 1.5 ($P < 0.001$) for attractiveness, and 1.0 ($P < 0.001$) for helpfulness. **CONCLUSION:** Data suggest that patients prefer patient-friendly reports over traditional reports and find them to be clearer, more comprehensible, more attractive, and more helpful.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[A Prediction Model for Postoperative Pulmonary Complication in Pulmonary Function-Impaired Patients Following Lung Resection](#)

J Multidiscip Healthc. 2021 Nov 15;14:3187-3194. doi: 10.2147/JMDH.S327285. eCollection 2021. Xiaowei Mao # 1 2 , Wei Zhang # 1 3 , Yi-Qian Ni 1 , Yanjie Niu 1 , Li-Yan Jiang 1

PURPOSE: Most patients with lung cancer have impaired pulmonary function. Single pulmonary function parameters have been suggested as good indices for predicting postoperative pulmonary complications (PPC). The **PURPOSE:** of this retrospective study was to construct a prediction model, including more than one pulmonary function parameter, for better prediction of PPC in patients with lung cancer and impaired pulmonary function. **PATIENTS AND METHODS:** Our database of patients who underwent lung resection for non-small cell lung cancer was reviewed and those with impaired pulmonary function were enrolled. Clinical data, including PPC, were recorded. Univariate and logistic regression

analyses were applied to explore potential predictors and a prediction model constructed based on the results of logistic regression. **RESULTS:** Patients with impaired pulmonary function (n = 124) were enrolled. Most patients were male, current smokers, >60 years old, and had adenocarcinoma and mild ventilatory dysfunction or diffusion dysfunction. In univariate analysis, we identified six pulmonary function parameters that differed significantly between the PPC and non-PPC groups. Receiver operating characteristic curves were used to determine the best cutoff values. In logistic regression, only forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC%), peak expiratory flow (PEF%), and post predictive operation (ppo)-FEV1% remained significant. Based on these results, we constructed a prediction model for PPC including FEV1/FVC%, PEF%, and ppo-FEV1%, which had an good diagnostic performance of, with 76.7% sensitivity and 67.6% specificity. **CONCLUSION:** Our prediction model, including the pulmonary function parameters, FEV1/FVC%, PEF%, and ppo-FEV1%, shows excellent performance for predicting PPC in patients with lung cancer and impaired pulmonary function following resection, and has potential for wide application in clinical practice.

[The influence of tobacco load versus smoking status on outcomes following lobectomy for lung cancer in a statewide quality collaborative](#)

J Thorac Cardiovasc Surg. 2021 Nov;162(5):1375-1385.e1. doi: 10.1016/j.jtcvs.2020.10.162. Epub 2020 Dec 10. Riad H Al Natour 1 , Chang He 2 , Melissa J Clark 2 , Robert Welsh 3 , Andrew C Chang 4 , Kumari N Adams 5

BACKGROUND: Collaborative quality consortia can facilitate implementation of quality measures arising from clinical databases. Our statewide general thoracic surgery (GTS) collaborative investigated the influences of cigarette smoking status on mortality and major morbidity following lobectomy for lung cancer. **METHODS:** Society of Thoracic Surgeons General Thoracic Surgery Database records were identified from 14 institutions participating in a statewide thoracic surgical quality collaborative between 2012 and 2017. We excluded patients with nonelective procedures, stage 0 tumors, American Society of Anesthesiologists class VI disease, and missing clinical characteristics. Outcomes analysis included the combined mortality and major postoperative morbidity rates and the influence of patient characteristics, including smoking status, on composite rate and on postoperative complications. **RESULTS:** The study cohort included 2267 patient records for analysis. Overall combined mortality and major morbidity rate was 10.2% (n = 231). Postoperative 30-day mortality was 1.5%, and major morbidity 9.6%. Significant predictors of the combined outcome included male sex (P = .004), body mass index (P < .001), Zubrod score (P = .02), smoking pack-years (P = .03), and thoracotomy (P < .001). Higher American Society of Anesthesiologists disease class and advanced tumor stage were marginally associated with worse combined outcome (P = .06). Smoking status; that is, current, past (no smoking within 30 days), or never smoked, was not associated with worse combined outcome (P = .56) and had no significant influence on major complications. **CONCLUSIONS:** Smoking status was not associated with worse outcomes; however, smoking dose (pack-years) was associated with worse combined mortality and major morbidity. A statewide quality collaborative provides constructive feedback for participating institutions and surgeons, promoting quality improvement in perioperative patient care strategies and improved outcomes.

[Venous Thromboembolism in Surgical Lung Cancer Patients: A Provincial Population-Based Study](#)

Ann Thorac Surg. 2021 Nov 13;S0003-4975(21)01906-8. doi: 10.1016/j.athoracsur.2021.10.018. Online ahead of print. Gileh-Gol Akhtar-Danesh 1 , Noori Akhtar-Danesh 2 , Yaron Shargall 3

BACKGROUND: Venous thromboembolism (VTE) is a significant cause of morbidity and mortality in surgical patients. Thoracic surgery patients are at increased risk due to inherent technical and disease-specific factors. Other surgical specialties have adopted post-discharge extended VTE prophylaxis; however, evidence is scarce in thoracic surgery. This study aims to identify VTE risk factors and associated mortality among surgical lung cancer patients. **METHODS:** Using administrative databases, all patients in the province of Ontario undergoing lung cancer surgery from 2007 to 2017 were identified.

Logistic regression identified VTE risk factors at 90-days and one-year postoperatively. A flexible parametric survival analysis compared mortality and survival up to 5 years after surgery between patients with and without VTE. **RESULTS:** Of 65,513 patients diagnosed with lung cancer, 12,626 (19.3%) underwent surgery. VTE incidence at 90-days and 1-year postoperatively was 1.3% and 2.7%, respectively. Open and more extensive resections carried an increased VTE-risk, with pneumonectomy conferring the highest risk (OR = 2.36; $p < 0.001$). Stage III and IV disease carried a 3.19 and 4.97-times higher risk of VTE, respectively, compared to stage I ($p < 0.001$). The hazard ratio for mortality at one year for patients with a VTE was 2.01 ($p < 0.001$). Patients suffering a VTE had reduced 5-year survival. **CONCLUSIONS:** Patients undergoing pneumonectomy and those with advanced stage have an increased VTE-risk. Patients suffering a thrombotic complication have an increased risk of mortality and decreased 5-year survival. Accordingly, strategies to reduce VTE risk should be considered in patients undergoing high risk operations to reduce the mortality of VTEs.

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

[Impact of Checkpoint Inhibitor Immunotherapy, Primarily Pembrolizumab, on Infection Risk in Patients With Advanced Lung Cancer: A Comparative Retrospective Cohort Study](#) Clin Infect Dis. 2021 Nov 2;73(9):e2697-e2704. doi: 10.1093/cid/ciaa802. Alexandre E Malek¹, Melissa Khalil¹, Ray Hachem¹, et al.

BACKGROUND: Checkpoint inhibitor (CPI) immunotherapy has revolutionized cancer treatment. However, immune-related adverse events and the risk of infections are not well studied. To assess the infectious risk of CPIs, we evaluated the incidence of infections in lung cancer patients treated with CPIs plus conventional chemotherapy (CC) vs CC alone. **METHODS:** We performed a retrospective comparative study of patients with advanced non-small cell lung cancer who received CPIs combined with CC and those treated with CC alone at our institution during January 2016 to February 2019. We compared clinical characteristics, treatments, and outcomes including infection rate and mortality between the groups. **RESULTS:** We identified 123 patients for the CPI group and 147 patients for the control (CC) group. Eighteen patients (15%) in the CPI group and 33 patients (22%) in the control group developed infections ($P = .1$). Pneumonia was the most common infection encountered in both groups. Urinary tract infection was higher in the CC group (40%) than in the CPI group (9%) ($P = .01$). On multivariable analysis, chronic obstructive pulmonary disease ($P = .024$), prior use of corticosteroids ($P = .021$), and neutropenia ($P < .001$) were independent risk factors for infection and severe infection requiring hospital admission. Chronic kidney disease ($P = .02$), prior cancer treatment ($P = .023$), and neutropenia ($P < .0001$) were identified as independent risk factors for all-cause mortality. **CONCLUSIONS:** Lung cancer patients treated with CPIs combined with CC have a comparable risk of infection to those treated with CC alone, although there is a trend towards fewer infections in those given CPIs, particularly when it comes to urinary tract infections.

[Ensartinib vs Crizotinib for Patients With Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer: A Randomized Clinical Trial](#) JAMA Oncol. 2021 Nov 1;7(11):1617-1625. doi: 10.1001/jamaoncol.2021.3523. Leora Horn^{1,2}, Ziping Wang³, Gang Wu⁴, et al.

IMPORTANCE: Ensartinib, an oral tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK), has shown systemic and central nervous system efficacy for patients with ALK-positive non-small cell lung cancer (NSCLC). **OBJECTIVE:** To compare ensartinib with crizotinib among patients with advanced ALK-positive NSCLC who had not received prior treatment with an ALK inhibitor. Design, setting, and participants: This open-label, multicenter, randomized, phase 3 trial conducted in 120 centers in 21 countries enrolled 290 patients between July 25, 2016, and November 12, 2018. Eligible patients were 18

years of age or older and had advanced, recurrent, or metastatic ALK-positive NSCLC. Interventions: Patients were randomized (1:1) to ensartinib, 225 mg once daily, or crizotinib, 250 mg twice daily. **MAIN OUTCOMES AND MEASURES:** The primary end point was blinded independent review committee-assessed progression-free survival (PFS). Secondary end points included systemic and intracranial response, time to central nervous system progression, and overall survival. Efficacy was evaluated in the intent-to-treat (ITT) population as well as a prespecified modified ITT (mITT) population consisting of patients with central laboratory-confirmed ALK-positive NSCLC. **RESULTS:** A total of 290 patients (149 men [51.4%]; median age, 54 years [range, 25-90 years]) were randomized. In the ITT population, the median PFS was significantly longer with ensartinib than with crizotinib (25.8 [range, 0.03-44.0 months] vs 12.7 months [range, 0.03-38.6 months]; hazard ratio, 0.51 [95% CI, 0.35-0.72]; log-rank $P < .001$), with a median follow-up of 23.8 months (range, 0-44 months) for the ensartinib group and 20.2 months (range, 0-38 months) for the crizotinib group. In the mITT population, the median PFS in the ensartinib group was not reached, and the median PFS in the crizotinib group was 12.7 months (95% CI, 8.9-16.6 months; hazard ratio, 0.45; 95% CI, 0.30-0.66; log-rank $P < .001$). The intracranial response rate confirmed by a blinded independent review committee was 63.6% (7 of 11) with ensartinib vs 21.1% (4 of 19) with crizotinib for patients with target brain metastases at baseline. Progression-free survival for patients without brain metastases was not reached with ensartinib vs 16.6 months with crizotinib as a result of a lower central nervous system progression rate (at 12 months: 4.2% with ensartinib vs 23.9% with crizotinib; cause-specific hazard ratio, 0.32; 95% CI, 0.16-0.63; $P = .001$). Frequencies of treatment-related serious adverse events (ensartinib: 11 [7.7%] vs crizotinib: 9 [6.1%]), dose reductions (ensartinib: 34 of 143 [23.8%] vs crizotinib: 29 of 146 [19.9%]), or drug discontinuations (ensartinib: 13 of 143 [9.1%] vs crizotinib: 10 of 146 [6.8%]) were similar, without any new safety signals. **CONCLUSIONS AND RELEVANCE:** In this randomized clinical trial, ensartinib showed superior efficacy to crizotinib in both systemic and intracranial disease. Ensartinib represents a new first-line option for patients with ALK-positive NSCLC.

[First-line osimertinib in elderly patients with epidermal growth factor receptor-mutated advanced non-small cell lung cancer: a retrospective multicenter study \(HOT2002\)](#) Sci Rep. 2021 Nov 30;11(1):23140. doi: 10.1038/s41598-021-02561-z. Gaku Yamamoto 1 , Hajime Asahina 2 , Osamu Honjo 3, et al.

Osimertinib is a standard of care therapy for previously untreated epidermal growth factor receptor mutation-positive non-small cell lung cancer. However, limited data exist regarding the efficacy and safety of osimertinib as a first-line therapy for elderly patients aged 75 years or older. To assess the potential clinical benefits of osimertinib in this population, this retrospective multi-institutional observational study included 132 patients with non-small cell lung cancer (age ≥ 75 years), who received osimertinib as first-line treatment. The proportion of patients with 1-year progression-free survival was 65.8% (95% confidence interval 57.1-73.5). The median progression-free survival was 19.4 (95% confidence interval 15.9-23.9) months. The median overall survival was not reached (95% confidence interval 24.6-not reached). The frequency of pneumonitis was 17.4%, with a grade 3 or higher rate of 9.1%. More than two-thirds of treatment discontinuations due to pneumonitis occurred within 3 months of starting osimertinib, and the prognosis of patients with pneumonitis was unsatisfactory. Osimertinib is one of the effective first-line therapeutic options for patients aged 75 years or older; however, special caution should be exercised due to the potential development of pneumonitis. Chronic kidney disease ($P = .02$), prior cancer treatment ($P = .023$), and neutropenia ($P < .0001$) were identified as independent risk factors for all-cause mortality. **CONCLUSIONS:** Lung cancer patients treated with CPIs combined with CC have a comparable risk of infection to those treated with CC alone, although there is a trend towards fewer infections in those given CPIs, particularly when it comes to urinary tract infections.

[Postoperative Chemotherapy Use and Outcomes From ADAURA: Osimertinib as Adjuvant Therapy for Resected EGFR-Mutated NSCLC](#)

J Thorac Oncol. 2021 Nov 2;S1556-0864(21)03285-8. doi: 10.1016/j.jtho.2021.10.014. Online ahead of print. Yi-Long Wu 1 , Thomas John 2 , Christian Grohe 3 , et al.

INTRODUCTION: Adjuvant chemotherapy is recommended in patients with resected stage II–IIIa (and select IB) NSCLC; however, recurrence rates are high. In the phase III, ADAURA study (NCT02511106), osimertinib demonstrated a highly statistically significant improvement in disease-free survival (DFS) in patients with resected stage IB–IIIa EGFRm NSCLC. Here, we report prespecified and exploratory analyses of adjuvant chemotherapy use and outcomes from ADAURA. **METHODS:** Patients with resected stage IB–IIIa EGFRm NSCLC were randomized 1:1 to receive osimertinib or placebo for 3 years. Adjuvant chemotherapy before randomization was not mandatory, per physician and patient choice. DFS in the overall population (IB–IIIa), with/without adjuvant chemotherapy, was a prespecified analysis. Exploratory analyses included: adjuvant chemotherapy use by patient age, disease stage and geographical location; DFS by adjuvant chemotherapy use and disease stage. **RESULTS:** Overall, 410/682 patients (60%) received adjuvant chemotherapy (osimertinib, n = 203; placebo, n = 207) for a median duration of 4.0 cycles. Adjuvant chemotherapy use was more frequent in patients: aged <70 years (338/509; 66%) versus ≥70 years (72/173; 42%); with stage II-IIIa disease (352/466; 76%) versus stage IB (57/216; 26%); enrolled in Asia (268/414; 65%) versus outside of Asia (142/268; 53%). A DFS benefit favoring osimertinib versus placebo was observed in patients with (DFS HR = 0.16, 95% CI: 0.10–0.26) and without adjuvant chemotherapy (HR = 0.23, 95% CI: 0.13–0.40), regardless of disease stage. **CONCLUSIONS:** These findings support adjuvant osimertinib as an effective treatment for patients with stage IB-IIIa EGFRm NSCLC after resection, with or without prior adjuvant chemotherapy.

[Technical Feasibility and Safety of Repeated Computed Tomography-Guided Transthoracic Intratumoral Injection of Gene-Modified Cellular Immunotherapy in Metastatic NSCLC](#)

JTO Clin Res Rep. 2021 Oct 14;2(11):100242. doi: 10.1016/j.jtocrr.2021.100242. eCollection 2021 Nov. Puja Shahrouki 1 , Jay M Lee 2 , Jonathan Barclay 1 , Sarah N Khan 1 , Scott Genshaft 1 , Fereidoun Abtin 1 , Steven M Dubinett 3 , Aaron Lisberg 4 , Sherven Sharma 3 , Edward B Garon 4 , Robert Suh 1

INTRODUCTION: To assess the technical feasibility and safety of repeated percutaneous computed tomography (CT)-guided transthoracic biopsies and intratumoral injections of gene-modified dendritic cells in metastatic NSCLC. **METHODS:** A total of 15 patients with 15 NSCLC lesions measuring greater than 1.0 cm underwent two cycles of intratumoral biopsies and CCL21 dendritic cell injections separated by 7 days. All needle placements and injections were done under CT guidance. Clinical and imaging follow-up was done approximately 4 weeks after the first procedure. Safety and feasibility were determined as: (1) safety and feasibility similar to that of single-needle biopsy, and (2) an absence of serious adverse events defined as grade greater than or equal to three according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. **RESULTS:** A total of 30 percutaneous, transthoracic intratumoral biopsies and injections into the lung cancer were performed, two cycles (at d 0 and 7) received by each patient (311 biopsies and 96 intratumoral injections). All percutaneous cases achieved technical success with respect to needle placement for both biopsy and injection of CCL21 dendritic cells. Only minor complications were observed (grade <3), including pneumothorax (n = 10, 33%) and small postbiopsy hemorrhage (n = 2, 7%). Pneumothorax was moderate (n = 1) or trace (n = 9), with resolution of the moderate pneumothorax after manual aspiration without chest tube placement. No patient required chest tube placement. No other complications or serious adverse effects related to the biopsy or dendritic cell injection were noted. All patients were in stable condition after up to 4 hours in the recovery unit and were discharged home on the same day. No procedure-related complications were observed on imaging or clinical follow-up at 4 weeks.

CONCLUSIONS: Repeated percutaneous, transthoracic CT-guided biopsies and intratumoral gene-

modified cell-based immunotherapy injections into lung cancers are technically feasible, safe, and reproducible. There were no procedure-related serious (defined as grade ≥ 3) adverse events.

[Knowledge About Risks, Benefits, and Curative Potential of Immunotherapy Among Patients with Advanced Cancer](#) Oncologist. 2021 Nov;26(11):e2090-e2093. doi: 10.1002/onco.13945. Epub 2021 Aug 28. Laura A Petrillo 1 , Ashley Z Zhou 1 , Ryan Sullivan 2 , Angelo Volandes 3 4 , Joseph A Greer 5 , Jennifer S Temel 2 , Areej El-Jawahri 2

BACKGROUND: Immunotherapy is the first-line treatment for melanoma and lung cancer and brings new risks of immune-related adverse events. We aimed to describe patients' knowledge about risks, benefits, and goals of immunotherapy. **MATERIALS AND METHODS:** We conducted a cross-sectional study of patients with advanced melanoma or non-small cell lung cancer that used a 9-item knowledge survey and questions from the Prognosis and Treatment Perceptions Questionnaire. **RESULTS:** We surveyed 105 participants (57 with melanoma, 48 with lung cancer) with median age 69 years (range 36-89). Participants' responses revealed knowledge deficits about immunotherapy mechanism of action and lack of awareness about the timing and severity of side effects. One third (34%; 36/105) of participants reported that the primary goal of their treatment is to cure their cancer. **CONCLUSION:** Given the widespread use of immunotherapy, patients would benefit from educational tools so that they know what to expect regarding side effects and prognosis.

[A plain language summary of results from the ADAURA study: osimertinib after surgery for patients who have early-stage EGFR-mutated non-small cell lung cancer](#) Future Oncol. 2021 Dec 1;17(35):4827-4835. doi: 10.2217/fon-2021-0752. Epub 2021 Nov 1. Yi-Long Wu 1 , Masahiro Tsuboi 2 , Thomas John 3 , et al.

Here, we summarize the initial results from the ADAURA clinical study looking at treatment with osimertinib in patients with a specific type of non-small cell lung cancer (also called NSCLC). Osimertinib (TAGRISSO®) is a medication used to treat a type of NSCLC with a change (mutation) in the EGFR gene, known as EGFR-mutated NSCLC. EGFR stands for 'epidermal growth factor receptor'. It is a protein present on the surface of both healthy and cancer cells that can regulate how cells grow and divide. Sometimes, certain mutations in EGFR can result in the EGFR protein malfunctioning, which can lead to the formation of cancer, like EGFR-mutated NSCLC. Based on previous clinical studies, osimertinib is already approved for use in patients with EGFR-mutated NSCLC that has spread beyond the lung (metastatic disease). This medication works to stop, prevent, or slow the growth of EGFR-mutated NSCLC tumors, by specifically blocking the activity of EGFR. In the ADAURA clinical study, participants had resectable EGFR-mutated NSCLC, which means they had tumors that can be removed by surgery. Participants took either osimertinib or a placebo (a dummy drug with no active ingredient) after having their tumors removed by surgery. Post-surgery chemotherapy was allowed, but not compulsory (this was decided by the participant and their doctor). To date, the study has shown that osimertinib could be beneficial for patients with resectable EGFR-mutated NSCLC. Participants who took osimertinib have stayed cancer-free for longer than those who took the placebo, regardless of whether or not they received chemotherapy after surgery. Osimertinib treatment also reduced the risk of tumors spreading to the brain and spinal cord, otherwise known as the central nervous system (also called CNS). The side effects experienced by the participants taking osimertinib have been consistent with what we already know. Based on the results from ADAURA, osimertinib has been approved for the treatment of resectable EGFR-mutated NSCLC after tumor removal. The ADAURA study is still ongoing and more results are expected to be released in the future. ClinicalTrials.gov NCT number: NCT02511106.

[Real-world efficacy and safety of anlotinib as third- or further-line treatment in refractory small cell lung cancer](#) J Cancer Res Clin Oncol. 2021 Nov 8. doi: 10.1007/s00432-021-03848-4. Online ahead of print. Xuetian Gao 1 , Ling Peng 2 , Li Zhang 3, Kai Huang 4, Cuihua Yi 4 , Bei Li 4, Xue Meng 1, Jisheng Li 5

PURPOSE: As a novel antiangiogenic multi-target tyrosine kinase inhibitor recently approved in China, anlotinib has exhibited promising anticancer efficacy and acceptable safety profile in the salvage treatment of small cell lung cancer (SCLC) in clinical trials. Here we retrospectively investigated the efficacy and safety of anlotinib as third- or further-line treatment in patients with refractory SCLC. Patients and **METHODS:** A total of 40 patients with refractory SCLC treated with anlotinib monotherapy were included in this study. The clinicopathological data, treatment information, survival data and safety data were retrospectively collected. Survival curves were constructed using the Kaplan-Meier method. Univariate analysis was performed by log-rank testing. **RESULTS:** Altogether, 40 patients of extensive-stage SCLC or progressive limited-stage SCLC received anlotinib monotherapy as third- or further-line treatment from July 2018 to June 2020. Four patients achieved partial response (PR), 14 patients achieved stable disease (SD), no complete response (CR) was recorded, and 22 patients experienced progressive disease (PD). The disease control rate (DCR) was 45.0%. The median progression-free survival (PFS) was 3.0 months (95% CI 2.241-3.759), and the median overall survival (OS) was 7.8 months (95% CI 3.190-12.410). The common adverse effects (AEs) included hypertension, fatigue, anorexia, cough, rash and nausea. Grade 3 treatment-related AEs occurred in 3 (7.5%) patients. One patient interrupted anlotinib treatment due to repeated grade 1 epistaxis. Univariate analysis revealed that patients without liver metastases, previously treated with radiotherapy or with Eastern Cooperative Oncology Group (ECOG) scores of 0 or 1 had longer OS with anlotinib treatment. Cox regression analysis demonstrated that patients without liver metastases and patients with ECOG score ≤ 1 had longer PFS, while patients without liver metastases had longer OS. **CONCLUSION:** Anlotinib is beneficial to refractory SCLC as third- or further-line treatment, especially in patients without liver metastasis and with better physical status. Related adverse effects are tolerable and manageable.

[Comparative Effectiveness of Atezolizumab, Nivolumab, and Docetaxel in Patients With Previously Treated Non-Small Cell Lung Cancer](#) JAMA Netw Open. 2021 Nov 1;4(11):e2134299. doi: 10.1001/jamanetworkopen.2021.34299. Sreeram Ramagopalan 1 , Alind Gupta 2 , Paul Arora 2 , Kristian Thorlund 2 , Joshua Ray 1 , Vivek Subbiah 3

IMPORTANCE: Evidence regarding real-world effectiveness of therapies for patients with advanced non-small cell lung cancer (NSCLC) whose tumors are resistant to platinum-based chemotherapy is lacking. Objective: To compare the effectiveness of the immune checkpoint inhibitors atezolizumab (programmed cell death ligand 1 inhibitor) and nivolumab (programmed cell death 1 inhibitor) and the chemotherapy drug docetaxel in patients with advanced NSCLC resistant to platinum-based chemotherapy. **DESIGN, SETTING, AND PARTICIPANTS:** This comparative effectiveness study compared patients aged 18 years or older with advanced NSCLC who initiated atezolizumab, docetaxel, or nivolumab and who had previously been exposed to platinum-based chemotherapy using nationally representative real-world data from more than 280 US cancer clinics. Patients were followed-up from May 2011 to March 2020. Data analysis was performed between April and June 2021. Comparisons of interest were between atezolizumab vs docetaxel and atezolizumab vs nivolumab. **EXPOSURES:** Initiation of atezolizumab, nivolumab, or docetaxel monotherapy. Main outcome and measures: The main outcome was overall survival (OS). **RESULTS:** A total of 3336 patients (mean [SD] age, 67.1 [9.49] years; 1820 [54.6%] men and 1516 [45.4%] women) were assessed in the main analysis, including 206 patients receiving atezolizumab, 500 receiving docetaxel, and 2630 receiving nivolumab. Patients receiving atezolizumab were older than those treated with docetaxel (mean age [SD], 68.3 [9.4] years vs 65.6 [9.5] years), and were more likely to have been treated in an academic setting (39 patients [18.9%])

than those receiving docetaxel (49 patients [9.8%]) and nivolumab (128 patients [4.9%]). After adjustment for baseline characteristics, atezolizumab was associated with a significantly longer OS compared with docetaxel (adjusted hazard ratio [aHR], 0.79; 95% CI, 0.64-0.97). No significant difference in OS was observed between atezolizumab and nivolumab (aHR, 1.07; 95% CI, 0.89-1.28). These findings were consistent across all patient subgroups tested, and robust to plausible deviations from random missingness for Eastern Cooperative Oncology Group performance status in real-world data (eg, the tipping point for loss of a significantly beneficial effect for atezolizumab vs docetaxel was achieved if patients in the docetaxel group missing baseline Eastern Cooperative Oncology Group performance status had a mean performance status of 1.43 higher than expected). **CONCLUSIONS AND RELEVANCE:** In this comparative effectiveness study, atezolizumab was superior to docetaxel and matched nivolumab in prolonging OS in a real-world cohort of patients with advanced NSCLC who previously received platinum-based chemotherapy.

Evorpaccept alone and in combination with pembrolizumab or trastuzumab in patients with advanced solid tumours (ASPEN-01): a first-in-human, open-label, multicentre, phase 1 dose-escalation and dose-expansion study Lancet Oncol. 2021 Nov 15;S1470-2045(21)00584-2. doi:

10.1016/S1470-2045(21)00584-2. Online ahead of print. Nehal J Lakhani¹, Laura Q M Chow², Justin F Gainor³, et al.

BACKGROUND: Both innate and adaptive immune responses are important components of anticancer immunity. The CD47-SIRP α interaction could represent an important pathway used by tumour cells to evade immune surveillance. We aimed to evaluate the safety, pharmacokinetics, pharmacodynamics, and anticancer activity of evorpaccept (also known as ALX148), a high-affinity CD47-blocking protein with an inactive IgG Fc region in patients with solid tumours. **METHODS:** We did a first-in-human, open-label, multicentre, phase 1 dose-escalation and dose-expansion study at nine hospitals and one clinic in the USA and Korea. Eligible patients for the dose-escalation and safety lead-in phases were aged 18 years or older with histological or cytological diagnosis of advanced or metastatic solid tumours with no available standard therapy, measurable or unmeasurable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1, and an Eastern Cooperative Oncology Group performance status score of 0 or 1. In the dose-escalation phase, which used a 3 + 3 design, patients received intravenous evorpaccept at either 0.3, 1, 3, or 10 mg/kg once per week in 21-day cycles, or 30 mg/kg once every other week in 28-day cycles. In the safety lead-in phase, patients were given the maximum tolerable dose of evorpaccept from the dose-escalation phase plus either intravenous pembrolizumab (200 mg administered once every 3 weeks) or intravenous trastuzumab (8 mg/kg loading dose followed by 6 mg/kg once every 3 weeks). In the dose-expansion phase, additional patients aged 18 years or older with second-line or later-line advanced malignancies were enrolled into three parallel cohorts: those with head and neck squamous cell carcinoma (HNSCC) and those with non-small-cell lung cancer (NSCLC) were given the maximum tolerated dose of evorpaccept plus intravenous pembrolizumab (200 mg administered once every 3 weeks), and patients with HER2-positive gastric or gastroesophageal junction cancer were given the maximum tolerated dose of evorpaccept plus intravenous trastuzumab (8 mg/kg loading dose followed by 6 mg/kg once every 3 weeks) until disease progression, voluntary withdrawal from the study, or unacceptable toxicity. The primary endpoint was the maximum tolerated dose of evorpaccept administered as a single agent and in combination with pembrolizumab or trastuzumab, measured by the occurrence of dose-limiting toxicities during the first cycle, and was assessed in all patients who had received at least one dose of evorpaccept. Secondary outcomes included the safety, tolerability, and antitumour activity of evorpaccept, alone or in combination with pembrolizumab or trastuzumab. The primary outcome, safety, and tolerability were assessed in all patients who had received at least one dose of evorpaccept, and antitumour activity was assessed in those who received at least one dose of study treatment and underwent at least one post-baseline tumor assessment. This trial is registered with ClinicalTrials.gov,

NCT03013218. **FINDINGS:** Between March 6, 2017, and Feb 21, 2019, 110 patients received single-agent evorpacept (n=28), evorpacept plus pembrolizumab (n=52), or evorpacept plus trastuzumab (n=30), and were included in the safety analysis. Median follow-up was 29.1 months (95% CI not calculable [NC]-NC) in the single-agent cohort, 27.0 months (25.1-28.8) in the evorpacept plus pembrolizumab cohort, and 32.7 months (27.0-32.7) in the evorpacept plus trastuzumab cohort. Two (7%) dose-limiting toxicities in the first cycle were reported in patients who received single-agent evorpacept; neutropenia with an associated infection in one patient with gastroesophageal junction cancer who received 3 mg/kg once per week, and thrombocytopenia with associated bleeding in one patient with pancreatic cancer who received 30 mg/kg once every other week. No maximum tolerated dose was reached; the maximum administered doses were 10 mg/kg once per week or 30 mg/kg once every other week. The 10 mg/kg once per week dose was used in the expansion cohorts in combination with pembrolizumab or trastuzumab. The most common grade 3 or worse treatment-related adverse events were thrombocytopenia with single-agent evorpacept (two [7%] patients) and evorpacept plus pembrolizumab (two [4%]), and thrombocytopenia (two [7%]) and neutropenia (two [7%]) with evorpacept plus trastuzumab. In patients who received single-agent evorpacept, four treatment-related serious adverse events were reported. Five serious treatment-related adverse events related to evorpacept plus pembrolizumab were reported, and one serious adverse event related to evorpacept plus trastuzumab was reported. In response-evaluable patients in the dose-escalation phase (n=15) receiving single-agent evorpacept once per week, four (27%) had a best overall response of stable disease (two received 0.3 mg/kg, one received 3 mg/kg, and one received 10 mg/kg); in the 11 patients who received single-agent evorpacept at the highest dose of 30 mg/kg once every other week, two (18%) had stable disease. In the dose-expansion cohort, overall responses were recorded in four (20.0%; 95% CI 5.7-43.7) of 20 patients with HNSCC who received evorpacept plus pembrolizumab, in one (5.0%; 0.1-24.9) of 20 patients with NSCLC who received evorpacept plus pembrolizumab, and in four (21.1%; 6.1-45.6) of 19 patients with gastric or gastroesophageal junction cancer who received evorpacept plus trastuzumab. **INTERPRETATION:** The safety findings support the use of evorpacept in combination with pembrolizumab or trastuzumab for patients with advanced solid tumours. Preliminary antitumour activity results support future investigation of evorpacept combined with pembrolizumab or trastuzumab in patients with HNSCC, gastric or gastroesophageal junction cancer, and NSCLC.

NSCLC - RADIOTHERAPY

[Radiation Pneumonitis After Volumetric Modulated Arc Therapy for Non-small Cell Lung Cancer](#)

Anticancer Res. 2021 Nov;41(11):5793-5802. doi: 10.21873/anticancer.15396. Masayuki Fujiwara 1 , Hiroshi Doi 2 , Masataka Igeta 3 , et al.

BACKGROUND: aim: To evaluate the incidence and grade of radiation pneumonitis after volumetric modulated arc therapy (VMAT) performed for the treatment of non-small cell cancer (NSCLC). Patients and **METHODS:** Fifty consecutive non-surgical candidates with NSCLC underwent VMAT. Thirty-five patients had stage-III tumors and 15 had recurrent tumors. The prescribed radiation dose for the gross tumor and the elective nodal area was 69 Gy in 30 fractions and 51 Gy in 30 fractions, respectively.

RESULTS: Radiation pneumonitis developed in 38 patients (76%, 38/50), and grade ≥ 2 radiation pneumonitis developed in 11 patients (22%, 11/50). The percentage of lung volume that received a dose in excess of 5 Gy (V5), V10, V20, V30, and the mean lung dose (MLD) in the bilateral and ipsilateral lung were significantly associated with the development of grade ≥ 2 radiation pneumonitis.

CONCLUSION: The incidence and degree of radiation pneumonitis are acceptable following treatment of NSCLC with VMAT.

[Hypofractionated Proton Beam Therapy for cT1-2N0M0 Non-small Cell Lung Cancer Patients With Interstitial Lung Disease](#) Anticancer Res. 2021 Nov;41(11):5635-5642. doi:

10.21873/anticancerres.15379. Takashi Saito ¹, Kayoko Ohnishi ^{2,3}, Hitoshi Ishikawa ^{1,4}, et al.

BACKGROUND:/AIM: To evaluate the outcomes of proton beam therapy (PBT) for early-stage non-small cell lung cancer (NSCLC) in patients with interstitial lung disease (ILD). Patients and **METHODS:** Between 2002 and 2017, 110 patients receiving hypofractionated PBT for cT1-2N0M0 NSCLC were reviewed. **RESULTS:** Of the 110 patients, 17 were diagnosed with ILD. The median follow-up period was 37.8 months. No significant difference in the 1-year cumulative rate of grade ≥ 2 pneumonitis was observed between patients with and those without ILD (17.6% vs. 14.1%, $p=0.708$). The lung doses were significantly lower in patients with than in those without ILD among patients without grade ≥ 2 pneumonitis. There were no significant differences in overall survival or local recurrence-free rates according to the presence of ILD. **CONCLUSION:** PBT appears to be a feasible and effective treatment for cT1-2N0M0 NSCLC in patients with ILD, but the lung dose should be strictly reduced.

[Clinically validated model predicts the effect of intratumoral heterogeneity on overall survival for non-small cell lung cancer \(NSCLC\) patients](#) Comput Methods Programs Biomed. 2021

Nov;212:106455. doi: 10.1016/j.cmpb.2021.106455. Epub 2021 Oct 12. Nima Ghaderi ¹, Joseph H Jung ², David J Odde ³, Jeffrey Peacock ⁴

BACKGROUND: AND OBJECTIVE: Radiation therapy is used in nearly 50% of cancer treatments in the developed world. Currently, radiation treatments are homogenous and fail to take into consideration intratumoral heterogeneity. We demonstrate the importance of considering intratumoral heterogeneity and the development of resistance during fractionated radiotherapy when the same dose of radiation is delivered for all fractions (Fractional Equivalent Dosing FED). **METHODS:** A mathematical model was developed with the following parameters: a starting population of 10¹¹ non-small cell lung cancer (NSCLC) tumor cells, 48 h doubling time, and cell death per the linear-quadratic (LQ) model with α and β values derived from $RSI\alpha/\beta$, in a previously described gene expression based model that estimates α and β . To incorporate both inter- and intratumor radiation sensitivity, $RSI\alpha/\beta$ output for each patient sample is assumed to represent an average value in a gamma distribution with the bounds set to -50% and +50% of $RSI\alpha/b$. Therefore, we assume that within a given tumor there are subpopulations that have varying radiation sensitivity parameters that are distinct from other tumor samples with a different mean $RSI\alpha/\beta$. A simulation cohort (SC) comprised of 100 lung cancer patients with available $RSI\alpha/\beta$ (patient specific α and β values) was used to investigate 60 Gy in 30 fractions with fractionally equivalent dosing (FED). A separate validation cohort (VC) of 57 lung cancer patients treated with radiation with available local control (LC), overall survival (OS), and tumor gene expression was used to clinically validate the model. Cox regression was used to test for significance to predict clinical outcomes as a continuous variable in multivariate analysis (MVA). Finally, the VC was used to compare FED schedules with various altered fractionation schema utilizing a Kruskal-Wallis test. This was examined using the end points of end of treatment log cell count (LCC) and by a parameter described as mean log kill efficiency (LKE) defined as: $LCC = \log_{10}(\text{tumor cell count})$ [Formula: see text] **RESULTS:** Cox regression analysis on LCC for the VC demonstrates that, after incorporation of intratumoral heterogeneity, LCC has a linear correlation with local control ($p = 0.002$) and overall survival ($p = < 0.001$). Other suggested treatment schedules labeled as High Intensity Treatment (HIT) with a total 60 Gy delivered over 6 weeks have a lower mean LCC and an increased LKE compared to standard of care 60 Gy delivered in FED in the VC. **CONCLUSION:** We find that LCC is a clinically relevant metric that is correlated with local control and overall survival in NSCLC. We conclude that 60 Gy delivered over 6 weeks with altered HIT fractionation leads to an enhancement in tumor control compared to FED when intratumoral heterogeneity is considered.

Cost-Effectiveness of Carbon-Ion Radiotherapy versus Stereotactic Body Radiotherapy for Non-Small Cell Lung Cancer Cancer Sci. 2021 Nov 25. doi: 10.1111/cas.15216. Online ahead of print.

Shohei Okazaki 1 2, Kei Shibuya 1, Tomoyuki Takura 3, Yuhei Miyasaka 1, Hidemasa Kawamura 2, Tatsuya Ohno 1 2

Carbon-ion radiotherapy (CIRT) for clinical stage I non-small-cell lung cancer (NSCLC) is performed as an advanced medical treatment regimen in Japan. CIRT reportedly aids in achieving excellent treatment outcomes, despite its high medical costs. We aimed to compare CIRT with stereotactic body radiotherapy (SBRT) in terms of cost-effectiveness for treating clinical stage I NSCLC. Data of patients with clinical stage I NSCLC treated with CIRT or SBRT at Gunma University during 2010-2015 were analyzed. The CIRT and SBRT groups included 62 and 27 patients, respectively. After propensity-score matching, both groups comprised 15 patients. Life year (LY) was used as an indicator of outcome. The CIRT technical fee was 3,140,000 JPY. There was no technical fee for the second CIRT performed on the same organ within 2 years. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental cost by the incremental LY for 5 years after treatment. Sensitivity analysis was performed to evaluate the impact of LY or costs of each group on ICER. The ICERs were 7,491,017 JPY/LY and 3,708,330 JPY/LY for all patients and matched patients, respectively. Hospitalization and examination costs were significantly higher in the CIRT group, and the impact of the CIRT technical costs was smaller than other costs and LY. CIRT is a cost-effective treatment approach. However, our findings suggest that reducing excessive costs by considering the validity and necessity of examinations and hospitalizations would make CIRT a more cost-effective approach.

Effect of brain radiotherapy strategies on prognosis of patients with EGFR-mutant lung adenocarcinoma with brain metastasis J Transl Med. 2021 Nov 30;19(1):486. doi: 10.1186/s12967-021-03161-1.

Guangchuan Deng 1 2, Yingyun Zhang 1 2, Jiaojiao Ke 3, Qi Wang 1 2, Hongyue Qin 1 2, Jianbin Li 4 5, Zhenxiang Li 6

PURPOSE: Epidermal growth factor receptor (EGFR)-mutant lung cancers have a high risk of developing brain metastases (BM). Whole brain radiotherapy (WBRT), local radiotherapy, and WBRT + Boost are frequently used for treatment of BM. This retrospective study aimed to evaluate the difference in efficacy of these radiotherapy modes in patients with EGFR-mutant lung adenocarcinoma with BMs. Further, we determined the optimal radiotherapy regimen for patients based on Lung-molGPA.

METHODS AND MATERIALS: We retrospectively enrolled 232 patients with EGFR-mutant lung adenocarcinoma with BMs. Patients were divided into three groups based on the different modes of brain radiotherapy: WBRT group, local radiotherapy group, and WBRT + Boost group. Graded prognostic assessment for lung cancer using molecular markers (Lung molGPA), overall survival (OS), and intracranial progression-free survival (iPFS) were calculated. Kaplan-Meier was used to compare iPFS and OS in different groups. **RESULTS:** The median OS for the WBRT (n = 84), local radiotherapy (n = 65), and WBRT + Boost (n = 83) cohorts was 32.8, 59.1, and 41.7 months, respectively (P = 0.0002). After stratification according to the Lung-molGPA score, the median OS for the WBRT (n = 56), local radiotherapy (n = 19), and WBRT + Boost (n = 28) cohorts was 32.5, 30.9, and 30.8 months, respectively, in subgroup with score 1-2 (P = 0.5097). In subgroup with score 2.5-4, the median OS for the WBRT (n = 26), local radiotherapy (n = 45), and WBRT + Boost (n = 54) cohorts was 32, 68.4, and 51 months, respectively (P = 0.0041). **CONCLUSION:** The present study showed that in patients with EGFR-mutant lung adenocarcinoma with BM, local radiotherapy and WBRT + Boost perform similarly well both in the subgroups with low and high scores of Lung-molGPA. Considering the side effect caused by whole brain radiotherapy, we recommended local radiotherapy as optimal brain radiation mode for those subtype lung cancer patients.

[Implementation of a Knowledge-Based Treatment Planning Model for Cardiac-Sparing Lung Radiation Therapy](#) Adv Radiat Oncol. 2021 Jun 24;6(6):100745. doi: 10.1016/j.adro.2021.100745. eCollection Nov-Dec 2021. Joseph Harms 1 2 , Jiahn Zhang 1 , Oluwatosin Kayode 1 , Jonathan Wolf 1 , Sibio Tian 1 , Neal McCall 1 , Kristin A Higgins 1 , Richard Castillo 1 , Xiaofeng Yang 1 Affiliations

PURPOSE: High radiation doses to the heart have been correlated with poor overall survival in patients receiving radiation therapy for stage III non-small cell lung cancer (NSCLC). We built a knowledge-based planning (KBP) tool to limit the dose to the heart during creation of volumetric modulated arc therapy (VMAT) treatment plans for patients being treated to 60 Gy in 30 fractions for stage III NSCLC. **METHODS AND MATERIALS:** A previous study at our institution retrospectively delineated intracardiac volumes and optimized VMAT treatment plans to reduce dose to these substructures and to the whole heart. Two RapidPlan (RP) KBP models were built from this cohort, 1 model using the clinical plans and a separate model using the cardiac-optimized plans. Using target volumes and 6 organs at risk (OARs), models were trained to generate treatment plans in a semiautomated process. The cardiac-sparing KBP model was tested in the same cohort used for training, and both models were tested on an external validation cohort of 30 patients. **RESULTS:** Both RP models produced clinically acceptable plans in terms of target coverage, dose uniformity, and dose to OARs. Compared with the previously created cardiac-optimized plans, cardiac-sparing RPs showed significant reductions in the mean dose to the esophagus and lungs while performing similarly or better in all evaluated heart dose metrics. When comparing the 2 models, the cardiac-sparing RP showed reduced ($P < .05$) heart mean and maximum doses as well as volumes receiving 60 Gy, 50 Gy, and 30 Gy. **CONCLUSIONS:** By using a set of cardiac-optimized treatment plans for training, the proposed KBP model provided a means to reduce the dose to the heart and its substructures without the need to explicitly delineate cardiac substructures. This tool may offer reduced planning time and improved plan quality and might be used to improve patient outcomes.

[Association Between Physician and Patient Reported Symptoms in Patients Treated with Definitive Radiotherapy for Locally Advanced Lung Cancer in a Statewide Consortium](#) Int J Radiat Oncol Biol Phys. 2021 Nov 25;S0360-3016(21)03222-3. doi: 10.1016/j.ijrobp.2021.11.024. Online ahead of print. Joel R Wilkie 1 , Kimberly A Hochstedler 2 , Matthew J Schipper 3 , et al.

INTRODUCTION: Little data have been reported about the patient experience during curative radiotherapy for lung cancer in routine clinical practice, or how this relates to treatment toxicity reported by clinicians. The **PURPOSE:** of this study was to compare clinician-reported adverse events (AEs) with patient-reported outcomes (PROs) including both specific symptoms/side effects as well as overall quality of life (QOL) during and after definitive radiotherapy (RT) for locally advanced lung cancer (LALC) in a large statewide cohort. **Methods and materials:** Patient-reported outcomes (PROs) were prospectively collected from patients treated with definitive radiotherapy for LALC at 24 institutions within the XXXX Radiation Oncology Quality Consortium between 2012-2018 using the Functional Assessment of Cancer Therapy Trial Outcome Index (FACT-TOI). Physicians prospectively recorded adverse events (AEs) using CTCAE version 4.0. Patient-reported quality of life (QOL) changes from baseline were assessed during and after radiotherapy using the FACT-TOI. Spearman correlation coefficients were calculated for AEs and similar PROs, and multivariable analysis was used to assess associations with QOL. **RESULTS:** 1361 patients were included and 53% of respondents reported clinically meaningful declines in QOL at the end of RT. Correlation between clinician-reported esophagitis and patient-reported trouble swallowing was moderate ($R=0.67$) while correlations between clinician-reported pneumonitis and patient-reported shortness of breath ($R=0.13$) and cough ($R=0.09$) were weak. Clinician-reported AEs were significantly associated with clinically meaningful declines inpatient-reported QOL, with $R=-0.46$ for a summary AE-score. QOL was more strongly associated with fatigue ($R=-0.41$) than lung-specific AEs.

CONCLUSIONS: AEs are associated with clinically meaningful declines in QOL during and after RT for LALC, but associations between AEs and QOL are only modest. This highlights the importance of PRO data, and future research should assess whether earlier detection of PRO changes could allow for interventions that reduce the frequency of treatment-related clinically meaningful declines in QOL.

[Treatment outcomes of re-irradiation using stereotactic ablative radiotherapy to lung: a propensity score matching analysis](#) Radiat Oncol. 2021 Nov 18;16(1):222. doi: 10.1186/s13014-021-01948-6. Tae

Hoon Lee # 1 , Dong-Yun Kim # 1 , Hong-Gyun Wu 1 2 3 , Joo Ho Lee 1 , Hak Jae Kim 4 5 6

BACKGROUND: The PURPOSE: of this study was to compare the treatment efficacy and safety of re-irradiation (re-RT) using stereotactic ablative radiotherapy (SABR) and initial SABR for primary, recurrent lung cancer or metastatic lung tumor. **METHODS:** A retrospective review of the medical records of 336 patients who underwent lung SABR was performed. Re-RT was defined as the overlap of the 70% isodose line of second-course SABR with that of the initial radiotherapy, and 20 patients were classified as the re-RT group. The median dose of re-RT using SABR was 54 Gy (range 48-60 Gy), and the median fraction number was 4 (range 4-6). One-to-three case-matched analysis with propensity score matching was used, and 60 patients were included in the initial SABR group of the matched cohort.

RESULTS: The 1- and 2-year local control rates for the re-RT group were 73.9% and 63.3% and those for the initial SABR group in the matched cohort were 92.9% and 87.7%, respectively (P = 0.013). There was no difference in distant metastasis-free, progression-free, and overall survival rates. The crude grade ≥ 2 toxicity rates were 40.0% for the re-RT group and 25.0% for the initial SABR group (P = 0.318). Re-RT group had higher acute grade ≥ 2 toxicity rates (25.0% vs 5.0%, P = 0.031). One incident of grade 3 toxicity (pulmonary) was reported in the re-RT group; there was no grade 4–5 toxicity.

CONCLUSIONS: The local control rate of the in-field re-RT SABR was lower than that of the initial SABR without compromising the survival rates. The toxicity of re-RT using SABR was acceptable.

[Toxicity and efficacy of stereotactic body radiotherapy for ultra-central lung tumours: a single institution real life experience](#) Br J Radiol. 2021 Nov 26;20210533. doi: 10.1259/bjr.20210533. Online

ahead of print. Elodie Guillaume 1 2 , Ronan Tanguy 1 , Myriam Ayadi 1 , et al.

OBJECTIVES: The use of stereotactic body radiotherapy (SBRT) to treat ultra-central lung tumours remains more controversial than for peripheral and central tumours. Our objective was to assess toxicities, local control (LC) rate and survival data in patients with ultra-central lung tumours treated with SBRT.

METHODS: We conducted a retrospective and monocentric study about 74 patients with an ultra-central lung tumour, consecutively treated between 2012 and 2018. Ultra-central tumours were defined as tumours whose planning target volume overlapped one of the following organs at risk (OARs): the trachea, right and left main bronchi, intermediate bronchus, lobe bronchi, oesophagus, heart. **RESULTS:** Median follow-up was 25 months. Two patients (2.7%) showed Grade 3 toxicity. No Grade 4 or 5 toxicity was observed. 11% of patients experienced primary local relapse. LC rate was 96.7% at 1 year and 87.6% at 2 years. Median progression free survival was 12 months. Median overall survival was 31 months.

CONCLUSION: SBRT for ultra-central tumours remains safe and effective as long as protecting organs at risk is treatment-planning priority. **ADVANCES IN KNOWLEDGE:** The present study is one of the rare to describe exclusively ultra-central tumours through real-life observational case reports. Globally, literature analysis reveals a large heterogeneity in ultra-central lung tumours definition, prescribed dose, number of fractions. In our study, patients treated with SBRT for ultra-central lung tumours experienced few Grade 3 toxicities (2.7%) and no Grade 4 or 5 toxicities, due to the highest compliance with dose constraints to OARs. LC remained efficient.

[Integration of deep learning radiomics and counts of circulating tumor cells improves prediction of outcomes of early stage NSCLC patients treated with SBRT](#) Int J Radiat Oncol Biol Phys. 2021 Nov 11;S0360-3016(21)03114-X. doi: 10.1016/j.ijrobp.2021.11.006. Online ahead of print. Dr Zhicheng Jiao 1 , Dr Hongming Li 2 , Professor Ying Xiao 3 , Dr Jay Dorsey 3 , Dr Charles B Simone 4 , Professor Steven Feigenberg 3 , Dr Gary Kao 3 , Dr Yong Fan 5

PURPOSE: We develop a deep learning (DL) radiomics model and integrate it with circulating tumor cell (CTC) counts as a clinically useful prognostic marker for predicting recurrence outcomes of early-stage non-small cell lung cancer (ES-NSCLC) patients treated with stereotactic body radiation therapy (SBRT). **METHODS AND MATERIALS:** A cohort of 421 NSCLC patients was used to train a DL model for gleaning informative imaging features from computed tomography (CT) data. The learned imaging features were optimized on a cohort of 98 ES-NSCLC patients treated with SBRT for predicting individual patient recurrence risks by building DL models on CT data and clinical measures. These DL models were validated on the third cohort of 60 ES-NSCLC patients treated with SBRT to predict recurrent risks and stratify patients into subgroups with distinct outcomes in conjunction with CTC counts. **RESULTS:** The DL model obtained a concordance-index of 0.880 (95% confidence interval: 0.879, 0.881). Patient subgroups with low and high DL risk scores had significantly different recurrence outcomes ($p = 3.5e-04$). The integration of DL risk scores and CTC measures identified 4 subgroups of patients with significantly different risks of recurrence ($\chi^2 = 20.11, p = 1.6e-04$). Patients with positive CTC measures post-SBRT were associated with increased risks of recurrence that were significantly different from patients with negative CTC measures ($\chi^2 = 4.03, p = 0.0447$). **CONCLUSION:** In this first-ever study integrating DL radiomics models and CTC counts, our results suggested that this integration improves patient stratification compared with either imaging data or CTC measures alone in predicting recurrence outcomes for patients treated with SBRT for ES-NSCLC.

[A million persons, a million dreams: a vision for a national center of radiation epidemiology and biology](#) Int J Radiat Biol. 2021 Nov 3;1-27. doi: 10.1080/09553002.2021.1988183. Online ahead of print. John D Boice Jr 1 2 , Brian Quinn 3 , Isaf Al-Nabulsi 4 , et al.

BACKGROUND: Epidemiologic studies of radiation-exposed populations form the basis for human safety standards. They also help shape public health policy and evidence-based health practices by identifying and quantifying health risks of exposure in defined populations. For more than a century, epidemiologists have studied the consequences of radiation exposures, yet the health effects of low levels delivered at a low-dose rate remain equivocal. **MATERIALS AND METHODS:** The Million Person Study (MPS) of U.S. Radiation Workers and Veterans was designed to examine health effects following chronic exposures in contrast with brief exposures as experienced by the Japanese atomic bomb survivors. Radiation associations for rare cancers, intakes of radionuclides, and differences between men and women are being evaluated, as well as noncancers such as cardiovascular disease and conditions such as dementia and cognitive function. The first international symposium, held November 6, 2020, provided a broad overview of the MPS. Representatives from four U.S. government agencies addressed the importance of this research for their respective missions: U.S. Department of Energy (DOE), the Centers for Disease Control and Prevention (CDC), the U.S. Department of Defense (DOD), and the National Aeronautics and Space Administration (NASA). The major components of the MPS were discussed and recent findings summarized. The importance of radiation dosimetry, an essential feature of each MPS investigation, was emphasized. **RESULTS:** The seven components of the MPS are DOE workers, nuclear weapons test participants, nuclear power plant workers, industrial radiographers, medical radiation workers, nuclear submariners, other U.S. Navy personnel, and radium dial painters. The MPS cohorts include tens of thousands of workers with elevated intakes of alpha particle emitters for which organ-specific doses are determined. Findings to date for chronic radiation exposure suggest that leukemia risk is lower than after acute exposure; lung cancer risk is much lower and there is little difference in risks

between men and women; an increase in ischemic heart disease is yet to be seen; esophageal cancer is frequently elevated but not myelodysplastic syndrome; and Parkinson's disease may be associated with radiation exposure. **CONCLUSIONS:** The MPS has provided provocative insights into the possible range of health effects following low-level chronic radiation exposure. When the 34 MPS cohorts are completed and combined, a powerful evaluation of radiation-effects will be possible. This final article in the MPS special issue summarizes the findings to date and the possibilities for the future. A National Center for Radiation Epidemiology and Biology is envisioned.

SMALL CELL LUNG CANCER - SCLC

[Integrated exposure-response analysis of efficacy and safety of lurbinectedin to support the dose regimen in small-cell lung cancer](#) Cancer Chemother Pharmacol. 2021 Nov 5. doi: 10.1007/s00280-021-04366-3. Online ahead of print. Carlos Fernández-Teruel 1 , Salvador Fudio 1 , Rubin Lubomirov 2

PURPOSE: These exposure-response (E-R) analyses integrated lurbinectedin effects on key efficacy and safety variables in relapsed SCLC to determine the adequacy of the dose regimen of 3.2 mg/m² 1-h intravenous infusion every 3 weeks (q3wk). **METHODS:** Logistic models and Cox regression analyses were applied to correlate lurbinectedin exposure metrics (AUC_{tot} and AUC_u) with efficacy and safety endpoints: objective response rate (ORR) and overall survival (OS) in SCLC patients (n = 99) treated in study B-005 with 3.2 mg/m² q3wk, and incidence of grade 4 (G4) neutropenia and grade 3-4 (G ≥ 3) thrombocytopenia in a pool of cancer patients from single-agent phase I to III studies (n = 692) treated at a wide range of doses. A clinical utility index was used to assess the appropriateness of the selected dose. **RESULTS:** Effect of lurbinectedin AUC_u on ORR best fitted to a sigmoid-maximal response (E_{max}) logistic model, where E_{max} was dependent on chemotherapy-free interval (CTFI). Cox regression analysis with OS found relationships with both CTFI and AUC_u. An E_{max} logistic model for G4 neutropenia and a linear logistic model for G ≥ 3 thrombocytopenia, which retained platelets and albumin at baseline and body surface area, best fitted to AUC_{tot} and AUC_u. AUC_u between approximately 1000 and 1700 ng·h/L provided the best benefit/risk ratio, and the dose of 3.2 mg/m² provided median AUC_u of 1400 ng·h/L, thus maximizing the proportion of patients within that lurbinectedin target exposure range. **CONCLUSIONS:** The relationships evidenced in this integrated E-R analysis support a favorable benefit-risk profile for lurbinectedin 3.2 mg/m² q3wk.

[Identification of Potential Prognostic and Predictive Biomarkers for Immune-Checkpoint Inhibitor Response in Small Cell Lung Cancer](#) Med Sci Monit. 2021 Nov 1;27:e932275. doi: 10.12659/MSM.932275. Chanchan Gao 1 , Xuyu Gu 1 , Yan Chen 1 , Min Zhou 1 , Feng Jiang 1 , Shiya Zheng 2

BACKGROUND: Immune-checkpoint inhibitors have propelled the field of therapeutics for small cell lung cancer (SCLC) treatment, but are only beneficial to some patients. The objective of this study was to identify valid biomarkers for good potential response to immunotherapy. **MATERIAL AND METHODS:** We performed an integrated analysis of the available datasets from the Gene Expression Omnibus (GEO) projects, Cancer Cell Line Encyclopedia (CCLE), TISIDB database, and Lung Cancer Explorer (LCE) database. Six prognosis-related genes (MCM2, EZH2, CENPK, CHEK1, CDKN2A, and EXOSC2) were identified utilizing the meta workflow of data analysis methods. We performed subclass mapping to compare their expression profiles to other datasets of patients who responded to immunotherapy. A drug sensitivity predictive model was used to predict the chemotherapeutic response to cisplatin and etoposide. **RESULTS:** Our results showed that the expression of the 6 key genes was significantly associated with the overall survival of patients with SCLC. Lower expression of these 6 genes was correlated to the response to anti-PD-1 treatment. Additionally, low expression of MCM2, EZH2, CENPK, and CHEK1 was correlated with increased sensitivity to cisplatin, but not etoposide.

CONCLUSIONS: Overall, our data showed that MCM2, EZH2, CENPK, CHEK1, CDKN2A, and EXOSC2 are potential prognostic and predictive biomarkers for response to immune-checkpoint inhibitor treatment in patients with SCLC. Further studies with large sample sizes are required to validate our findings and to explore the detailed mechanisms underlying the role of these genes in SCLC.

PALLIATIVE AND SUPPORTIVE CARE

[Symptom Treatment Preferences of Cancer Survivors: Does Fatigue Level Make a Difference?](#)

Cancer Nurs. 2021 Nov-Dec 01;44(6):E540-E546. doi: 10.1097/NCC.0000000000000941. Ellen Krueger 1, Ekin Secinti, Catherine E Mosher, Patrick V Stutz, Andrea A Cohee, Shelley A Johns

BACKGROUND: Cancer-related fatigue (CRF) is among the most prevalent symptoms in cancer survivors and often co-occurs with other symptoms. However, little is known about survivors' preferences for treating CRF and associated symptoms. Objective: The aim of this study was to examine cancer survivors' interest in learning skills to manage CRF and associated symptoms and their interest in various nonpharmacologic interventions and modalities. These outcomes were compared between survivors with high and normal fatigue. **METHODS:** Breast, gastrointestinal, lung, and prostate cancer survivors (N = 338) completed a 1-time survey, including a Patient-Reported Outcomes Measurement Information System fatigue measure and a checklist assessing interest in learning skills to manage CRF and associated symptoms as well as interest in nonpharmacologic interventions and modalities. **RESULTS:** Many cancer survivors reported interest in learning skills to manage CRF (range, 35%-78%) and associated symptoms (range, 13%-48%). Compared with survivors with normal fatigue (n = 180), highly fatigued survivors (n = 158; Patient-Reported Outcomes Measurement Information System fatigue T score ≥ 55) were more likely to report interest in learning skills to manage various symptoms, self-compassion training, and programs offered individually and in person. Interest in other interventions and modalities did not vary by fatigue level. **CONCLUSIONS:** Many cancer survivors, especially those with high fatigue, report interest in learning symptom management skills. Given survivors' high level of interest in complementary and integrative health interventions, future research should continue to assess their impact on symptoms and functioning. Implications for practice: Nurses can offer a menu of evidence-based options for symptom management, given survivors' diverse preferences. Nurses can also provide psychoeducation regarding their preferred treatments.

[Post-diagnosis BMI change is associated with non-small cell lung cancer survival](#) Cancer Epidemiol Biomarkers Prev. 2021 Nov 2;cebp.0503.2021. doi: 10.1158/1055-9965.EPI-21-0503. Online ahead of print. Qianyu Yuan 1, Mulong Du 2, Elizabeth Loehrer 3, Bruce E Johnson 4, Justin F Gainor 5, Michael Lanuti 5, Yi Li 6, David C Christiani 7

BACKGROUND: Body mass index (BMI) change after a lung cancer diagnosis has been associated with non-small cell lung cancer (NSCLC) survival. This study aimed to quantify the association based on a large-scale observational study. **METHODS:** Included in the study were 7,547 NSCLC patients with prospectively collected BMI data from Massachusetts General Hospital and Brigham and Women's Hospital/Dana Faber Cancer Institute. Cox proportional hazards regression with time-dependent covariates was used to estimate effect of time varying post-diagnosis BMI change rate (% per month) on overall survival (OS), stratified by clinical subgroups. Spline analysis was conducted to quantify the non-linear association. A Mendelian Randomization (MR) analysis with a total of 3,495 patients further validated the association. **RESULTS:** There was a J-shape association between post-diagnosis BMI change and OS among NSCLC patients. Specifically, a moderate BMI decrease (0.5-2.0; HR = 2.45, 95% CI = 2.25-2.67) and large BMI decrease (≥ 2.0 ; HR = 4.65, 95% CI = 4.15-5.20) were strongly associated with worse OS, whereas moderate weight gain (0.5-2.0) reduced the risk for mortality (HR = 0.78, 95% CI = 0.68-0.89) and large weight gain (≥ 2.0) slightly increased the risk of mortality without

reaching statistical significance (HR = 1.10, 95% CI = 0.86-1.42). MR analyses supported the potential causal roles of post-diagnosis BMI change in survival. **CONCLUSIONS:** This study indicates that BMI change after diagnosis was associated with mortality risk.

Anesthetic Management for Pulmonary Resection: Current Concepts and Improving Safety of Anesthesia Thorac Surg Clin. 2021 Nov;31(4):509-517. doi: 10.1016/j.thorsurg.2021.07.009. Daniel Ankeny 1 , Hovig Chitilian 2 , Xiaodong Bao 1

Increasingly complex procedures are routinely performed using minimally invasive approaches, allowing cancers to be resected with short hospital stays, minimal postsurgical discomfort, and improved odds of cancer-free survival. Along with these changes, the focus of anesthetic management for lung resection surgery has expanded from the provision of ideal surgical conditions and safe intraoperative patient care to include preoperative patient training and optimization and postoperative pain management techniques that can impact pulmonary outcomes as well as patient lengths of stay.

Implementation and Effectiveness of a Veterans Affairs-Based Comprehensive Lung Cancer Survivorship Program J Cardiopulm Rehabil Prev. 2021 Nov 24. doi:

10.1097/HCR.0000000000000658. Online ahead of print. Brian J Rabe 1 , Jordan W Stafford, Alisa D Hassinger, Harry S Swartzwelder, Scott L Shofer

PURPOSE: Few programs exist to address persistent impairment in functional status, quality of life, and mental health in lung cancer survivors. We aimed to determine whether a 12-wk multimodal survivorship program imparts clinical benefit. **METHODS:** Any patient at the Durham Veterans Affairs Medical Center with lung cancer and a Karnofsky score of ≥ 60 could participate. Chronic obstructive pulmonary disease medications were optimized at the enrollment visit. Participants with a Hospital Anxiety and Depression Scale (HADS) score of >8 were offered pharmacotherapy and mental health referral. Participants did home-based exercise with a goal of 1 hr/d, 5 d/wk. They were called weekly to assess exercise progress and review depression/anxiety symptoms. Participants were offered pharmacotherapy for smoking cessation. **RESULTS:** Twenty-three (50%) of the first 46 enrollees completed the full 12-wk program. Paired changes from enrollment to completion (mean \pm SD) were observed in 6-min walk test (73.6 ± 96.9 m, $P = .002$), BODE (Body mass index, airflow Obstruction, Dyspnea, and Exercise) index (-1.45 ± 1.64 points, $P < .001$), Duke Activity Status Index (3.84 ± 7.12 points, $P = .02$), Fried Frailty Index (-0.588 ± 0.939 points, $P = .02$), modified Medical Research Council dyspnea scale (-0.619 ± 1.284 points, $P = .04$), Functional Assessment of Cancer Therapy-Lung Emotional subscale score (1.52 ± 2.96 points, $P = .03$), HADS total score (-2.63 ± 4.34 points, $P = .02$), and HADS Anxiety subscale score (-1.47 ± 2.29 points, $P = .01$). **CONCLUSIONS:** A comprehensive Lung Cancer Survivorship Program provides clinically meaningful improvements in functional status, quality of life, and mental health.

Hope and advance care planning in advanced cancer: Is there a relationship? Cancer. 2021 Nov 17. doi: 10.1002/cncr.34034. Online ahead of print. Michael G Cohen 1 , Andrew D Althouse 2 , Robert M Arnold 3 , Hailey W Bulls 3 , Douglas B White 4 , Edward Chu 5 , Margaret Q Rosenzweig 6 , Kenneth J Smith 2 , Yael Schenker 3

BACKGROUND: Clinicians often cite a fear of giving up hope as a reason they defer advance care planning (ACP) among patients with advanced cancer. The objective of this study was to determine whether engagement in ACP affects hope in these patients. **METHODS:** This was a secondary analysis of a randomized controlled trial of primary palliative care in advanced cancer. Patients who had not completed ACP at baseline were included in the analysis. ACP was assessed in the forms of an end-of-life (EOL) conversation with one's oncologist and completion of a living will or advance directive (AD). Measurements were obtained at baseline and at 3 months. Hope was measured using the Herth Hope Index (HHI) (range, 12-48; higher scores indicate higher hope). Multivariate regression was performed to

assess associations between ACP and hope, controlling for baseline HHI score, study randomization, patient age, religious importance, education, marital status, socioeconomic status, time since cancer diagnosis, pain/symptom burden (Edmonton Symptom Assessment System), and anxiety/depression score (Hospital Anxiety and Depression Scale)-all variables known to be associated with ACP and/or hope. **RESULTS:** In total, 672 patients with advanced cancer were enrolled in the overall study. The mean age was 69 ± 10 years, and the most common cancer types were lung cancer (36%), gastrointestinal cancer (20%) and breast/gynecologic cancers (16%). In this group, 378 patients (56%) had not had an EOL conversation at baseline, of whom 111 of 378 (29%) reported having an EOL conversation by 3 months. Hope was not different between patients who did or did not have an EOL conversation over the study period (mean \pm standard deviation Δ HHI, 0.20 ± 5.32 vs -0.53 ± 3.80 , respectively; $P = .136$). After multivariable adjustment, hope was significantly increased in patients who had engaged in an EOL conversation (adjusted mean difference in Δ HHI, 0.95; 95% CI, 0.08-1.82; $P = .032$). Similarly, of 216 patients (32%) without an AD at baseline, 67 (31%) had subsequently completed an AD. Unadjusted hope was not different between those who did and did not complete an AD (Δ HHI, 0.20 ± 3.89 vs -0.91 ± 4.50 , respectively; $P = .085$). After adjustment, hope was significantly higher in those who completed an AD (adjusted mean difference in Δ HHI, 1.31; 95% CI, 0.13-2.49; $P = .030$). **CONCLUSIONS:** The current results demonstrate that hope is not decreased after engagement in ACP and indeed may be increased. These findings may provide reassurance to clinicians who are apprehensive about having these important and difficult conversations. **LAY SUMMARY:** Many oncologists defer advance care planning (ACP) out of concern for giving up hope. This study demonstrates that hope is not decreased in patients who have engaged in ACP either as a conversation with their oncologists or by completing an advance directive. With this information, providers may feel more comfortable having these important conversations with their patients.

[Emotional Distress in Cancer Patients During the First Wave of the COVID-19 Pandemic](#) Front Psychol. 2021 Nov 5;12:755965. doi: 10.3389/fpsyg.2021.755965. eCollection 2021.

Patricia Toquero ¹, Carmen Blanco Fernández ², María Pilar López Martí ¹, et al.

BACKGROUND: The COVID-19 pandemic has caused mental health problems worldwide. The psychopathological implications of COVID-19 in cancer patients have rarely been addressed. Considering the increased vulnerability of oncology patients, this issue needs to be addressed to improve the long-term mental health status of these patients. **METHODS:** We conducted a prospective study in outpatients under active cancer treatment during the first wave of the COVID-19 pandemic. A semi-structured 24-question survey was designed to measure baseline sociodemographic, psychosocial and COVID-19 exposure characteristics. The Hospital Anxiety and Depression Scale was used to measure psychological symptoms. A descriptive and analytical univariate analysis of the variables studied was performed. We used the Z-score to compare different populations (experimental and historical control cohort).

RESULTS: 104 patients were included, the majority of which were women (64.4%), were above 65 years of age (57.7%), had either lung and breast cancer (56.7%), had advanced disease (64%) and were undergoing chemotherapy (63.5%). 51% of them expressed greater fear of cancer than of COVID-19 infection or both. In relation to HADS, 52.8% of emotional distress, 42.3% of anxiety and 58.6% of depression rates were detected. The main factors related with higher rates of psychological symptomatology were history of previous psychotropic drug consumption and the adoption of additional infection prevention measures because they considered themselves at risk of severe COVID-19 infection ($p = 0.008$; $p = 0.003$ for emotional distress, $p = 0.026$; $p = 0.004$ for anxiety, and $p = 0.013$; $p = 0.008$ for depression). Tumor type, stage, oncologic treatment or rescheduling of cancer treatments were not related to higher levels of psychological symptomatology. Comparison of our results with another population of similar characteristics was not significant (Z score = -1.88; $p = 0.060$). **CONCLUSIONS:** We detected high rates of emotional distress during the first wave of the COVID-19 pandemic among cancer patients

in active treatment (52.8%). This was higher and clinically relevant than observed in a comparable population (42.5%), although not significant. Cancer itself is the main factor of concern for cancer patients, above and beyond the emotional distress generated by COVID-19 pandemic.

[Providers' mediating role for medication adherence among cancer survivors](#) PLoS One. 2021 Nov 29;16(11):e0260358. doi: 10.1371/journal.pone.0260358. eCollection 2021. Justin G Trogon 1 2 , Krutika Amin 1 , Parul Gupta 2 , et al.

BACKGROUND: We conducted a mediation analysis of the provider team's role in changes to chronic condition medication adherence among cancer survivors. **METHODS:** We used a retrospective, longitudinal cohort design following Medicare beneficiaries from 18-months before through 24-months following cancer diagnosis. We included beneficiaries aged ≥ 66 years newly diagnosed with breast, colorectal, lung or prostate cancer and using medication for non-insulin anti-diabetics, statins, and/or anti-hypertensives and similar individuals without cancer from Surveillance, Epidemiology, and End Results-Medicare data, 2008-2014. Chronic condition medication adherence was defined as a proportion of days covered $\geq 80\%$. Provider team structure was measured using two factors capturing the number of providers seen and the historical amount of patient sharing among providers. Linear regressions relying on within-survivor variation were run separately for each cancer site, chronic condition, and follow-up period. **RESULTS:** The number of providers and patient sharing among providers increased after cancer diagnosis relative to the non-cancer control group. Changes in provider team complexity explained only small changes in medication adherence. Provider team effects were statistically insignificant in 13 of 17 analytic samples with significant changes in adherence. Statistically significant provider team effects were small in magnitude (<0.5 percentage points). **CONCLUSIONS:** Increased complexity in the provider team associated with cancer diagnosis did not lead to meaningful reductions in medication adherence. Interventions aimed at improving chronic condition medication adherence should be targeted based on the type of cancer and chronic condition and focus on other provider, systemic, or patient factors.

[Fear of Palliative Care: Roles of Age and Depression Severity](#) J Palliat Med. 2021 Nov 11. doi: 10.1089/jpm.2021.0359. Online ahead of print. Sarah Alonzi 1 , Laura M Perry 1 , Ashley B Lewson 2 , Brenna Mossman 1 , Madison W Silverstein 3 , Michael Hoerger 1 4 5

BACKGROUND: Palliative care is underutilized due in part to fear and misunderstanding, and depression might explain variation in fear of palliative care. **OBJECTIVE:** Informed by the socioemotional selectivity theory, we hypothesized that older adults with cancer would be less depressed than younger adults, and subsequently less fearful of utilizing palliative care. **SETTING/SUBJECTS:** Patients predominately located in the United States with heterogeneous cancer diagnoses ($n = 1095$) completed the Patient-Reported Outcomes Information System (PROMIS) Depression scale and rated their fear of palliative care using the Palliative Care Attitudes Scale (PCAS). We examined the hypothesized intercorrelations, followed by a bootstrapped analysis of indirect effects in the PROCESS macro for SPSS. **RESULTS:** Participants ranged from 26 to 93 years old (mean [M] = 60.40, standard deviation = 11.45). The most common diagnoses were prostate (34.1%), breast (23.3%), colorectal (17.5%), skin (15.3%), and lung (13.5%) cancer. As hypothesized, older participants had lower depression severity ($r = -0.20$, $p < 0.001$) and were less fearful of palliative care ($r = -0.11$, $p < 0.001$). Participants who were more depressed were more fearful of palliative care ($r = 0.21$, $p < 0.001$). An indirect effect ($\beta = -0.04$, standard error = .01, 95% confidence interval: -0.06 to -0.02) suggested that depression severity may account for up to 40% of age-associated differences in fear of palliative care. **CONCLUSIONS:** Findings indicate that older adults with cancer are more likely to favor palliative care, with depression symptom severity accounting for age-related differences. Targeted interventions among younger patients with depressive symptoms may be helpful to reduce fear and misunderstanding and increase utilization of palliative care.

[The natural product berberine synergizes with osimertinib preferentially against MET-amplified osimertinib-resistant lung cancer via direct MET inhibition](#) Pharmacol Res. 2021 Nov

24;175:105998. doi: 10.1016/j.phrs.2021.105998. Online ahead of print. Zhen Chen ¹, Karin A Vallega ¹, Haiying Chen ², Jia Zhou ², Suresh S Ramalingam ¹, Shi-Yong Sun ³

Berberine is a natural product that has long been used in traditional Chinese medicine due to its antimicrobial, anti-inflammatory and metabolism-regulatory properties. Osimertinib is the first third-generation EGFR-tyrosine kinase inhibitor (TKI) approved for the treatment of non-small cell lung cancer (NSCLC) with activating EGFR mutations and those resistant to earlier generation EGFR-TKIs due to a T790M mutation. However, emergence of acquired resistance to osimertinib limits its long-term efficacy in the clinic. One known mechanism of acquired resistance to osimertinib and other EGFR-TKIs is MET (c-MET) gene amplification. Here, we report that berberine, when combined with osimertinib, synergistically and selectively decreased the survival of several MET-amplified osimertinib-resistant EGFR mutant NSCLC cell lines with enhanced induction of apoptosis likely through Bim elevation and Mcl-1 reduction. Importantly, this combination effectively enhanced suppressive effect on the growth of MET-amplified osimertinib-resistant xenografts in nude mice and was well tolerated. Molecular modeling showed that berberine was able to bind to the kinase domain of non-phosphorylated MET, occupy the front of the binding pocket, and interact with the activation loop, in a similar way as other known MET inhibitors do. MET kinase assay showed clear concentration-dependent inhibitory effects of berberine against MET activity, confirming its kinase inhibitory activity. **These findings collectively suggest** that berberine can act as a naturally-existing MET inhibitor to synergize with osimertinib in overcoming osimertinib acquired resistance caused by MET amplification.

MISCELLANEOUS WORKS

[Promoting early diagnosis and recovering from the COVID-19 pandemic in lung cancer through public awareness campaigns: learning from patient and public insight work](#) BMJ Open Respir Res.

2021 Nov;8(1):e001120. doi: 10.1136/bmjresp-2021-001120. Matthew Evison ^{1 2}, Sarah Taylor ³, Seamus Grundy ⁴, Anna Perkins ⁵, Michael Peake ^{6 7}

COVID-19 has had a devastating impact on outcomes in lung cancer leading to later stage presentation, less curative treatment and higher mortality. This has amplified the existing problem of late-stage presentation in lung cancer and is a call to arms for a multifaceted strategy to address this, including public awareness campaigns to promote healthcare review in patients with persistent chest symptoms. We report the learning from patient and public insight work from across the North of England exploring the barriers to seeking healthcare review with persistent chest symptoms. Members of the public described how a lack of importance is placed on the common symptoms of lung cancer and a feeling of being unworthy of review by healthcare professionals. They would feel motivated to seek review by dispelling the nihilism of lung cancer and would be able to take action more easily by removing the logistical hassle in the process. We propose a four-pillar framework (validation-endorsement-motivation-action) for developing the content of any public awareness campaigns promoting early diagnosis of lung cancer based on the findings of this comprehensive insight work. All providers and commissioners must work together to overcome the perceived and real barriers to patients with persistent chest symptoms.

[Lung Cancer Risk among Patients with Asthma-Chronic Obstructive Pulmonary Disease Overlap](#)

Ann Am Thorac Soc. 2021 Nov;18(11):1894-1900. doi: 10.1513/AnnalsATS.202010-1280OC.

Antonios Charokopos ^{1 2}, Sidney S Braman ¹, Stacey A Whittaker Brown ¹, et al.

RATIONALE: Chronic obstructive pulmonary disease (COPD) is a well-established independent risk factor for lung cancer; however, the literature on the association between asthma and lung cancer is mixed. Whether asthma-COPD overlap (ACO) is associated with lung cancer has not been studied. Objectives: We aimed to compare lung cancer risk among patients with ACO versus COPD and other conditions associated with airway obstruction. **METHODS:** We studied 13,939 smokers from the National Lung Cancer Screening Trial who had baseline spirometry and used spirometric indices and history of childhood asthma to categorize participants into five specific airway disease subgroups. We used Poisson regression to compare unadjusted and adjusted lung cancer risk. **RESULTS:** The incidence rate of lung cancer per 1,000 person-years was as follows: ACO, 13.2 (95% confidence interval [CI], 8.1-21.5); COPD, 11.7 (95% CI, 10.5-13.1); asthmatic smokers, 1.8 (95% CI, 0.6-5.4); Global Initiative for Chronic Obstructive Lung Disease-Unclassified, 7.7 (95% CI, 6.4-9.2); and normal spirometry smokers, 4.1 (95% CI, 3.5-4.8). Patients with ACO had increased adjusted risk of lung cancer compared with patients with asthma (incidence rate ratio [IRR], 4.5; 95% CI, 1.3-15.8) and normal spirometry smokers (IRR, 2.3; 95% CI, 1.3-4.2) in models adjusting for other risk factors. Adjusted lung cancer incidence in patients with ACO and COPD were not found to be different (IRR, 1.2; 95% CI, 0.7-2.1). **CONCLUSIONS:** The risk of lung cancer among patients with ACO is similar to those with COPD and higher than other groups of smokers. These results provide further evidence that COPD, with or without a history of childhood asthma, is an independent risk factor for lung cancer.

[Health Disparities in Cancer Among American Indians and Alaska Natives](#) Acad Radiol. 2021 Nov 18;S1076-6332(21)00480-3. doi: 10.1016/j.acra.2021.10.011. Online ahead of print. Marilyn A Roubidoux ¹, Judith S Kaur ², Dorothy A Rhoades ³

American Indians and Alaska Natives (AI/AN) are underserved populations who suffer from several health disparities, 1 of which is cancer. Malignancies, especially cancers of the breast, liver, and lung, are common causes of death in this population. Health care disparities in this population include more limited access to diagnostic radiology because of geographic and/or health system limitations. Early detection of these cancers may be enabled by improving patient and physician access to medical imaging. Awareness by the radiology community of the cancer disparities among this population is needed to support research targeted to this specific ethnic group and to support outreach efforts to provide more imaging opportunities. Providing greater access to imaging facilities will also improve patient compliance with screening recommendations, ultimately improving mortality in these populations.

[Impact of Clinical Trial Participation on Survival of Patients with Metastatic Non-Small Cell Lung Cancer](#) Clin Lung Cancer. 2021 Nov;22(6):523-530. doi: 10.1016/j.clcc.2021.04.003. Epub 2021 Apr 22. Cristina M Merkhofer ¹, Keith D Eaton ², Renato G Martins ³, Scott D Ramsey ⁴, Bernardo H L Goulart ⁵

INTRODUCTION: The impact of clinical trial participation on overall survival is unclear. We hypothesized that enrollment in a therapeutic drug clinical trial is associated with longer overall survival in patients with metastatic non-small cell lung cancer (NSCLC). Patients and **METHODS:** We linked electronic medical record and Washington State cancer registry data to identify patients with metastatic NSCLC diagnosed between January 1, 2007, and December 31, 2015 who received treatment at a National Cancer Institute-designated cancer center. The exposure was trial enrollment. The primary outcome was overall survival, defined as the date of second-line treatment initiation to date of death or last follow-up. We used a conditional landmark analysis starting at the date of second-line treatment initiation and propensity scores with inverse probability of treatment weighting to estimate the association between trial enrollment and survival. **RESULTS:** Of 215 patients, 40 (19%) participated in a second-line trial. Trial participants were more likely to be never smokers (45% vs 27%), have a good performance status (88% vs 77%) and have EGFR (48% vs 14%) and ALK mutations (8% vs 5%) than

nonparticipants. Trial participants had similar overall survival to nonparticipants (HR 1.05; 95% CI, 0.72, 1.53; $p = 0.81$) after adjusting for sociodemographic and disease characteristics. **CONCLUSION:** Accounting for the immortal time bias and selection bias, trial participation does not appear detrimental to survival. This finding may be reassuring to patients and supports programs and policies to improve clinical trial access.

Predictors of Enrollment of Older Smokers in Six Smoking Cessation Trials in the Lung Cancer

Screening Setting: The Smoking Cessation at Lung Examination (SCALE) Collaboration Nicotine Tob Res. 2021 Nov 5;23(12):2037-2046. doi: 10.1093/ntr/ntab110. Ellie Eyestone 1 , Randi M Williams 1 , George Luta 2 , et al.

SIGNIFICANCE: Increased rates of smoking cessation will be essential to maximize the population benefit of low-dose CT screening for lung cancer. The NCI's Smoking Cessation at Lung Examination (SCALE) Collaboration includes eight randomized trials, each assessing evidence-based interventions among smokers undergoing lung cancer screening (LCS). We examined predictors of trial enrollment to improve future outreach efforts for cessation interventions offered to older smokers in this and other clinical settings. **METHODS:** We included the six SCALE trials that randomized individual participants. We assessed demographics, intervention modalities, LCS site and trial administration characteristics, and reasons for declining. **RESULTS:** Of 6285 trial- and LCS-eligible individuals, 3897 (62%) declined and 2388 (38%) enrolled. In multivariable logistic regression analyses, Blacks had higher enrollment rates (OR 1.5, 95% CI 1.2,1.8) compared to Whites. Compared to "NRT Only" trials, those approached for "NRT + prescription medication" trials had higher odds of enrollment (OR 6.1, 95% CI 4.7,7.9). Regarding enrollment methods, trials using "Phone + In Person" methods had higher odds of enrollment (OR 1.6, 95% CI 1.2,1.9) compared to trials using "Phone Only" methods. Some of the reasons for declining enrollment included "too busy" (36.6%), "not ready to quit" (8.2%), "not interested in research" (7.7%), and "not interested in the intervention offered" (6.2%). **CONCLUSION:** Enrolling smokers in cessation interventions in the LCS setting is a major priority that requires multiple enrollment and intervention modalities. Barriers to enrollment provide insights that can be addressed and applied to future cessation interventions to improve implementation in LCS and other clinical settings with older smokers. **IMPLICATIONS:** We explored enrollment rates and reasons for declining across six smoking cessation trials in the lung cancer screening setting. Offering multiple accrual methods and pharmacotherapy options predicted increased enrollment across trials. Enrollment rates were also greater among Blacks compared to Whites. The findings offer practical information for the implementation of cessation trials and interventions in the lung cancer screening context and other clinical settings, regarding intervention modalities that may be most appealing to older, long-term smokers.

A Potential Serum Biomarker for Screening Lung Cancer Risk in High Level Environmental

Radon Areas: A Pilot Study Life (Basel). 2021 Nov 21;11(11):1273. doi: 10.3390/life11111273.

Narongchai Autsavapornporn 1 , Pitchayaponne Klunklin 1 , Imjai Chitapanarux 1 , et al.

Radon is a major cause of lung cancer (LC) deaths among non-smokers worldwide. However, no serum biomarker for screening of LC risk in high residential radon (HRR) areas is available. Therefore, the aim of this study was to determine diagnostic values of serum carcinoembryonic antigen (CEA), cytokeratin 19 fragment (Cyfra21-1), human epididymis protein 4 (HE4), interleukin 8 (IL-8), migration inhibitory factor (MIF), tumor nuclear factor-alpha (TNF- α) and vascular endothelial growth factors (VEGF) occurring in high radon areas. Seventy-five LC non-smoker patients and seventy-five healthy controls (HC) were enrolled in this study. Among the HC groups, twenty-five HC were low residential radon (LRR) and fifty HC were HRR. Significantly higher ($p < 0.0004$) serum levels of CEA, Cyfra21-1, IL-8 and VEGF were found in the LC compared with the LRR and HRR groups. More importantly, significantly higher levels ($p < 0.009$) of serum CEA, Cyfra21-1 and IL-8 were observed in HRR

compared with the LRR group. Likewise, a ROC curve demonstrated that serum CEA and Cyfra21-1 could better distinguish LC risk from HRR groups than IL-8. These results indicated that serum CEA and Cyfra21-1 were significantly increased in the HRR group and may be considered as potential biomarkers for individuals at high-risk to develop LC.

[Using Patient-Generated Health Data From Twitter to Identify, Engage, and Recruit Cancer Survivors in Clinical Trials in Los Angeles County: Evaluation of a Feasibility Study](#) JMIR Form

Res. 2021 Nov 26;5(11):e29958. doi: 10.2196/29958. Katja Reuter ^{1 2}, Praveen Angyan ², NamQuyen Le ³, Thomas A Buchanan ^{2 4}

BACKGROUND: Failure to find and attract clinical trial participants remains a persistent barrier to clinical research. Researchers increasingly complement recruitment methods with social media-based methods. We hypothesized that user-generated data from cancer survivors and their family members and friends on the social network Twitter could be used to identify, engage, and recruit cancer survivors for cancer trials. **OBJECTIVE:** This pilot study aims to examine the feasibility of using user-reported health data from cancer survivors and family members and friends on Twitter in Los Angeles (LA) County to enhance clinical trial recruitment. We focus on 6 cancer conditions (breast cancer, colon cancer, kidney cancer, lymphoma, lung cancer, and prostate cancer). **METHODS:** The social media intervention involved monitoring cancer-specific posts about the 6 cancer conditions by Twitter users in LA County to identify cancer survivors and their family members and friends and contacting eligible Twitter users with information about open cancer trials at the University of Southern California (USC) Norris Comprehensive Cancer Center. We reviewed both retrospective and prospective data published by Twitter users in LA County between July 28, 2017, and November 29, 2018. The study enrolled 124 open clinical trials at USC Norris. We used descriptive statistics to report the proportion of Twitter users who were identified, engaged, and enrolled. **RESULTS:** We analyzed 107,424 Twitter posts in English by 25,032 unique Twitter users in LA County for the 6 cancer conditions. We identified and contacted 1.73% (434/25,032) of eligible Twitter users (127/434, 29.3% cancer survivors; 305/434, 70.3% family members and friends; and 2/434, 0.5% Twitter users were excluded). Of them, 51.4% (223/434) were female and approximately one-third were male. About one-fifth were people of color, whereas most of them were White. Approximately one-fifth (85/434, 19.6%) engaged with the outreach messages (cancer survivors: 33/85, 38% and family members and friends: 52/85, 61%). Of those who engaged with the messages, one-fourth were male, the majority were female, and approximately one-fifth were people of color, whereas the majority were White. Approximately 12% (10/85) of the contacted users requested more information and 40% (4/10) set up a prescreening. Two eligible candidates were transferred to USC Norris for further screening, but neither was enrolled. **CONCLUSIONS:** Our findings demonstrate the potential of identifying and engaging cancer survivors and their family members and friends on Twitter. Optimization of downstream recruitment efforts such as screening for digital populations on social media may be required. Future research could test the feasibility of the approach for other diseases, locations, languages, social media platforms, and types of research involvement (eg, survey research). Computer science methods could help to scale up the analysis of larger data sets to support more rigorous testing of the intervention.

[Disparities and trends in the participation of minorities, women, and the elderly in breast, colorectal, lung, and prostate cancer clinical trials](#) Cancer. 2021 Nov 22. doi: 10.1002/cncr.33991.

Online ahead of print. Juan Javier-DesLoges ¹, Tyler J Nelson ², James D Murphy ², et al.

BACKGROUND: This study was done to determine the representation of minorities, women, and the elderly in National Cancer Institute (NCI) clinical trials. **METHODS:** This is an analysis in the NCI Clinical Data Update System. Patients were evaluated in breast, colorectal, lung, and prostate cancer trials from 2000 to 2019. Representation in a trial was determined by race/ethnicity, sex, and age. Secondly,

the change in trial participation by multivariable analysis by comparing years 2000 through 2004 to 2015 through 2019 was evaluated. **RESULTS:** The cohort included 242,720 participants: 197,320 Non-Hispanic White (81.3%), 21,190 Black (8.7%), 11,587 Hispanic (4.8%), and 6880 Asian/Pacific Islander (2.8%). Black and Hispanic patients were underrepresented for colorectal (odds ratio [OR], 0.58; 95% confidence interval [CI], 0.50-0.67; $P < .001$ and OR, 0.74; 95% CI, 0.64-0.87; $P < .001$, respectively), lung (OR, 0.83; 95% CI, 0.76-0.91; $P < .001$ and 0.66; 95% CI, 0.57-0.77; $P < .001$, respectively), and prostate cancer trials (OR, 0.85; 95% CI, 0.79-0.92; $P < .001$ and OR, 0.58; 95% CI, 0.51-0.66; $P < .001$) between 2015 and 2019. The odds of participation in 2015 to 2019 increased among Black patients in breast (OR, 2.19; 95% CI, 2.07-2.32; $P < .001$), lung (OR, 1.54; 95% CI, 1.38-1.73; $P < .001$), and prostate cancer trials (OR, 1.14; 95% CI, 1.04-1.26; $P < .001$). The odds of participation in a trial among Hispanic patients increased for breast (OR, 3.32; 95% CI, 3.09-3.56; $P < .001$), colorectal (OR, 2.46; 95% CI, 2.04-2.96; $P < .001$), lung (OR, 3.88; 95% CI, 3.20-4.69; $P < .001$), and prostate cancer (OR, 1.70; 95% CI, 1.42-2.04; $P = .005$). **CONCLUSIONS:** This study identified that Black and Hispanic patients remain underrepresented in trials, but in recent years, participation has increased. These findings indicate that minority participation has increased over time, but further efforts are needed.

[Immune checkpoint inhibitor therapy for malignant pleural mesothelioma](#) Lung Cancer. 2021 Nov 16;162:162-168. doi: 10.1016/j.lungcan.2021.11.006. Online ahead of print. Anna K Nowak 1 , Wee Loong Chin 2 , Synat Keam 3 , Alistair Cook 4

Mesothelioma is a rare and universally fatal cancer linked to exposure to asbestos. Until recently, standard of care treatment was chemotherapy; a treatment resulting in a minimal survival extension, and not improved upon for almost twenty years. However, the advent of cancer immunotherapy - and in particular the immune checkpoint inhibitor class of drugs - has resulted in recently approved new treatment options, with more currently under investigation. Here, we review clinical trials of both single agent and combination checkpoint inhibitors in mesothelioma, plus studies investigating their combination with chemotherapy. We also describe current advances in biomarker identification regarding prediction of patient response to checkpoint inhibitors. Finally, we assess the probable future direction of the field; including where current and developing technologies are likely to lead - in terms of both biomarker discovery and treatment options.

[The need to study rural cancer outcome disparities at the local level: a retrospective cohort study in Kansas and Missouri](#) BMC Public Health. 2021 Nov 24;21(1):2154. doi: 10.1186/s12889-021-12190-w. Jeffrey A Thompson 1 2 , Lynn Chollet-Hinton 3 4 , John Keighley 3 , Audrey Chang 5 , Dinesh Pal Mudaranthakam 3 4 , David Streeter 3 4 , Jinxiang Hu 3 4 , Michele Park 4 , Byron Gajewski 3 4

BACKGROUND: Rural residence is commonly thought to be a risk factor for poor cancer outcomes. However, a number of studies have reported seemingly conflicting information regarding cancer outcome disparities with respect to rural residence, with some suggesting that the disparity is not present and others providing inconsistent evidence that either urban or rural residence is associated with poorer outcomes.

We suggest a simple explanation for these seeming contradictions: namely that rural cancer outcome disparities are related to factors that occur differentially at a local level, such as environmental exposures, lack of access to care or screening, and socioeconomic factors, which differ by type of cancer.

METHODS: We conducted a retrospective cohort study examining ten cancers treated at the University of Kansas Medical Center from 2011 to 2018, with individuals from either rural or urban residences. We defined urban residences as those in a county with a U.S. Department of Agriculture Urban Influence Code (UIC) of 1 or 2, with all other residences defines a rural. Inverse probability of treatment weighting was used to create a pseudo-sample balanced for covariates deemed likely to affect the outcomes modeled with cumulative link and weighted Cox-proportional hazards models. **RESULTS:** We found that rural residence is not a simple risk factor but rather appears to play a complex role in cancer outcome

disparities. Specifically, rural residence is associated with higher stage at diagnosis and increased survival hazards for colon cancer but decreased risk for lung cancer compared to urban residence.

CONCLUSION: Many cancers are affected by unique social and environmental factors that may vary between rural and urban residents, such as access to care, diet, and lifestyle. Our results show that rurality can increase or decrease risk, depending on cancer site, which suggests the need to consider the factors connected to rurality that influence this complex pattern. Thus, we argue that such disparities must be studied at the local level to identify and design appropriate interventions to improve cancer outcomes.

Internalized stigma among cancer patients enrolled in a smoking cessation trial: The role of cancer type and associations with psychological distress Psychooncology. 2021 Nov 19. doi:

10.1002/pon.5859. Online ahead of print. Erica T Warner¹, Elyse R Park^{2 3 4}, Christina M Luberto^{2 3}, Julia Rabin^{3 4}, Giselle K Perez^{2 3 4}, Jamie S Ostroff⁵

PURPOSE: Cancer patients who smoke may experience significant stigma due both to their disease, and negative attitudes and beliefs regarding smoking. We investigated whether internalized stigma differed between currently smoking cancer patients diagnosed with lung or head and neck cancers, other smoking-related cancers, and non smoking-related cancers, and whether internalized stigma was associated with psychological distress. **METHODS:** This cross-sectional analysis used baseline data on 293 participants enrolled in a multi-site randomized smoking cessation intervention trial of patients with recently diagnosed cancer. Internalized stigma was assessed using five Internalized Shame items from the Social Impact of Disease Scale. Smoking-related cancers included lung, head and neck, esophageal, bladder, kidney, liver, pancreatic, colorectal, anal, small intestinal, gastric, and cervical. We used multivariable linear regression to examine whether mean internalized stigma levels differed between individuals with lung and head and neck cancers, other smoking-related cancers, and non smoking-related cancers, adjusting for potential confounders. We further examined the association of internalized stigma with depression, anxiety, and perceived stress, overall and among cancer type groups. **RESULTS:** Thirty-nine percent of participants were diagnosed with lung or head and neck cancer, 21% with another smoking-related cancer, and 40% with a non smoking-related cancer. In multivariable-adjusted models, participants with lung or head and neck cancers (11.6, 95% confidence intervals (CI) = 10.8-12.2; $p < 0.0001$) or other smoking-related cancers (10.7, 95% CI = 9.8-11.7; $p = 0.03$) had higher mean internalized stigma scores compared to those non-smoking-related cancers (9.3, 95% CI = 8.6-10.0). We observed similar positive associations between internalized stigma and depressive symptoms, anxiety, and perceived stress among participants with smoking-related and non smoking-related cancers. **CONCLUSIONS:** Among smokers, those with smoking-related cancers experienced the highest levels of internalized stigma, and greater internalized stigma was associated with greater psychological distress across cancer types. Providers should assess patients for internalized and other forms of stigma, refer patients for appropriate psychosocial support services, and address stigma in smoking cessation programs.

Racial and Ethnic Disparities Among Participants in Precision Oncology Clinical Studies JAMA Netw Open. 2021 Nov 1;4(11):e2133205. doi: 10.1001/jamanetworkopen.2021.33205.

Christopher M Aldrighetti¹, Andrzej Niemierko¹, Eliezer Van Allen^{2 3 4}, Henning Willers¹, Sophia C Kamran^{1 3}

IMPORTANCE: Precision oncology is revolutionizing cancer care, allowing for personalized treatments to improve outcomes. Cancer research has benefitted from well-designed studies incorporating precision medicine objectives, but it is unclear if these studies are representative of the diverse cancer population.

OBJECTIVE: To evaluate racial and ethnic representation in breast, prostate, lung, and colorectal cancer studies incorporating precision oncology objectives in the Clinicaltrials.gov registry and compare with the incidence of these cancer types in racial and ethnic minority groups in the US population. **DESIGN, SETTING, AND PARTICIPANTS:** This cross-sectional study identified US-based breast, prostate,

lung, and colorectal cancer studies incorporating precision oncology objectives for reporting of race and ethnicity. The Surveillance, Epidemiology, and End Results and US Census databases were used to determine cancer incidence by race and ethnicity, linked with cancer type and median year of enrollment for each trial. Data were collected and analyzed between December 2020 and April 2021. **MAIN OUTCOMES AND MEASURES:** The expected number of participants per study by each racial and ethnic group was calculated based on the corresponding US-based proportion. Under- and overrepresentation was defined as the ratio of the actual number of enrolled cases to the expected number of cases for each trial by cancer type. Ratios above 1 indicated overrepresentation while a ratio below 1 indicated underrepresentation. Random-effects meta-analysis of representation ratios of individual trials was performed to weigh each individual study. **RESULTS:** Of 93 studies encompassing 5867 enrollees with race and ethnicity data; 4826 participants (82.3%) were non-Hispanic White, 587 (10.0%) were Black, and 238 (4.1%) were Asian. Per observed-to-expected ratios, White participants were overrepresented in all studies, with a ratio of 1.35 (95% CI, 1.30-1.37), as well as Asian participants, with a ratio of 1.46 (95% CI, 1.28-1.66), while Black participants (ratio, 0.49; 95% CI, 0.45-0.54), Hispanic participants (ratio, 0.24; 95% CI, 0.20-0.28), and American Indian and Alaskan Native participants (ratio, 0.43; 95% CI, 0.24-0.78) were underrepresented. By individual cancer site, White participants were consistently overrepresented in all studies, while Black and Hispanic participants were underrepresented. **ONCLUSIONS AND RELEVANCE:** THIS analysis found that precision oncology studies for breast, lung, prostate, and colorectal cancers vastly underrepresent racial and ethnic minority populations relative to their cancer incidence in the US population. It is imperative to increase diversity among enrollees so that all individuals may benefit from cancer research breakthroughs and personalized treatments.

[Twenty-Year Reflection on the Impact of World Trade Center Exposure on Pulmonary Outcomes in Fire Department of the City of New York \(FDNY\) Rescue and Recovery Workers](#) Lung. 2021

Dec;199(6):569-578. doi: 10.1007/s00408-021-00493-z. Epub 2021 Nov 11. Krystal L Clevlen 1 , Carla Rosenzvit 2 , Anna Nolan 3 4 5 , Rachel Zeig-Owens 2 3 6 , Sophia Kwon 4 , Michael D Weiden 3 4 5 , Molly Skerker 2 3 , Allison Halpren 3 , David J Prezant 2 3 6

After the terrorist attacks on September 11, 2001 (9/11), many rescue/recovery workers developed respiratory symptoms and pulmonary diseases due to their extensive World Trade Center (WTC) dust cloud exposure. Nearly all Fire Department of the City of New York (FDNY) workers were present within 48 h of 9/11 and for the next several months. Since the FDNY had a well-established occupational health service for its firefighters and Emergency Medical Services workers prior to 9/11, the FDNY was able to immediately start a rigorous monitoring and treatment program for its WTC-exposed workers. As a result, respiratory symptoms and diseases were identified soon after 9/11. This focused review summarizes the WTC-related respiratory diseases that developed in the FDNY cohort after 9/11, including WTC cough syndrome, obstructive airways disease, accelerated lung function decline, airway hyperreactivity, sarcoidosis, and obstructive sleep apnea. Additionally, an extensive array of biomarkers has been identified as associated with WTC-related respiratory disease. Future research efforts will not only focus on further phenotyping/treating WTC-related respiratory disease but also on additional diseases associated with WTC exposure, especially those that take decades to develop, such as cardiovascular disease, cancer, and interstitial lung disease.