



Caring Ambassadors Lung Cancer Program

Literature Review, May 2019

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BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Diosmetin induces apoptosis and enhances the chemotherapeutic efficacy of paclitaxel in non-small cell lung cancer cells via Nrf2 inhibition.](#) Chen X1,2,3, Wu Q1,2,3, Chen Y1,2,3, et al. Br J Pharmacol. 2019 Jun;176(12):2079-2094. doi: 10.1111/bph.14652. Epub 2019 May 11.

BACKGROUND AND PURPOSE: Non-small-cell lung cancer (NSCLC) accounts for up to 80-85% of all lung cancers and has a disappointing prognosis. Flavonoids exert anticancer properties, mostly involving stimulation of ROS production without significant toxicity to normal cells. This study was aimed to delineate the effect of diosmetin, a natural flavonoid, on NSCLC cells and its ability to enhance the antitumour activity of paclitaxel. **EXPERIMENTAL APPROACH:** NSCLC cells, normal cell lines HLF-1 and BEAS-2B, and immunodeficient mice were chosen as models to study the effects of diosmetin. Changes in cell viability, apoptosis, and ROS were analysed by MTT assay, flow cytometry assay, and fluorescent probe DCFH-DA. Expression of proteins and mRNA was determined by Western blotting and real-time RT-PCR. Growth of xenografted tumours was measured. Spleens and other vital organs were analysed with histological and immunohistochemical techniques. **KEY RESULTS:** Diosmetin induced selective apoptotic death in NSCLC cells but spared normal cells, via ROS accumulation. Diosmetin induced ROS production in NSCLC cells probably via reducing Nrf2 stability through disruption of the PI3K/Akt/GSK-3 β pathway. The in vitro and in vivo xenograft studies showed that combined treatment of diosmetin and paclitaxel synergistically suppressed NSCLC cells. Histological analysis of vital organs showed no obvious toxicity of diosmetin, which matched our in vitro findings. **CONCLUSIONS AND IMPLICATIONS:** Diosmetin selectively induced apoptosis and enhanced the efficacy of paclitaxel in NSCLC cells via ROS accumulation through disruption of the PI3K/Akt/GSK-3 β /Nrf2 pathway. Therefore, diosmetin may be a promising candidate for adjuvant treatment of NSCLC.

[High developmental pluripotency-associated 4 expression promotes cell proliferation and glycolysis, and predicts poor prognosis in non-small-cell lung cancer.](#) Li L1, Wang Y2, Wang Q3, et al. Mol Med Rep. 2019 May 22. doi: 10.3892/mmr.2019.10272. [Epub ahead of print]

The developmental pluripotency-associated 4 (Dppa4) gene serves critical roles in cell self-renewal, as well as in cancer development and progression. However, the regulatory role of Dppa4 in non-small-cell

lung cancer (NSCLC) and its underlying mechanisms remain elusive. The aim of the present study was to investigate the biological function of Dppa4 in NSCLC and its underlying mechanism of action. Dppa4 expression was measured in NSCLC tissue samples and cell lines, and its effect on cell proliferation and the expression of glycolytic enzymes was determined. In addition, the underlying mechanisms of Dppa4-induced alterations in glycolysis were analyzed. Univariate and multivariate analyses were also performed to analyze the prognostic significance of clinicopathological characteristics. Dppa4 was found to be highly expressed in NSCLC tissues and cell lines. Furthermore, it was observed that Dppa4 was correlated with the degree of tumor differentiation and TNM stage. Univariate and multivariate analyses identified Dppa4 expression and clinical stage as prognostic factors for NSCLC patients. Kaplan-Meier analysis further revealed that patients with lower Dppa4 expression exhibited a better prognosis. In NSCLC cells, Dppa4 knockdown inhibited cell proliferation, while Dppa4 overexpression enhanced cell proliferation, which was likely mediated by glycolysis promotion. Dppa4 knockdown had no evident effect on the majority of enzymes examined; however, glucose transporter type 4 (GLUT-4) and pyruvate kinase isozyme M2 were significantly upregulated, and hexokinase II (HK-II) and lactate dehydrogenase B (LDHB) were downregulated following Dppa4 knockdown. By contrast, Dppa4 overexpression resulted in downregulation of GLUT-4, and upregulation of HK-II, enolase and LDHB, whereas it had no effect on other enzymes. Since the most evident effect was observed on LDHB, further functional experiments demonstrated that this enzyme reversed the promoting effects of Dppa4 in NSCLC. In conclusion, Dppa4 promotes NSCLC progression, partly through glycolysis by LDHB. Thus, the Dppa4-LDHB axis critically contributes to glycolysis in NSCLC cells, thereby promoting NSCLC development and progression.

[Subcellular compartmentalization of PKM2 identifies anti-PKM2 therapy response in vitro and in vivo mouse model of human non-small-cell lung cancer.](#) Suzuki A1, Puri S2, Leland P1, Puri A1, Moudgil T2, Fox BA2,3, Puri RK1, Joshi BH1. PLoS One. 2019 May 23;14(5):e0217131. doi: 10.1371/journal.pone.0217131. eCollection 2019.

Pyruvate kinase M2 (PKM2) is an alternatively spliced variant, which mediates the conversion of glucose to lactate in cancer cells under normoxic conditions, known as the Warburg effect. Previously, we demonstrated that PKM2 is one of 97 genes that are overexpressed in non-small-cell lung cancer (NSCLC) cell lines. Herein, we demonstrate a novel role of subcellular PKM2 expression as a biomarker of therapeutic response after targeting this gene by shRNA or small molecule inhibitor (SMI) of PKM2 enzyme activity in vitro and in vivo. We examined two established lung cancer cell lines, nine patients derived NSCLC and three normal lung fibroblast cell lines for PKM2 mRNA, protein and enzyme activity by RT-qPCR, immunocytochemistry (ICC), and Western blot analysis. All eleven NSCLC cell lines showed upregulated PKM2 enzymatic activity and protein expression mainly in their cytoplasm. Targeting PKM2 by shRNA or SMI, NSCLC cells showed significantly reduced mRNA, enzyme activity, cell viability, and colony formation, which also downregulated cytosolic PKM2 and upregulated nuclear enzyme activities. Normal lung fibroblast cell lines did not express PKM2, which served as negative controls. PKM2 targeting by SMI slowed tumor growth while gene-silencing significantly reduced growth of human NSCLC xenografts. Tumor sections from responding mice showed >70% reduction in cytoplasmic PKM2 with low or undetectable nuclear staining by immunohistochemistry (IHC). In sharp contrast, non-responding tumors showed a >38% increase in PKM2 nuclear staining with low or undetectable cytoplasmic staining. In conclusion, these results confirmed PKM2 as a target for cancer therapy and an unique function of subcellular PKM2, which may characterize therapeutic response to anti-PKM2 therapy in NSCLC.

[The effect of mouse strain, sex and carcinogen dose on toxicity and the development of lung dysplasia and squamous cell carcinomas in mice.](#) Riobos L1, Gad EA2, Treuting PM3, et al. Cancer

Prev Res (Phila). 2019 May 17. pii: canprevres.0442.2018. doi: 10.1158/1940-6207.CAPR-18-0442. [Epub ahead of print]

In order to translate new treatments to the clinic, it is necessary to use animal models that closely recapitulate human disease. Lung cancer develops after extended exposure to carcinogens. It has one of the highest mutation rates of all cancer and is highly heterogenic. Topical treatment with N-nitrosotris-(2-chloroethyl) urea (NTCU) induces lung squamous cell carcinoma (SCC) with nonsynonymous mutation rates similar to those reported for human non-small cell lung cancer. However, NTCU induces lung cancer with variable efficacy and toxicity depending on the mouse strain. A detailed characterization of the NTCU model is needed. We have compared the effect of three different NTCU doses (20, 30 and 40 mM) in female and male of NIH Swiss, Black Swiss and FVB mice on tumor incidence, survival and toxicity. The main findings in this study are: (1) NIH Swiss mice present with a higher incidence of SCC and lower mortality compared with Black Swiss and FVB mice; (2) 30 mM NTCU dose induces SCC at the same rate and incidence as the 40 mM dose with lower mortality; (3) female mice present higher grade and incidence of pre-invasive lesions and SCC compared with males; (4) NTCU induced transformation is principally within the respiratory system; and (5) NTCU treatment does not impact the ability to elicit a specific adaptive immune response. This study provides a reference point for experimental designs to evaluate either preventive or therapeutic treatments for lung SCC, including immunotherapies, before initiating human clinical trials.

SCREENING, BIOMARKER TESTING, DIAGNOSIS AND STAGING

[Safety and Success of Repeat Lung Needle Biopsies in Patients with Epidermal Growth Factor Receptor-Mutant Lung Cancer.](#)

Fintelmann FJ1, Troschel FM2, Kuklinski MW2, et al. Oncologist. 2019 May 31. pii: theoncologist.2019-0158. doi: 10.1634/theoncologist.2019-0158. [Epub ahead of print]

BACKGROUND: Postprogression repeat biopsies are critical in caring for patients with lung cancer with epidermal growth factor receptor (EGFR) mutations. However, hesitation about invasive procedures persists. We assessed safety and tissue adequacy for molecular profiling among repeat postprogression percutaneous transthoracic needle aspirations and biopsies (rebiopsies). **MATERIALS AND**

METHODS: All lung biopsies performed at our hospital from 2009 to 2017 were reviewed.

Complications were classified by Society of Interventional Radiology criteria. Complication rates between rebiopsies in EGFR-mutants and all other lung biopsies (controls) were compared using Fisher's exact test. Success of molecular profiling was recorded. **RESULTS:** During the study period, nine thoracic radiologists performed 107 rebiopsies in 75 EGFR-mutant patients and 2,635 lung biopsies in 2,347 patients for other indications. All biopsies were performed with computed tomography guidance, coaxial technique, and rapid on-site pathologic evaluation (ROSE). The default procedure was to take 22-gauge fine-needle aspirates (FNA) followed by 20-gauge tissue cores. Minor complications occurred in 9 (8.4%) rebiopsies and 503 (19.1%; $p = .004$) controls, including pneumothoraces not requiring chest tube placement (4 [3.7%] vs. 426 [16.2%] in rebiopsies and controls, respectively; $p < .001$). The only major complication was pneumothorax requiring chest tube placement, occurring in zero rebiopsies and 38 (1.4%; $p = .4$) controls. Molecular profiling was requested in 96 (90%) rebiopsies and successful in 92/96 (96%). **CONCLUSION:** At our center, repeat lung biopsies for postprogression molecular profiling of EGFR-mutant lung cancers result in fewer complications than typical lung biopsies. Coaxial technique, FNA, ROSE, and multiple 20-gauge tissue cores result in excellent specimen adequacy.

IMPLICATIONS FOR PRACTICE: Repeat percutaneous transthoracic needle aspirations and biopsies for postprogression molecular profiling of epidermal growth factor receptor (EGFR)-mutant lung cancer are safe in everyday clinical practice. Coaxial technique, fine-needle aspirates, rapid on-site pathologic evaluation, and multiple 20-gauge tissue cores result in excellent specimen adequacy. Although liquid biopsies are increasingly used, their sensitivity for analysis of resistant EGFR-mutant lung cancers

remains limited. Tissue biopsies remain important in this context, especially because osimertinib is now in the frontline setting and T790M is no longer the major finding of interest on molecular profiling.

Determining malignancy in CT guided fine needle aspirate biopsy of subsolid lung nodules: Is core biopsy necessary? Kiranantawat N1, McDermott S1, Petranovic M1, et al. Eur J Radiol Open. 2019 May 4;6:175-181. doi: 10.1016/j.ejro.2019.04.006. eCollection 2019.

PURPOSE: To assess the success of determining malignancy in subsolid lung nodules by fine needle aspirate of CT-guided transthoracic needle biopsy. **MATERIAL AND METHOD:** This IRB approved retrospective study analyzed CTguided transthoracic needle biopsy of 86 consecutive subsolid nodules (size 25 + 14 mm; Age 71 + 10 years: M: F, 27:59), with ground glass opacity of = 50% in 64 (74%) and size < 2 cm in 38 (44%). Fine needle aspirate was performed in all and additional core biopsy in 21 (24%). The biopsy results were correlated with resected surgical pathology in 59 (69%) and by long term clinical and imaging follow-up in 27 (31%). The statistical analysis was performed by Fischer exact test to determine the success rate in < 2cm and =2cm nodules and those with <50% and =50% ground glass opacity. **RESULTS:** The technical success of performing the biopsy was 94.7%. The sensitivity for making a diagnosis of malignancy in small and large subsolid nodules was 88.6 and 95.6% (p=>0.05), with a specificity 100% in both groups. Core biopsy altered the diagnosis only in 1/21 (4.8%). The nondiagnostic biopsy rate was 18 and 11% for lesions with =50% and <50% ground glass opacity (p=>0.05). The incidence of pneumothorax was 21%, none requiring chest tube, and mild hemoptysis in 8%. **CONCLUSION:** CT-guided transthoracic needle biopsy of both small and large subsolid nodules is highly sensitive and very specific for making the diagnosis of malignancy with a low rate of complications. Additional core biopsy offered no significant advantage over fine needle aspirate biopsy alone.

Biomarker Testing for Patients With Advanced Non-Small Cell Lung Cancer: Real-World Issues and Tough Choices. Pennell NA1, Arcila ME2, Gandara DR3, West H4. Am Soc Clin Oncol Educ Book. 2019 Jan;39:531-542. doi: 10.1200/EDBK_237863. Epub 2019 May 17.

Over the last decade, the treatment of patients with advanced non-small cell lung cancer (NSCLC) has become reliant on tissue and/or blood biomarkers to help guide treatment decisions. There are now multiple biomarker-defined patient subgroups, with evidence showing that treatment with targeted therapies has superior clinical outcomes when compared with traditional cytotoxic chemotherapy. However, rapid change in the field of precision oncology brings with it the challenge of translating recommendations into clinical practice. In this review, we discuss the major guidelines recommending biomarker testing in NSCLC, as well the logistical challenges to applying these guidelines to patients with NSCLC both in the United States and worldwide. The techniques commonly used for biomarker testing will be discussed, both for tissue- and blood-based biomarkers. Finally, we discuss the challenge of interpreting the results of biomarker testing and using these results to guide treatment decisions.

Investigation of Low-Dose CT Lung Cancer Screening Scan "Over-Range" Issue Using Machine Learning Methods. Huo D1, Kiehn M2, Scherzinger A3. J Digit Imaging. 2019 May 17. doi: 10.1007/s10278-019-00233-z. [Epub ahead of print]

Low-dose computed tomography (CT) lung cancer screening is recommended by the US Preventive Services Task Force for high lung cancer-risk populations. In this study, we investigated an important factor affecting the CT dose-the scan length, for this CT exam. A neural network model based on the "UNET" framework was established to segment the lung region in the CT scout images. It was trained initially with 247 chest X-ray images and then with 40 CT scout images. The mean Intersection over Union (IOU) and Dice coefficient were reported to be 0.954 and 0.976, respectively. Lung scan boundaries were determined from this segmentation and compared with the boundaries marked by an

expert for 150 validation images, resulting an average 4.7% difference. Seven hundred seventy CT low-dose lung screening exams were retrospectively analyzed with the validated model. The average "desired" scan length was 252 mm with a standard deviation of 28 mm. The average "over-range" was 58.5 mm or 24%. The upper boundary (superior) on average had an "over-range" of 17 mm, and the lower boundary (inferior) on average had an "over-range" of 41 mm. Further analysis of this data showed that the extent of "over-range" was independent of acquisition date, acquisition time, acquisition station, and patient age, but dependent on technologist and patient weight. We concluded that this machine learning method could effectively support quality control on the scan length for CT low-dose screening scans, enabling the eliminations of unnecessary patient dose.

Effectiveness of Lung Cancer Screening Implementation in the Community Setting in the United States. Copeland A1, Criswell A1, Ciupek A1, King JC1. J Oncol Pract. 2019 May 31;JOP1800788. doi: 10.1200/JOP.18.00788. [Epub ahead of print]

PURPOSE: The National Lung Screening Trial demonstrated a 20% relative reduction in lung cancer mortality with low-dose computed tomography screening, leading to implementation of lung cancer screening across the United States. The Centers for Medicare and Medicaid Services approved coverage, but questions remained about effectiveness of community-based screening. To assess screening implementation during the first full year of CMS coverage, we surveyed a nationwide network of lung cancer screening centers, comparing results from academic and nonacademic centers. **METHODS:** One hundred sixty-five lung cancer screening centers that have been designated Screening Centers of Excellence responded to a survey about their 2016 program data and practices. The survey included 21 pretested, closed- and open-ended quantitative and qualitative questions covering implementation, workflow, numbers of screening tests completed, and cancers diagnosed. **RESULTS:** Centers were predominantly community based (62%), with broad geographic distribution. In both community and academic centers, more than half of lung cancers were diagnosed at stage I or limited stage, demonstrating a clear stage shift compared with historical data. Lung-RADS results were also comparable. There are wide variations in the ways centers address Centers for Medicare and Medicaid Services requirements. The most significant barriers to screening implementation were insurance and billing issues, lack of provider referral, lack of patient awareness, and internal workflow challenges. **CONCLUSION:** These data validate that responsible screening can take place in a community setting and that lung cancers detected by low-dose computed tomography screening are often diagnosed at an early, more treatable stage. Lung cancer screening programs have developed different ways to address requirements, but many implementation challenges remain.

Assessing Eligibility for Lung Cancer Screening Among Women Undergoing Screening Mammography: Cross-Sectional Survey Results From the National Health Interview Survey. López D1, Flores EJ2, Miles RC2, Wang G2, Glover M 4th3, Shepard JA2, Lehman CD2, Narayan AK4. J Am Coll Radiol. 2019 May 8. pii: S1546-1440(19)30439-9. doi: 10.1016/j.jacr.2019.04.006. [Epub ahead of print]

PURPOSE: Millions of women undergo mammography screening each year, presenting an opportunity for radiologists to identify women eligible for lung cancer screening with low-dose chest CT (LCS) and smoking cessation counseling. The purpose of our study was to estimate the proportion of women eligible for LCS and tobacco cessation counseling among women reporting mammography screening within the previous 2 years using nationally representative cross-sectional survey data. **METHODS:** Women between the ages of 55 and 74 years in the 2015 National Health Interview Survey without history of lung or breast cancer who reported mammography use in the previous 2 years were included. The primary outcome was the weighted proportion of women eligible for LCS. Secondary outcomes included self-reported receipt of LCS and current smoking. Bivariate and multiple variable logistic regression analyses

were performed to evaluate the association between primary and secondary outcomes and sociodemographics, accounting for complex survey design elements. **RESULTS:** Among 3,806 women meeting inclusion criteria, 7.1% were eligible for LCS and 9.8% were current smokers. Multivariable analyses demonstrated that LCS-eligible women were more likely to be white, younger, and non-college-educated and have lower household incomes (all $P < .001$). Among all LCS-eligible women, 58% reported undergoing mammography screening within the previous 2 years. Among LCS-eligible women who underwent screening mammography, 7.9% reported undergoing LCS. **CONCLUSIONS:** The majority of LCS-eligible women received mammography screening but did not receive LCS. Mammography encounters may represent prime opportunities to increase LCS participation among patients already receiving imaging-based screening services.

Diagnostic Performance of Radial Probe Endobronchial Ultrasound without a Guide-Sheath and the Feasibility of Molecular Analysis. Moon SM1, Choe J1, Jeong BH1, Um SW1, Kim H1, Kwon OJ1, Lee K2. *Tuberc Respir Dis (Seoul)*. 2019 May 31. doi: 10.4046/trd.2018.0082. [Epub ahead of print] **BACKGROUND:** Radial probe endobronchial ultrasound (R-EBUS), is effective for tissue diagnosis of lung lesions. We evaluated the diagnostic performance of R-EBUS both a guide-sheath and fluoroscopy and identified factors associated with accurate diagnosis. The feasibility of molecular and genetic testing, using specimens obtained by R-EBUS, was also investigated. **METHODS:** The study retrospectively reviewed 211 patients undergoing R-EBUS without a guide-sheath and fluoroscopy, June 2016-May 2017. After excluding 27 patients of which the target lesion was not reached, 184 were finally included. Multivariate logistic regression was used, to identify factors associated with accurate diagnosis. **RESULTS:** Among 184 patients, R-EBUS-guided biopsy diagnosed malignancy in 109 patients (59%). The remaining 75 patients (41%) with non-malignant results underwent additional work-ups, and 34 were diagnosed with malignancy. Based on final diagnosis, diagnostic accuracy was 80% (136/170), and sensitivity and specificity for malignancy were 76% (109/143) and 100% (27/27), respectively. In multivariate analysis, peripheral location (adjusted odds ratio [aOR], 3.925; 95% confidence interval [CI], 1.203-12.811; $p=0.023$), and central position of the probe (aOR, 2.435; 95% CI, 1.424-7.013; $p=0.035$), were associated with accurate diagnosis of malignancy. Molecular and genetic analyses were successful, in all but one case, with inadequate specimens. **CONCLUSION:** R-EBUS-guided biopsy without equipment, is effective for tissue diagnosis. Peripheral location and central position of the radial probe, were crucial for accurate diagnosis. Performance of molecular and genetic testing, using samples obtained by R-EBUS, was satisfactory.

Immunocytochemistry for predictive biomarker testing in lung cancer cytology. Jain D1, Nambirajan A1, Borczuk A2, et al. *Cancer Cytopathol*. 2019 May;127(5):325-339. doi: 10.1002/cncy.22137. Epub 2019 May 3.

With an escalating number of predictive biomarkers emerging in non-small cell lung carcinoma (NSCLC), immunohistochemistry (IHC) is being used as a rapid and cost-effective tool for the screening and detection of many of these markers. In particular, robust IHC assays performed on formalin-fixed, paraffin-embedded (FFPE) tumor tissue are widely used as surrogate markers for ALK and ROS1 rearrangements and for detecting programmed death ligand 1 (PD-L1) expression in patients with advanced NSCLC; in addition, they have become essential for treatment decisions. Cytology samples represent the only source of tumor in a significant proportion of patients with inoperable NSCLC, and there is increasing demand for predictive biomarker testing on them. However, the wide variation in the types of cytology samples and their preparatory methods, the use of alcohol-based fixatives that interfere with immunocytochemistry results, the difficulty in procurement of cytology-specific controls, and the uncertainty regarding test validity have resulted in underutilization of cytology material for predictive immunocytochemistry (ICC), and most cytopathologists limit such testing to FFPE cell blocks (CBs). The

purpose of this review is to: 1) analyze various preanalytical, analytical, and postanalytical factors influencing ICC results; 2) discuss measures for validation of ICC protocols; and 3) summarize published data on predictive ICC for ALK, ROS1, EGFR gene alterations and PD-L1 expression on lung cancer cytology. Based on our experience and from a review of the literature, we conclude that cytology specimens are in principal suitable for predictive ICC, but proper optimization and rigorous quality control for high-quality staining are essential, particularly for non-CB preparations.

[Low Rates of Patient-Reported Physician-Patient Discussion about Lung Cancer Screening among Current Smokers: Data from Health Information National Trends Survey.](#) Huo J1, Hong YR2, Bian J3, Guo Y3, Wilkie DJ4, Mainous AG 3rd2. *Cancer Epidemiol Biomarkers Prev.* 2019 May;28(5):963-973. doi: 10.1158/1055-9965.EPI-18-0629.

BACKGROUND: Many professional societies published guidelines recommending lung cancer screening with low-dose CT scan. We examined the temporal trends in patient-reported physician-patient discussions about lung cancer screening, and aimed to determine the association of discussions of lung cancer screening with the smokers' attempt to quit and intent to quit. **METHODS:** Data from years 2012, 2014, and 2017 of the National Cancer Institute's Health Information National Trends Survey (HINTS) were combined to create a multiple-year analytic dataset. We calculated the association between samples' characteristics and the presence of discussion about lung cancer screening. Using logistic regression, we estimated the probability of smokers' attempt to quit and intent to quit. **RESULTS:** Among 9,443 subjects, the crude estimated rates of physician-patient discussion decreased from 6.7% in 2012, to 4.2% in 2014 and 4.3% in 2017. Across the age and smoking status groups, the current smokers ages 55 to 74 in 2012 (26.8%), and current smokers older than 74 years in 2014 (23.5%) and 2017 (22.1%) had the highest rates of discussion. The physician-patient discussion about lung cancer screening was not associated with patients' intent to quit or attempt to quit in a multivariable analysis. **Conclusions:** Efforts are needed to improve the physician-patient discussion about lung cancer screening among individuals across a spectrum of lung cancer risk. **IMPACT:** Developing communication strategies for promoting beneficial lung cancer screening among lung cancer screening-eligible smokers and strategies for improving the quality of discussion on lung cancer screening integrating smoking cessation are needed to reduce the burden of lung cancer.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[Clinical features of HIV-infected patients with non-small-cell lung cancer after lung resection.](#)

Asakawa A1, Horio H2, Yamamichi T2, Okui M2, Harada M2. *Gen Thorac Cardiovasc Surg.* 2019 May 31. doi: 10.1007/s11748-019-01149-9. [Epub ahead of print]

OBJECTIVE: The purpose of this study was to clarify the surgical outcome for HIV-infected patients with non-small-cell lung cancer (NSCLC). **METHODS:** Six HIV-positive patients underwent lung resection as treatment for NSCLC at our hospital from July 2010 to December 2017. Their clinical information was collected based upon review of their medical records. **RESULTS:** All the patients included in this study had received highly active antiretroviral therapy (HAART) before lung resection with a mean duration of 99 months. Five patients underwent lobectomy and one patient underwent segmentectomy. Median preoperative CD4-positive T-cell count was 234/ μ L (range 138-428/ μ L). One patient contracted pneumonitis within 30 days post-surgery, whereas others had no postoperative complications. There was no postoperative mortality. For four patients, the pathological stage was upstaged compared to their clinical stage; IA1-IA3 (1 patient), IA3-IIB (1 patient), IB-IIIA (1 patient), and IB-IIIB (1 patient). Two patients died of lung cancer 2 years after surgery. **CONCLUSION:** Surgical

treatment for HIV-infected patients with NSCLC receiving HAART therapy and keeping adequate CD4-positive T-cell counts is safe and feasible. Preoperative precise staging using diagnostic imaging is difficult for these patients.

[Short-Term Readmissions After Open, Thoracoscopic, and Robotic Lobectomy for Lung Cancer Based on the Nationwide Readmissions Database.](#) Bailey KL1, Merchant N1, Seo YJ1, Elashoff D2, Benharash P1,3, Yanagawa J4,5. World J Surg. 2019 May;43(5):1377-1384. doi: 10.1007/s00268-018-04900-0.

BACKGROUND: Readmission after surgery is an established surrogate indicator of quality of care. We aimed to compare short-term readmission rates and patient outcomes between open, video-assisted thoracoscopic (VATS), and robotic lobectomies in the Nationwide Readmissions Database (NRD).

METHODS: Adults who underwent open, VATS, or robotic lobectomy for lung cancer from 2010 to 2014 were evaluated. Propensity-matched analysis was used to assess differences in readmission characteristics, GDP-adjusted cost, and mortality. **RESULTS:** Of the 129,539 lobectomies for lung cancer, 74,493 (57.5%) were open, 48,185 (37.2%) VATS, and 6861 (5.3%) robotic. Open surgery was associated with significantly higher readmission rate (10.5 vs 9.3%, $p < 0.001$), mortality (2 vs 1.2%, $p < 0.001$), index hospitalization cost [\$21,846 (16,158-31,034) vs \$20,779 (15,619-27,920), $p < 0.001$], and length of stay [6 (5-9) vs 4 (3-7) days, $p < 0.001$] compared to minimally invasive surgery. The robotic approach had similar mortality, readmission rate, and length of stay compared to VATS, but higher index cost [\$23,870 (18,372-31,300) vs \$20,279 (15,275-27,375), $p < 0.001$] and incidence of pulmonary complication (35.9 vs 31.6%, $p < 0.001$). The robotic approach was associated with greater direct discharges to home. **CONCLUSIONS:** Analysis of the NRD revealed significantly reduced readmission rates, better clinical outcomes, and lower cost in the minimally invasive approach compared to open surgery. Although VATS and robotic surgery had similar readmission and mortality rates, VATS is associated with significantly reduced risk of short-term complications and lower cost.

[Persistent opioid use is associated with worse survival after lobectomy for stage i non-small cell lung cancer.](#) Nelson DB1, Cata JP2, Niu J3, et al. Pain. 2019 May 29. doi: 10.1097/j.pain.0000000000001630. [Epub ahead of print]

The incidence of persistent opioid use after lung surgery is high. Although adverse effects by opioids have been well described, it is unknown whether persistent opioid use is associated with worse survival. Patients who received a lobectomy for stage I NSCLC from 2007 - 2013 were identified from the SEER-Medicare database. Opioid use was ascertained through records of prescriptions filled through Part D. Patients were matched 2:1 according to their likelihood of persistent opioid use, which was defined as any opioid prescription filled 3-6 months after surgery. 2,884 patients were identified. The incidence of persistent opioid use 3-6 months after surgery was 27.0%. After matching, persistent opioid use was associated with worse overall survival ($p < 0.001$) and cancer-specific survival ($p < 0.001$). Those who used the lowest quartile of opioids, which was often manifested as a single opioid prescription, showed similar overall survival as no opioid use (HR 1.27, 95% CI 0.93 - 1.72). However, the second and third quartile of opioid use were associated with decreased overall survival (HR 1.53, 95% CI 1.14 - 2.03 and HR 1.39, 95% CI 1.04 - 1.86, respectively) that was nonetheless less severe than the highest quartile of opioid use (HR 2.50, 95% CI 1.95 - 3.21). Age, sex, marital status, comorbidity, tumor size, tumor grade and radiation were also associated with worse overall survival, with chemotherapy use and VATS being associated with improved overall survival. Persistent opioid use 3 to 6 months after lobectomy is independently associated with worse overall survival and worse cancer-specific survival.

[Outcomes Of Uniportal Vs Multiportal Video-Assisted Thoracoscopic Lobectomy.](#) Bourdages-Pageau E1, Vieira A1, Lacasse Y1, Figueroa PU2. *Semin Thorac Cardiovasc Surg.* 2019 May 28. pii: S1043-0679(19)30170-4. doi: 10.1053/j.semtevs.2019.05.021. [Epub ahead of print]

OBJECTIVE: The optimal number of incisions for video-assisted thoracoscopic surgery (VATS) lobectomy, the standard treatment for early-stage non-small cell lung cancer (NSCLC), is still a matter of great debate. To compare single-incision (uniportal) VATS (U-VATS) with traditional multiportal VATS (M-VATS), we retrospectively reviewed the surgical outcomes of a large cohort of patients. **METHODS:** Our prospectively maintained institutional database was queried retrospectively. All patients from 2014 to 2017 who underwent VATS lobectomy as the primary procedure for clinical stage I or II NSCLC were identified. A univariate comparison and a propensity-matched analysis incorporating preoperative variables were performed. The incidence of postoperative complications was compared. **RESULTS:** During the study period, 722 patients underwent VATS lobectomy for early-stage NSCLC, 62% by M-VATS and 38% by U-VATS. In the univariate analysis, U-VATS performed by an experienced surgeon was associated with decreased intraoperative bleeding and shortened duration of surgery, duration of chest tube drainage and length of hospital stay as compared with M-VATS ($p < 0.001$). Mediastinal lymph node dissection and complete resection were accomplished similarly using U-VATS and M-VATS. When the 2 approaches were compared through propensity matching, U-VATS was associated with fewer pneumonias ($p = 0.012$), as well as decreased intraoperative bleeding ($p < 0.001$), faster surgery ($p < 0.001$), shorter duration of chest tube drainage ($p = 0.001$), and shorter hospital stay ($p < 0.001$). **CONCLUSION:** At our institution, in the hands of an experienced surgeon, uniportal VATS lobectomy is safe, feasible and can result in similar short-term outcomes for early-stage NSCLC as compared with multiportal VATS.

[Invasive mediastinal staging for resected non-small cell lung cancer in a population-based cohort.](#)

Osarogiagbon RU1, Lee YS2, Faris NR3, Ray MA2, Ojeabulu PO3, Smeltzer MP2. *J Thorac Cardiovasc Surg.* 2019 May 2. pii: S0022-5223(19)30968-7. doi: 10.1016/j.jtcvs.2019.04.068. [Epub ahead of print]

OBJECTIVES: Invasive mediastinal nodal staging is recommended before curative-intent resection in patients with non-small cell lung cancer deemed at risk for mediastinal lymph node involvement. We evaluated the use and survival effect of preoperative invasive mediastinal nodal staging in a population-based non-small cell lung cancer cohort. **METHODS:** We analyzed all curative-intent resections for non-small cell lung cancer from 2009 to 2018 in 11 hospitals in 4 contiguous Dartmouth Hospital Referral Regions, comparing patients who did not have invasive mediastinal nodal staging with those who did. **RESULTS:** Preoperative invasive nodal staging was used in 22% of 2916 patients, including mediastinoscopy only in 13%, minimally invasive procedures only in 6%, and both approaches in 3%. Sixty-three percent of patients at risk for nodal disease (tumor size ≥ 3.0 cm/T2-T4; N1-N3 by computed tomography or positron-emission tomography-computerized tomography criterion) did not undergo invasive staging; among those who did not have invasive testing, 47% had at least 1 of the 3 clinical indications. Mediastinoscopy yielded a median of 3 lymph nodes and 2 nodal stations; 17% of mediastinoscopies and 31% of endobronchial ultrasound procedures yielded no lymph node material. Patients not invasively staged were more likely to have no nodes (6% vs 2%; $P < .0001$) and no mediastinal nodes (20% vs 11%; $P < .0001$) examined at surgery. Invasive staging was associated with significantly better survival ($P = .0157$). **CONCLUSIONS:** More than a decade after the 2001 American College of Surgeons Patient Care Evaluation report, preoperative invasive nodal staging remains underused and of variable quality, but was associated with survival benefit in high-risk patients.

[Severe immune-related adverse events are common with sequential PD-\(L\)1 blockade and osimertinib.](#) Schoenfeld AJ1, Arbour KC1, Rizvi H1, Iqbal AN1, Gadgeel SM2, Girshman J3, Kris MG1, Riely GJ1, Yu HA1, Hellmann MD1. *Ann Oncol.* 2019 May 1;30(5):839-844. doi: 10.1093/annonc/mdz077.

BACKGROUND: Concurrent programmed death-ligand-1 (PD-(L)1) plus osimertinib is associated with severe immune related adverse events (irAE) in epidermal growth factor receptor (EGFR)-mutant non-small-cell lung cancer (NSCLC). Now that PD-(L)1 inhibitors are routinely used as adjuvant and first-line treatments, sequential PD-(L)1 inhibition followed by osimertinib use may become more frequent and have unforeseen serious toxicity. **METHODS:** We identified patients with EGFR-mutant NSCLC who were treated with PD-(L)1 blockade and EGFR- tyrosine kinase inhibitors (TKIs), irrespective of drug or sequence of administration (total n = 126). Patient records were reviewed to identify severe (NCI-CTCAE v5.0 grades 3-4) toxicity. **RESULTS:** Fifteen percent [6 of 41, 95% confidence interval (CI) 7% to 29%] of all patients treated with sequential PD-(L)1 blockade followed later by osimertinib developed a severe irAE. Severe irAEs were most common among those who began osimertinib within 3 months of prior PD-(L)1 blockade (5 of 21, 24%, 95% CI 10% to 45%), as compared with >3-12 months (1 of 8, 13%, 95% CI 0% to 50%), >12 months (0 of 12, 0%, 95% CI 0% to 28%). By contrast, no severe irAEs were identified among patients treated with osimertinib followed by PD-(L)1 (0 of 29, 95% CI 0% to 14%) or PD-(L)1 followed by other EGFR-TKIs (afatinib or erlotinib, 0 of 27, 95% CI 0% to 15%). IrAEs occurred at a median onset of 20 days after osimertinib (range 14-167 days). All patients with irAEs required steroids and most required hospitalization. **CONCLUSION:** PD-(L)1 blockade followed by osimertinib is associated with severe irAE and is most frequent among patients who recently received PD-(L)1 blockade. No irAEs were observed when osimertinib preceded PD-(L)1 blockade or when PD-(L)1 was followed by other EGFR-TKIs. This association appears to be specific to osimertinib, as no severe irAEs occurred with administration of other EGFR-TKIs.

[Efficacy and Safety of Gefitinib as Third-line Treatment in NSCLC Patients With Activating EGFR Mutations Treated With First-line Gefitinib Followed by Second-line Chemotherapy: A Single-Arm, Prospective, Multicenter Phase II Study \(RE-CHALLENGE, CTONG1304\).](#) Song Y1, Wu YL2, Cao LJ3, et al. *Am J Clin Oncol.* 2019 May;42(5):432-439. doi: 10.1097/COC.0000000000000538.

OBJECTIVE: There is no standard care for advanced non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutation in the third line. Our study aimed to assess the efficacy and safety of gefitinib as a third-line re-challenge treatment for advanced NSCLC patients with EGFR mutation. **MATERIALS AND METHODS:** It was a multicenter, open-label, single-arm, phase II study. Stage IIIB/IV NSCLC patients with EGFR exon 19del/L858R mutation, who had benefited from first-line gefitinib treatment followed by second-line chemotherapy, received gefitinib 250 mg/d. The primary objective was disease control rate (DCR) at week 8. **RESULTS:** Predefined DCR was achieved in 69.8% (95% confidence interval, 49.87-74.91) patients and objective response rate was reported in 4.7% (95% confidence interval, 0.78-13.06) patients. Median progression-free survival (PFS) was 4.4 months and overall survival (OS) was 10.3 months. Baseline T790M-negative patients achieved favorable DCR compared with T790M-positive patients (78.1% vs. 45.5%, P=0.0418), significantly longer median PFS (4.7 vs. 2.0 mo, P=0.0009) and median OS (15.2 vs. 7.7 mo, P=0.0132). We observed a negative correlation of PFS ($r=-0.4396$, P=0.0032), and OS ($r=-0.3630$, P=0.0167) with mutation abundance of exon 19del/L858R at baseline. **CONCLUSIONS:** Re-challenge with gefitinib is effective and could be a choice for third-line patients after the first-line EGFR-TKI treatment and second-line chemotherapy, especially for the T790M-negative patients.

[Real-Life Efficacy of Osimertinib in Pretreated Octogenarian Patients with T790M-Mutated Advanced Non-small Cell Lung Cancer.](#)

Auliac JB1, Saboundji K2, Andre M3, et al. Target Oncol. 2019 May 22. doi: 10.1007/s11523-019-00646-4. [Epub ahead of print]

BACKGROUND: The resistance mutation T790M is reported in 50-60% of patients pretreated with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). Osimertinib has been approved in these patients, but data in octogenarians remain rare. **OBJECTIVE:** The objective of this retrospective analysis was to evaluate in real life the efficacy of osimertinib in a population of octogenarian patients. **METHODS:** This retrospective multicentric study included pretreated octogenarian patients with EGFR T790M-mutated advanced non-small cell lung cancer (NSCLC) in the setting of the French early access program for osimertinib. The primary endpoints were progression-free survival (PFS) and overall survival (OS) from osimertinib initiation. **RESULTS:** In total, 43 patients were included (mean age 84.6 years; women 90.7%; adenocarcinoma 100%; never smokers 90.5%; at osimertinib initiation: performance status ≥ 2 , 42.4%; stage 4, 93.0%; brain metastases 16.3%). Patients received a median of two lines of treatment before osimertinib initiation, and all received first- or second-generation EGFR TKIs before osimertinib (first line in 79.1%). Osimertinib was used as a second-line treatment in 41.9% of cases and third line or more in 58.1%. Median PFS was 17.5 (95% confidence interval [CI] 12.2-19.0) months for the entire population: 20.6 (95% CI 18.8-not reached) months in patients with brain metastases and 16.7 (95% CI 10.4-18.9) months in patients without ($p = 0.1$). There was no significant difference for osimertinib treatment as second or third line or more (17.1 vs. 18.6 months, respectively). OS was 22.8 (95% CI 15.7-not reached) months from osimertinib initiation. **CONCLUSION:** The efficacy of osimertinib as second-line treatment or more in octogenarian pretreated patients with EGFR T790M-mutated advanced NSCLC in a real-life setting was similar to that in randomized controlled trials.

[First-line treatment for patients with advanced non-small cell lung carcinoma and high PD-L1 expression: pembrolizumab or pembrolizumab plus chemotherapy.](#)

Zhou Y1,2,3, Lin Z1,2,4, Zhang X1,2,5, Chen C1,2,6, Zhao H1,2,4, Hong S7,8,9, Zhang L10,11,12. J Immunother Cancer. 2019 May 3;7(1):120. doi: 10.1186/s40425-019-0600-6.

Pembrolizumab monotherapy has become the preferred treatment for patients with advanced non-small cell lung carcinoma (NSCLC) and a programmed cell death-ligand 1 (PD-L1) tumor proportion score (TPS) of at least 50%. However, little is known about the value of adding chemotherapy to pembrolizumab in this setting. Therefore, we performed an indirect comparison for pembrolizumab plus chemotherapy versus pembrolizumab, using the frequentist methods. The primary outcomes were overall survival (OS), progression-free survival (PFS) and objective response rate (ORR). Data were retrieved from randomized trials comparing pembrolizumab plus chemotherapy or pembrolizumab monotherapy against chemotherapy. Five trials involving 1289 patients were included. Direct meta-analysis showed that both pembrolizumab plus chemotherapy (ORR: relative risk (RR) 2.16; PFS: hazard ratio (HR) 0.36; OS: HR 0.51) and pembrolizumab alone (ORR: RR 1.33; PFS: HR, 0.65; OS: HR 0.67) improved clinical outcomes compared with chemotherapy. Indirect comparison showed that pembrolizumab plus chemotherapy was superior to pembrolizumab alone, in terms of ORR (RR 1.62, 1.18-2.23) and PFS (HR 0.55, 0.32-0.97). A trend towards improved OS was also observed (HR 0.76, 0.51-1.14). In conclusion, the addition of chemotherapy to pembrolizumab further improves the outcomes of patients with advanced NSCLC and a PD-L1 TPS of at least 50%.

[NCCN Guidelines Updates: New Immunotherapy Strategies for Improving Outcomes in Non-Small Cell Lung Cancer.](#)

Gubens MA, Davies M. J Natl Compr Canc Netw. 2019 May 1;17(5.5):574-578. doi: 10.6004/jnccn.2019.5005.

For the use of immunotherapy in metastatic non-small cell lung cancer (NSCLC), the NCCN Guidelines for NSCLC reflect the importance of assessing levels of PD-L1 expression to determine the best use of PD-1/PD-L1 inhibitors, whether alone or in combination with chemotherapy. Patients who lack a driver mutation and have tumor PD-L1 expression $\geq 50\%$ are recommended to receive single-agent pembrolizumab, although combining with carboplatin/pemetrexed is also a reasonable choice, especially if there is higher burden of disease. For tumors with PD-L1 expression $< 50\%$, it is important to distinguish between nonsquamous and squamous cell carcinoma (SCC). For patients with non-SCC disease, pembrolizumab + carboplatin/pemetrexed is preferred. Alternately, a 4-drug regimen of carboplatin/paclitaxel/bevacizumab/atezolizumab is reasonable, especially for patients ineligible for pemetrexed. In patients with SCC, carboplatin + paclitaxel or nab-paclitaxel with pembrolizumab is a category 1 recommendation. Tumor mutational burden is emerging as a biomarker for efficacy but is not yet ready to be used in patient selection. Optimal management of the unique toxicities associated with immunotherapy, which can be more frequent with these combinations, is also critical for good outcomes.

[Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer \(IMpower130\): a multicentre, randomised, open-label, phase 3 trial.](#) West H1, McCleod M2, Hussein M3, et al. *Lancet Oncol.* 2019 May 20. pii: S1470-2045(19)30167-6. doi: 10.1016/S1470-2045(19)30167-6. [Epub ahead of print]

BACKGROUND: Atezolizumab (a monoclonal antibody against PD-L1), which restores anticancer immunity, improved overall survival in patients with previously treated non-small-cell lung cancer and also showed clinical benefit when combined with chemotherapy as first-line treatment of non-small-cell lung cancer. IMpower130 aimed to assess the efficacy and safety of atezolizumab plus chemotherapy versus chemotherapy alone as first-line therapy for non-squamous non-small-cell lung cancer.

METHODS: IMpower130 was a multicentre, randomised, open-label, phase 3 study done in 131 centres across eight countries (the USA, Canada, Belgium, France, Germany, Italy, Spain, and Israel). Eligible patients were aged 18 years or older, and had histologically or cytologically confirmed stage IV non-squamous non-small-cell lung cancer, an Eastern Cooperative Oncology Group performance status of 0 or 1, and received no previous chemotherapy for stage IV disease. Patients were randomly assigned (2:1; permuted block [block size of six] with an interactive voice or web response system) to receive atezolizumab (1200 mg intravenously every 3 weeks) plus chemotherapy (carboplatin [area under the curve 6 mg/mL per min every 3 weeks] plus nab-paclitaxel [100 mg/m² intravenously every week]) or chemotherapy alone for four or six 21-day cycles followed by maintenance therapy. Stratification factors were sex, baseline liver metastases, and PD-L1 tumour expression. Co-primary endpoints were investigator-assessed progression-free survival and overall survival in the intention-to-treat wild-type (ie, EGFRwt and ALKwt) population. The safety population included patients who received at least one dose of the study drug. This study is registered with ClinicalTrials.gov, number NCT02367781. **FINDINGS:** Between April 16, 2015, and Feb 13, 2017, 724 patients were randomly assigned and 723 were included in the intention-to-treat population (one patient died before randomisation, but was assigned to a treatment group; this patient was excluded from the intention-to-treat population) of the atezolizumab plus chemotherapy group (483 patients in the intention-to-treat population and 451 patients in the intention-to-treat wild-type population) or the chemotherapy group (240 patients in the intention-to-treat population and 228 patients in the intention-to-treat wild-type population). Median follow-up in the intention-to-treat wild-type population was similar between groups (18.5 months [IQR 15.2-23.6] in the atezolizumab plus chemotherapy group and 19.2 months [15.4-23.0] in the chemotherapy group). In the intention-to-treat wild-type population, there were significant improvements in median overall survival (18.6 months [95% CI 16.0-21.2] in the atezolizumab plus chemotherapy group and 13.9 months [12.0-18.7] in the chemotherapy group; stratified hazard ratio [HR] 0.79 [95% CI 0.64-0.98]; $p=0.033$) and median

progression-free survival (7.0 months [95% CI 6.2-7.3] in the atezolizumab plus chemotherapy group and 5.5 months [4.4-5.9] in the chemotherapy group; stratified HR 0.64 [95% CI 0.54-0.77]; $p < 0.0001$). The most common grade 3 or worse treatment-related adverse events were neutropenia (152 [32%] of 473 in the atezolizumab plus chemotherapy group vs 65 [28%] of 232 in the chemotherapy group), anaemia (138 [29%] vs 47 [20%]), and decreased neutrophil count (57 [12%] vs 19 [8%]). Treatment-related serious adverse events were reported in 112 (24%) of 473 patients in the atezolizumab plus chemotherapy group and 30 (13%) of 232 patients in the chemotherapy group. Treatment-related (any treatment) deaths occurred in eight (2%) of 473 patients in the atezolizumab plus chemotherapy group and one (<1%) of 232 patients in the chemotherapy group. **INTERPRETATION:** IMpower130 showed a significant and clinically meaningful improvement in overall survival and a significant improvement in progression-free survival with atezolizumab plus chemotherapy versus chemotherapy as first-line treatment of patients with stage IV non-squamous non-small-cell lung cancer and no ALK or EGFR mutations. No new safety signals were identified. This study supports the benefit of atezolizumab, in combination with platinum-based chemotherapy, as first-line treatment of metastatic non-small-cell lung cancer. **FUNDING:** F. Hoffmann-La Roche.

[Outcome Differences Between First- and Second-generation EGFR Inhibitors in Advanced EGFR Mutated NSCLC in a Large Population-based Cohort.](#) Lau SC1, Chooback N2, Ho C3, Melosky B4. Clin Lung Cancer. 2019 May 11. pii: S1525-7304(19)30107-X. doi: 10.1016/j.clcc.2019.05.003. [Epub ahead of print]

INTRODUCTION: Second-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) appear superior to first-generation TKIs in clinical trials, but at the cost of greater toxicity. It is unclear whether real-world patients, who often suffer worse outcomes, experience similar survival benefits. Using population-based data, we aim to characterize outcome differences by type of treatment. **PATIENTS AND METHODS:** We reviewed all patients with advanced non-small-cell lung cancer who initiated treatment with an EGFR TKI at BC Cancer between 2010 and 2015. A propensity score was generated to account for imbalances in patient characteristics between treatment groups. A Cox proportional hazards model based on the propensity score was then used to estimate effects of treatment on survival. **RESULTS:** A total of 484 patients were identified for analysis. Patients in the second-generation cohort were younger (62 vs. 67 years), had less baseline central nervous system metastases (9% vs. 22%), and more uncommon EGFR mutations (13% vs. 7%). Patients receiving a second-generation TKI had an improved overall survival (hazard ratio, 0.69; $P = .05$), driven by the subgroup with an EGFR exon 19 deletion. Patients with a L858R mutation did not appear to derive benefit from a second-generation TKI (hazard ratio, 0.91; $P = .74$). Overall, 40% of patients receiving a second-generation TKI required a dose reduction, but only 1% required discontinuation. **CONCLUSIONS:** Second-generation TKIs tended to be chosen over first-generation TKIs as frontline therapy in younger patients with uncommon EGFR mutations and without central nervous system metastases. The survival benefit of a second-generation TKI seen in clinical trials appeared to be generalizable to real-world patients and is a reasonable first-line therapy.

[Brief Report: SWOG S1400B \(NCT02785913\), A Phase II Study of GDC-0032 \(Taselisib\) for Previously Treated PI3K-Positive Patients with Stage IV Squamous Cell Lung Cancer \(Lung-MAP Sub-Study\).](#)

Langer CJ1, Redman MW2, Wade JL 3rd3, Aggarwal C4, Bradley JD5, Crawford J6, Stella PJ7, Knapp MH8, Miao J2, Minichiello K2, Herbst RS9, Kelly K10, Gandara DR10, Papadimitrakopoulou VA11. J Thorac Oncol. 2019 May 31. pii: S1556-0864(19)30414-9. doi: 10.1016/j.jtho.2019.05.029. [Epub ahead of print]

BACKGROUND: S1400B is a biomarker-driven Lung-MAP sub-study evaluating the phosphatidylinositide 3-kinase (PI3K) inhibitor taselelisib (GDC-0032) in patients with PI3K pathway-activated squamous NSCLC (SqNSCLC). **METHODS:** Eligible patients had tumoral PIK3CA alterations by next generation sequencing and disease progression after at least one line of platinum-based therapy. Patients received 4 mg taselelisib orally daily. The primary analysis population (PAP) was a subset of patients having substitution mutations believed to be associated with clinical benefit of PI3K inhibitors. Primary endpoint was response by RECIST 1.1; secondary endpoints included progression-free survival (PFS), overall survival (OS) and duration of response (DoR). **RESULTS:** Twenty-six patients treated with taselelisib comprised the full eligible population (FEP); 21 patients comprised the PAP. Median age in FEP was 68 y (53-83), 19 were male (73%). The study was closed for futility at interim analysis with one responder in the PAP (5% RR, 95% CI 0%-24%). Two possibly treatment-related deaths (1 respiratory failure, 1 cardiac arrest) were observed; 1 patient had Grade 4 and 11 had Grade 3 adverse events. Median PFS and OS in the PAP were 2.9 months (95% CI, 1.8-4.0 mos) and 5.9 months (95% CI, 4.2-7.8 mos), respectively. These numbers were nearly the same in the FEP. **CONCLUSIONS:** Study S1400B evaluating taselelisib in PIK3CA altered SqNSCLC failed to meet its primary endpoint and was closed after an interim futility analysis. The trial is unique in cataloguing the diversity of PIK3CA mutations in SqNSCLC.

Updates in Local-Regionally Advanced Non-Small Cell Lung Cancer. Tsao AS1, Jolly S2, Lee JM3. Am Soc Clin Oncol Educ Book. 2019 Jan;39:553-562. doi: 10.1200/EDBK_237839. Epub 2019 May 17. The landscape for therapy in local-regionally advanced non-small cell lung cancer (NSCLC) has shifted dramatically in the last year as a result of the PACIFIC trial, which demonstrated a significant survival benefit with the addition of 1 year of durvalumab after concurrent chemoradiation. This is a new standard of care for unresectable local-regionally advanced NSCLC and is the first trial to show that immunotherapy can increase survival in earlier-stage NSCLC. Several clinical trials are underway or in development to explore the role of adding immunotherapy to concurrent chemoradiation, followed by a year of immunotherapy or to even replace chemotherapy in this treatment paradigm. In resectable disease, adjuvant chemotherapy is still the standard of care for stage IB (tumors \geq 4 cm) through stage III disease. However, new studies are investigating the role of adding immunotherapy to neoadjuvant chemotherapy or as adjuvant therapy for 1 year after resection. Molecular profiling for early-stage disease is not currently the standard of care, but several national clinical trials are studying the benefit of adding adjuvant-targeted therapies. This article will detail the current standard practices in early-stage and local-regionally advanced NSCLC and describe the evolving strategies that are under investigation that may further refine our current practice.

Advanced Non-Small Cell Lung Cancer: Sequencing Agents in the EGFR-Mutated/ALK-Rearranged Populations. Singhi EK1, Horn L1, Sequist LV2, Heymach J3, Langer CJ4. Am Soc Clin Oncol Educ Book. 2019 Jan;39:e187-e197. doi: 10.1200/EDBK_237821. Epub 2019 May 17. Personalized therapy based on actionable molecular markers has completely transformed the therapeutic landscape in advanced non-small cell lung cancer (NSCLC). In less than 15 years, multiple molecular targets, led by EGFR and anaplastic lymphoma kinase (ALK), have been identified, and myriad oral tyrosine kinase inhibitors (TKIs) are now available to target these oncogenic drivers, with the expectation that the majority of patients will respond to treatment and that progression-free survival (PFS) will exceed 10 to 30 months, far better than we observed historically with chemotherapy alone. As a result, prognosis has improved dramatically in this subset of patients. Osimertinib has largely displaced first- and second-generation EGFR TKIs, including gefitinib, erlotinib, and afatinib, in the management of EGFR-mutated NSCLC. PFS now exceeds 18 months, and central nervous system penetrance is enhanced. Dacomitinib has the distinction of being the first EGFR TKI to demonstrate a survival advantage compared with older

TKIs. Recent data suggest therapeutic additivity, if not synergy, for the concurrent use of chemotherapy, as well as monoclonal antibodies targeting angiogenesis, with EGFR TKIs. Alectinib and brigatinib, very specific ALK inhibitors, have proven superior to the erstwhile standard crizotinib in treatment-naive ALK+ NSCLC; PFS now routinely exceeds 2 to 3 years. In addition, these newer agents have far superior central nervous system penetration. As a result, many patients with ALK+ advanced NSCLC with brain metastases, even some who are symptomatic, can defer or indefinitely avoid brain irradiation. Mechanisms of resistance in ALK are complicated, with multiple new agents being developed in this arena. Although many patients with molecular targets can reasonably expect to live 5 years or more, the emergence of molecular resistance is virtually inevitable. In this regard, systemic platinum-based chemotherapy is the final common therapeutic pathway for virtually all patients with oncogenic drivers. Standard regimens include pemetrexed and carboplatin, as well as the E4599 regimen, combination solvent-based paclitaxel, carboplatin, and bevacizumab. Checkpoint inhibitors, as single agents, have not yielded much benefit, even in those with high levels of PD-L1 expression. However, in a subanalysis of patients with ALK and EGFR mutations enrolled in IMpower150, the addition of atezolizumab to the E4599 regimen led to a major overall survival benefit (hazard ratio < 0.40). In the absence of systemic chemotherapy, combining checkpoint inhibitors with TKIs in this setting remains investigational; several studies have demonstrated untoward pulmonary and hepatic toxicity.

[PD-L1 expression and tumor mutational burden status for prediction of response to chemotherapy and targeted therapy in non-small cell lung cancer.](#) Chen Y1, Liu Q2, Chen Z3, et al. J Exp Clin Cancer Res. 2019 May 14;38(1):193. doi: 10.1186/s13046-019-1192-1.

BACKGROUND: Several targeted immunotherapies have recently showed significant advances in treatment of non-small cell lung cancer (NSCLC), including antibodies and inhibitors targeting programmed death-1 (PD-1) and its ligand (PD-L1). **METHODS:** Tumor tissue samples were prospectively collected from 183 patients with NSCLC including lung adenocarcinoma (ADC) and squamous cell carcinoma (SQCC). PD-L1 expression level was measured by immunohistochemistry assay and tumor mutational burden (TMB) status was assessed by next generation sequencing. Correlations between PD-L1 expressions, TMB status with clinicopathological characteristics were analyzed. **RESULTS:** PD-L1 expression was detected in 37% of ADC group and 55% in SQCC group while all clinicopathological characteristics were found comparable between these two groups. PD-L1 expression was negatively associated with overall survival in ADC group ($P < 0.0001$) but not in SQCC group ($P = 0.418$). In consistent with PD-L1 expression level, TMB status was significantly lower in ADC subjects as compared to SQCC subjects ($P = 0.024$) while PD-L1 positive subgroup and TMB high subgroup shared less subjects within ADC group than SQCC group. More importantly, the combination of TMB status and PD-L1 expression successfully identified responders, who showed significant longer median overall survival than non-responders (32 months vs. 8.5 months) in ADC subjects ($P < 0.0001$) but not in SQCC subjects. **CONCLUSIONS:** Here we tested the hypothesis that monitoring TMB, in addition to the existing PD-L1 expression level, could represent valuable non-invasive biomarkers for the chemotherapy and targeted therapy. Further analyses are in need to further assess the prognostic value of TMB for ADC and SQCC patients receiving immunotherapy.

[EGFR mutation subtypes and response to immune checkpoint blockade treatment in non-small cell lung cancer.](#) Hastings K1, Yu H2,3, Wei W4, et al. Ann Oncol. 2019 May 14. pii: mdz141. doi: 10.1093/annonc/mdz141. [Epub ahead of print]

BACKGROUND: Although EGFR mutant tumors exhibit low response rates to immune checkpoint blockade overall, some EGFR mutant tumors do respond to these therapies. However, there is a lack of understanding of the characteristics of EGFR mutant lung tumors responsive to immune checkpoint blockade. **PATIENTS AND METHODS:** We retrospectively analyzed de-identified clinical and

molecular data on 171 cases of EGFR mutant lung tumors treated with immune checkpoint inhibitors from the Yale Cancer Center, Memorial Sloan Kettering Cancer Center, University of California Los Angeles, and Dana Farber Cancer Institute. A separate cohort of 383 EGFR mutant lung cancer cases with sequencing data available from the Yale Cancer Center, Memorial Sloan Kettering Cancer Center, and The Cancer Genome Atlas was compiled to assess the relationship between tumor mutation burden and specific EGFR alterations. **RESULTS:** Compared to 212 EGFR wild-type lung cancers, outcomes with PD-(L)1 blockade were worse in patients with lung tumors harboring alterations in exon 19 of EGFR (EGFR Δ 19) but similar in EGFR L858R lung tumors. EGFR T790M status and PD-L1 expression did not impact response or survival outcomes to immune checkpoint blockade. PD-L1 expression was similar across EGFR alleles. Lung tumors with EGFR Δ 19 alterations harbored a lower tumor mutation burden compared to EGFR L858R lung tumors despite similar smoking history. **CONCLUSIONS:** EGFR mutant tumors have generally low response to immune checkpoint inhibitors, but outcomes vary by allele. Understanding the heterogeneity of EGFR mutant tumors may be informative for establishing the benefits and uses of PD-(L)1 therapies for patients with this disease.

Comparative Effectiveness of Carboplatin/Pemetrexed With Versus Without Bevacizumab for Advanced Nonsquamous Non-Small Cell Lung Cancer. Bagley SJ1,2, Talento S3, Mitra N4, Meropol NJ5,6, Cohen RB1,2, Langer CJ1,2, Vachani A1,7,8. *Natl Compr Canc Netw.* 2019 May 1;17(5):469-477. doi: 10.6004/jnccn.2018.7102.

BACKGROUND: Despite recent advances in targeted therapy and immunotherapy for advanced non-small cell lung cancer (NSCLC), carboplatin/pemetrexed/bevacizumab remains a commonly used first-line regimen. However, it is unknown whether the addition of bevacizumab to carboplatin/pemetrexed improves overall survival (OS). **MATERIALS AND METHODS:** Using nationally representative curated electronic health record data from Flatiron Health, we performed a retrospective cohort study of patients diagnosed with advanced nonsquamous NSCLC who received ≥ 1 cycle of carboplatin/pemetrexed \pm bevacizumab as initial systemic therapy for stage IV or metastatic/recurrent disease. The OS impact of adding bevacizumab to carboplatin/pemetrexed was assessed using a Cox proportional hazards model to adjust for age, sex, race, original tumor stage, time between diagnosis of metastatic disease and start of chemotherapy, and performance status. In a secondary analysis of patients at a single academic institution, we also adjusted for the presence of brain metastases, hemoptysis, and anticoagulation. **RESULTS:** A total of 4,724 patients were included, of which 2,759 patients (58%) received carboplatin/pemetrexed and 1,965 (42%) received carboplatin/pemetrexed/bevacizumab. Median OS was 12.1 months (95% CI, 11.2-12.9 months) in the carboplatin/pemetrexed/bevacizumab group compared with 8.6 months (95% CI, 8.1-9.1 months) in the carboplatin/pemetrexed group ($P < .001$). Bevacizumab use remained associated with improved OS in a multivariate model (hazard ratio, 0.80; 95% CI, 0.75-0.86; $P < .001$). In the secondary, institutional analysis ($N = 539$), the effect of bevacizumab was unchanged (hazard ratio, 0.75; 95% CI, 0.59-0.96; $P = .02$). **CONCLUSIONS:** In this large, real-world dataset, the addition of bevacizumab to first-line carboplatin/pemetrexed for metastatic nonsquamous NSCLC was associated with improved OS.

Safety, Efficacy, and Patient-reported Health-related Quality of Life and Symptom Burden with Nivolumab in Patients with Advanced Non-Small Cell Lung Cancer, Including Patients Aged ≥ 70 Years or with Poor Performance Status (CheckMate 153). Spigel DR1, McCleod M2, Jotte RM3, et al. *J Thorac Oncol.* 2019 May 20. pii: S1556-0864(19)30376-4. doi: 10.1016/j.jtho.2019.05.010. [Epub ahead of print]

INTRODUCTION: CheckMate 153 (NCT02066636) is a phase 3B/4 study assessing nivolumab in previously treated patients with advanced non-small cell lung cancer (NSCLC). Eligibility criteria allowed enrollment of patients with poor prognostic features of advanced age or diminished Eastern

Cooperative Oncology Group performance status (ECOG PS), which are typically underrepresented in or excluded from randomized controlled trials. **METHODS:** Patients with stage IIIB/IV NSCLC and an ECOG PS of 0-2 with disease progression after ≥ 1 systemic therapy received nivolumab (3 mg/kg every 2 weeks) until progression, unacceptable toxicity, or consent withdrawal. The primary endpoint was the incidence of grade 3-5 treatment-related select adverse events (AEs). **RESULTS:** Among 1426 treated patients, 556 (39%) were aged ≥ 70 years and 128 (9%) had an ECOG PS of 2. Median treatment duration was 3.2 months. Across subgroups and the overall population, incidences of grade 3-5 treatment-related select AEs (6-9%) and grade 3-4 treatment-related AEs (TRAEs; 12-14%) were similar. One grade 5 TRAE was documented. Median overall survival (OS) was comparable in the overall population (9.1 months) and patients aged ≥ 70 years (10.3 months), but lower in patients with an ECOG PS of 2 (4.0 months). Patient-reported outcomes generally improved. **CONCLUSIONS:** Data from this large predominantly community-based study, which included patients aged ≥ 70 years and with an ECOG PS of 2, are consistent with registrational studies. As expected, the median OS for patients with an ECOG PS of 2 was lower than for the overall population, but comparable with historical data.

[Activity of Nivolumab and Utility of Neutrophil-to-Lymphocyte Ratio as a Predictive Biomarker for Advanced Non-Small-Cell Lung Cancer: A Prospective Observational Study.](#) Fukui T1, Okuma Y2, Nakahara Y2, et al. Clin Lung Cancer. 2019 May;20(3):208-214.e2. doi: 10.1016/j.clcc.2018.04.021. Epub 2018 May 5.

BACKGROUND: The immune checkpoint inhibitor nivolumab is entering routine oncologic practice. We investigated the safety and efficacy of nivolumab in the real world and alternative predictive factors for survival in patients with advanced non-small-cell lung cancer (NSCLC). **PATIENTS AND METHODS:** We performed a prospective observational study to evaluate the activity of nivolumab treatment for chemotherapy-refractory NSCLC. Patients were treated with nivolumab once every 2 weeks, and the efficacy was assessed every 8 ± 2 weeks. **RESULTS:** Fifty-two patients were enrolled after nivolumab approval in Japan. These patients received a median of 4 (range, 1-43) cycles of nivolumab. Overall objective response was observed in 12 patients (23.1%). Median progression-free survival was 2.1 (95% confidence interval, 1.0-3.2) months, and 1-year overall survival rate was 59.9%. A total of 23 immune-related adverse events occurred in 20 patients, as follows: 7 cases of pneumonitis, 6 of oral mucositis, 5 of hypothyroidism, 2 of colitis, 2 of liver dysfunction, and 1 of arthritis. All patients recovered after appropriate management. A pretreatment neutrophil-to-lymphocyte ratio (NLR) of ≥ 5 was significantly associated with poor prognosis compared to $\text{NLR} < 5$ (hazard ratio, 4.52; 95% confidence interval, 1.84-11.14; $P = .013$), independently. **CONCLUSION:** Nivolumab showed promising activity with a manageable safety profile in clinical practice, consistent with effects of previous clinical trials. This drug could affect a specific population of patients with advanced NSCLC, and pretreatment NLR was a candidate for surrogate markers for survival benefit of patients with NSCLC treated with nivolumab.

NSCLC - RADIOTHERAPY

[Treatment of T3N0 non-small cell lung cancer with chest wall invasion using stereotactic body radiotherapy.](#) Kennedy WR1, Gabani P1, Nikitas J1, Samson PP1, Robinson CG1, Bradley JD1, Roach MC1. Clin Transl Radiat Oncol. 2019 Feb 21;16:1-6. doi: 10.1016/j.ctro.2019.02.004. eCollection 2019 May.

OBJECTIVES: Chest wall invasion (CWI) is observed in 5% of localized non-small cell lung cancer (NSCLC). The role of stereotactic body radiotherapy (SBRT) in these patients is unknown. We investigate the safety and efficacy of SBRT in patients with T3N0 NSCLC due to CWI. **METHODS:** Patients with T3N0 NSCLC due to CWI were identified using a prospective registry. CWI was defined as

radiographic evidence of soft tissue invasion or bony destruction. We excluded patients with recurrent or metastatic disease. All patients were treated with definitive SBRT. Prescribed dose was 50 Gy in 5 fractions for most patients. Kaplan-Meier analysis was used to estimate survival outcomes. **RESULTS:** We identified 12 patients treated between 2006 and 2017. Median age was 70 (range, 58-85). Median tumor diameter was 3.0 cm (range, 0.9-7.2). Median survival was 12.0 months (range, 2.4-63). At a median follow-up of 8.9 months (range, 2.1-63), 1-year primary tumor control was 89%, involved lobar control was 89%, local-regional control was 82%, distant control was 91%, and survival was 63%. Of the 4 patients with pre-treatment chest wall pain, 3 reported improvement after SBRT. Two patients reported new grade 1-2 chest wall pain. No grade 3+ toxicity was reported, with 1 patient experiencing grade 1 skin toxicity and 3 patients experiencing grade 1-2 radiation pneumonitis. **CONCLUSIONS:** SBRT for CWI NSCLC is safe, with high early tumor control and low treatment-related toxicity. Most patients with pre-treatment chest wall pain experienced relief after SBRT, with no grade 3+ toxicity observed.

Postoperative radiotherapy is effective in improving survival of patients with stage pIII-N2 non-small-cell lung Cancer after pneumonectomy. Wang W1,2, Men Y1,3, Wang J1, et al. BMC Cancer. 2019 May 22;19(1):478. doi: 10.1186/s12885-019-5692-3.

BACKGROUND: There were few reports of postoperative radiotherapy (PORT) in stage pIII-N2 Non-small-cell Lung Cancer (NSCLC) patients receiving pneumonectomy followed by adjuvant chemotherapy. This study aims to evaluate safety and efficacy of PORT among these patients.

METHODS: Between Jan. 2004 and Dec. 2015, stage pIII-N2 NSCLC patients receiving pneumonectomy and adjuvant chemotherapy with or without PORT in our institution were retrospectively reviewed. **RESULTS:** Totally 119 patients were included, 32 patients receiving adjuvant chemotherapy and PORT (PORT group) and 87 receiving adjuvant chemotherapy alone (Control group). There were more patients with non-R0 resection in PORT group than Control group (25% vs. 8%, $p = 0.031$). In PORT group, \geq Grade 2 radiation-induced pneumonitis was 2/32. No severe radiation-related heart injury was observed. There was no PORT-related death. Of all patients, median follow-up time was 25 months. Median overall survival time (mOS) and median disease-free survival time (mDFS) were 46 months and 15 months, respectively. The PORT group had significantly better OS (not reached vs. 34 months, $p = 0.003$), DFS (19 months vs. 13 months, $p = 0.024$), local recurrence free survival (LRFS, $p = 0.012$), and distant metastasis free survival (DMFS, $p = 0.047$) than the Control group. As for failure pattern, PORT significantly reduced local regional failure rate (39.1% vs. 15.6%, $p = 0.016$). In subgroup analysis, patients with R0 resection ($n = 104$), OS and LRFS in PORT group were significantly longer, and PORT tended to increase DFS and DMFS. **CONCLUSION:** For patients with stage pIII-N2 NSCLC after pneumonectomy and adjuvant chemotherapy, PORT can improve OS, DFS, LRFS and DMFS with tolerable toxicity.

Prognostic value of two geriatric screening tools in a cohort of older patients with early stage Non-Small Cell Lung Cancer treated with hypofractionated stereotactic radiotherapy.

Cuccia F1, Mortellaro G2, Mazzola R3, et al. J Geriatr Oncol. 2019 May 20. pii: S1879-4068(18)30434-X. doi: 10.1016/j.jgo.2019.05.002. [Epub ahead of print]

OBJECTIVES: To investigate whether assessment with two geriatric screening tools shows a correlation with clinical outcomes of patients aged 65 years or more, with early-stage Non-Small Cell Lung Cancer (es-NSCLC) treated with hypofractionated stereotactic radiotherapy. **METHODS:** From March 2014 to June 2018 we retrospectively evaluated 42 patients with stage I and II lung tumors. Patients were assessed with Charlson Comorbidity Index (CCI) and G8 screening tool. Median age was 74 years (range, 65-91). Stereotactic radiotherapy was performed with Helical Tomotherapy delivering 50-70 Gray (Gy) in 8-10 fractions. Toxicity was evaluated using Common Terminology Criteria for Adverse Events v4.0 criteria.

RESULTS: Median CCI and G8 scores were 6 (4-11) and 14 (12-17), respectively. With a median follow-up of 14 months (3-37), we observed: 3 cases of acute Grade 2 (G2) radiation pneumonitis, 1 late G2 non-cardiac chest pain, 1 late G2 dysphagia and 1 case of late G2 radiation pneumonitis. At statistical analysis, G8 scores ≤ 14 were significantly associated with late toxicity rates ($p = .0073$). Local failure was predictive of disease free survival and Overall Survival ($p < .001$ and $p = .001$). Death occurred in 12 patients, 6 for non-cancer related causes, with 1- and 2-yrs cancer specific survival rates of 94.8% and 90%, 1- and 2-yrs OS rates of 93% and 80%, respectively. **CONCLUSIONS:** Our experience shows a correlation between G8 scores and late toxicity in older patients treated with stereotactic radiotherapy for lung cancer, suggesting the need for prospective studies evaluating its use for the identification of patients at higher risk of adverse events.

Hypofractionated proton beam therapy for centrally located lung cancer. Nakamura N1, Hotta K1, Zenda S1, et al. J Med Imaging Radiat Oncol. 2019 May 30. doi: 10.1111/1754-9485.12901. [Epub ahead of print]

INTRODUCTION: To clarify the efficacy and safety of hypofractionated proton beam therapy (PBT) for centrally located lung cancer. **METHODS:** We retrospectively reviewed 39 patients who received hypofractionated [≥ 3 Gy (relative biological effectiveness: RBE)/fraction] PBT for centrally located cT1-2N0M0 (8th edition) lung cancer between 1999 and 2015. A tumour within 2 cm of the proximal bronchial tree was defined as a centrally located tumour. **RESULTS:** Twenty-four patients (62%) were treated with 80 Gy (RBE) in 20 fractions (112 Gy₁₀), whereas eight (21%) were treated with 66 Gy (RBE) in 10 fractions (109.56 Gy₁₀). The median follow-up period for censored patients was 48 months (range: 4-140). The 2-year progression-free survival (PFS) and overall survival (OS) rates were 86 and 100% for T1 disease and 56 and 94% for T2 disease, respectively. Patients who received 110 Gy₁₀ or higher showed significantly better PFS than those who received less than 110 Gy₁₀, while no significant difference was noted in OS between the two groups. The sites of the first progression were local in six patients (27%), regional in seven (32%), distant in seven (32%), and local and distant in two (9%). Among the 13 patients with loco-regional recurrence, only two (15%) received treatments with curative intent. Dyspnoea of grade 3 was noted in one patient (3%), and pneumonitis of grade 2 was noted in four patients (10%). **CONCLUSION:** Hypofractionated PBT may be a very safe and effective treatment option for centrally located early lung cancer.

Sparing Cardiac Substructures with Optimized Volumetric Modulated Arc Therapy and Intensity-Modulated Proton Therapy in Thoracic Radiation for Locally Advanced Non-Small Cell Lung Cancer. Ferris MJ1, Sykes K2, Switchenko JM3, Kayode OA4, Wolf J4, Dang Q4, Press RH4, Curran WJ4, Higgins KA4. Pract Radiat Oncol. 2019 May 8. pii: S1879-8500(19)30125-0. doi: 10.1016/j.prro.2019.04.013. [Epub ahead of print]

PURPOSE: Increasing radiation dose to the heart is associated with worse survival in stage 3 non-small cell lung cancer (NSCLC). We sought to evaluate the abilities of optimized volumetric modulated arc therapy (VMAT) and intensity-modulated proton therapy (IMPT) to spare cardiac substructures, and sought to determine how a cardiac optimization treatment planning algorithm influences dose distribution to other thoracic organs at risk (OARs). **METHODS AND MATERIALS:** Cardiac substructures were retrospectively contoured for all stage 3 NSCLC patients treated at our institution with VMAT to 60 Gy in 2 Gy fractions, and included: valves, atrioventricular node, coronary arteries, chambers, and great vessels. New cardiac-optimized VMAT plans were created to spare these structures while preserving planning target volume (PTV) coverage and maintaining standard dose constraints to OARs. Dosimetry variables for the new cardiac-optimized VMAT plans were compared via paired t-test to the original VMAT plans. IMPT plans were also created, and the cardiac-optimized VMAT plans were then similarly compared to the IMPT plans. **RESULTS:** Twenty-six patients, treated from July 2013 to September 2017, were

included. Statistically significant improvements were demonstrated for all cardiac structures for the new cardiac-optimized VMAT plans compared to the original VMAT plans, while maintaining or improving appropriate lung, esophagus, and spinal cord constraints, and PTV coverage goals. Compared to cardiac-optimized VMAT, IMPT demonstrated additional statistically significant improvements for some cardiac dosimetry metrics, while also maintaining or improving other thoracic OAR constraints.

CONCLUSIONS: VMAT is now widely available, and high-quality VMAT plans that incorporate the cardiac substructures into the optimization process can provide overall improvements in doses to OARs and in particular substantial sparing of critical cardiac structures. IMPT provides some incremental dosimetric improvements beyond cardiac-optimized VMAT, the clinical significance of which remains uncertain.

SMALL CELL LUNG CANCER - SCLC

[Small-cell Lung Cancer in Very Elderly \(\$\geq 80\$ Years\) Patients.](#) Schild SE1, Zhao L2, Wampfler JA3, Daniels TB4, Sio T4, Ross HJ5, Paripati H5, Marks RS6, Yi J7, Liu H8, He Y9, Yang P10. Clin Lung Cancer. 2019 May 11. pii: S1525-7304(19)30111-1. doi: 10.1016/j.clcc.2019.05.007. [Epub ahead of print]

BACKGROUND: This analysis was performed to describe the outcome of very elderly (≥ 80 years) patients with small-cell lung cancer (SCLC) as there is no published data regarding these patients.

MATERIALS AND METHODS: One hundred forty-six very elderly patients with SCLC were identified from the Institutional Lung Cancer Database ranging in age from 80 to 92 years (median, 82 years). Of these, 47 (32%) patients had limited-stage SCLC (L-SCLC), and 99 (68%) had extensive-stage SCLC (E-SCLC). All were Caucasian, and the majority (64%) were female. Sixty-seven (46%) patients had Zubrod performance status (PS) of 0 to 1. **RESULTS:** Of the 146 patients, 44 (30%) received no therapy, 65 (45%) received chemotherapy alone, 27 (19%) received chemotherapy plus local therapy (thoracic radiotherapy [TRT] or surgery), and 10 (7%) received local therapy alone. The median survival was 5.4 months. On univariable analysis, age ($P = .019$), stage (L-SCLC vs. E-SCLC; $P = .0002$), PS ($P < .0001$), and treatment option ($P < .0001$) were associated with survival. On multivariable analysis, stage ($P = .011$), PS ($P = .029$), and treatment option ($P < .0001$) maintained significance. For entire cohort, the median survival was 1.3 months without active therapy, 6 months with local therapy alone, 7.2 months with chemotherapy alone, and 14.4 months with chemotherapy plus local therapy ($P < .0001$, univariable and multivariable). Similar survival findings in response to treatment were found when the L-SCLC and E-SCLC cohorts were separately analyzed. **CONCLUSIONS:** The survival of very elderly patients with SCLC was associated with stage (L-SCLC vs. E-SCLC), PS, and treatment option. Very elderly patients with SCLC often have limited functional reserve required to tolerate aggressive multimodality therapy but appeared to benefit from it. Geriatric assessments, careful monitoring, and extra support are warranted in elderly patients. Care should be individualized based on the desires and needs of each patient.

[Emerging therapies for small cell lung cancer.](#) Yang S1, Zhang Z1, Wang Q2. J Hematol Oncol. 2019 May 2;12(1):47. doi: 10.1186/s13045-019-0736-3.

Currently, chemotherapy remains the standard treatment for first- and second-line management of small cell lung cancer (SCLC). Immunotherapy has made progress in the treatment of SCLC, and nivolumab, pembrolizumab, atezolizumab, and durvalumab have led to significant improvements in clinical outcomes of SCLC. Regarding options in other classes of therapy, the cytotoxic drug lurbinectedin was granted orphan drug status based on a remarkable objective response rate of 39.3%. In addition, an increase in progression-free survival (PFS) was achieved in a phase II study of anlotinib (ALTER 1202). Future prospects for even better outcomes in SCLC lie in novel ways to integrate immunotherapy and small-

molecule TKI drugs. Innovative clinical trial designs are needed to efficiently explore the increasing number of options with new drugs and new combinations thereof for SCLC.

Small-cell Lung Cancer in Very Elderly (≥ 80 Years) Patients. Schild SE1, Zhao L2, Wampfler JA3, Daniels TB4, Sio T4, Ross HJ5, Paripati H5, Marks RS6, Yi J7, Liu H8, He Y9, Yang P10. Clin Lung Cancer. 2019 May 11. pii: S1525-7304(19)30111-1. doi: 10.1016/j.clcc.2019.05.007. [Epub ahead of print]

BACKGROUND: This analysis was performed to describe the outcome of very elderly (≥ 80 years) patients with small-cell lung cancer (SCLC) as there is no published data regarding these patients. **MATERIALS AND METHODS:** One hundred forty-six very elderly patients with SCLC were identified from the Institutional Lung Cancer Database ranging in age from 80 to 92 years (median, 82 years). Of these, 47 (32%) patients had limited-stage SCLC (L-SCLC), and 99 (68%) had extensive-stage SCLC (E-SCLC). All were Caucasian, and the majority (64%) were female. Sixty-seven (46%) patients had Zubrod performance status (PS) of 0 to 1. **RESULTS:** Of the 146 patients, 44 (30%) received no therapy, 65 (45%) received chemotherapy alone, 27 (19%) received chemotherapy plus local therapy (thoracic radiotherapy [TRT] or surgery), and 10 (7%) received local therapy alone. The median survival was 5.4 months. On univariable analysis, age ($P = .019$), stage (L-SCLC vs. E-SCLC; $P = .0002$), PS ($P < .0001$), and treatment option ($P < .0001$) were associated with survival. On multivariable analysis, stage ($P = .011$), PS ($P = .029$), and treatment option ($P < .0001$) maintained significance. For entire cohort, the median survival was 1.3 months without active therapy, 6 months with local therapy alone, 7.2 months with chemotherapy alone, and 14.4 months with chemotherapy plus local therapy ($P < .0001$, univariable and multivariable). Similar survival findings in response to treatment were found when the L-SCLC and E-SCLC cohorts were separately analyzed. **CONCLUSIONS:** The survival of very elderly patients with SCLC was associated with stage (L-SCLC vs. E-SCLC), PS, and treatment option. Very elderly patients with SCLC often have limited functional reserve required to tolerate aggressive multimodality therapy but appeared to benefit from it. Geriatric assessments, careful monitoring, and extra support are warranted in elderly patients. Care should be individualized based on the desires and needs of each patient.

Future Options of Molecular-Targeted Therapy in Small Cell Lung Cancer. Schulze AB1, Evers G2, Kerkhoff A3, Mohr M4, Schliemann C5, Berdel WE6, Schmidt LH7. Cancers (Basel). 2019 May 17;11(5). pii: E690. doi: 10.3390/cancers11050690.

Lung cancer is the leading cause of cancer-related deaths worldwide. With a focus on histology, there are two major subtypes: Non-small cell lung cancer (NSCLC) (the more frequent subtype), and small cell lung cancer (SCLC) (the more aggressive one). Even though SCLC, in general, is a chemosensitive malignancy, relapses following induction therapy are frequent. The standard of care treatment of SCLC consists of platinum-based chemotherapy in combination with etoposide that is subsequently enhanced by PD-L1-inhibiting atezolizumab in the extensive-stage disease, as the addition of immune-checkpoint inhibition yielded improved overall survival. Although there are promising molecular pathways with potential therapeutic impacts, targeted therapies are still not an integral part of routine treatment. Against this background, we evaluated current literature for potential new molecular candidates such as surface markers (e.g., DLL3, TROP-2 or CD56), apoptotic factors (e.g., BCL-2, BET), genetic alterations (e.g., CREBBP, NOTCH or PTEN) or vascular markers (e.g., VEGF, FGFR1 or CD13). Apart from these factors, the application of so-called 'poly-(ADP)-ribose polymerases' (PARP) inhibitors can influence tumor repair mechanisms and thus offer new perspectives for future treatment. Another promising therapeutic concept is the inhibition of 'enhancer of zeste homolog 2' (EZH2) in the loss of function of tumor suppressors or amplification of (proto-) oncogenes. Considering the poor prognosis of SCLC patients, new molecular pathways require further investigation to augment our therapeutic armamentarium in the future.

[Association of Twice-Daily Radiotherapy With Subsequent Brain Metastases in Adults With Small Cell Lung Cancer.](#) Zeng H1,2, Li R3, Hu C4, et al. JAMA Netw Open. 2019 May 3;2(5):e190103. doi: 10.1001/jamanetworkopen.2019.0103.

IMPORTANCE: Although thoracic twice-daily radiotherapy (TDRT) is one of the standards of care for small cell lung cancer, its association with brain metastases remains unknown. **OBJECTIVE:** To investigate the association of TDRT vs once-daily radiotherapy (ODRT) with brain metastases after prophylactic cranial irradiation in patients with small cell lung cancer. **DESIGN, SETTING, AND PARTICIPANTS:** In this multicenter cohort study, data on 778 consecutive patients with small cell lung cancer who had undergone thoracic radiotherapy (609 received ODRT and 169 received TDRT), chemotherapy, and prophylactic cranial irradiation were retrieved from the databases of 8 hospitals in China between July 1, 2003, and June 30, 2016. A 1:1 propensity score matching approach was used to control for confounding between the ODRT and TDRT groups. Confounding covariates included 8 demographic variables and 8 treatment-related covariates. Data analysis was conducted from November 1, 2017, to May 31, 2018, and reanalyzed for revision. **EXPOSURES:** The ODRT group received 50 to 66 Gy given in 25 to 33 fractions. The TDRT group received 45 Gy given in 30 fractions. **MAIN OUTCOMES AND MEASURES:** The primary end point was brain metastases. Secondary end points included progression-free survival and overall survival. **RESULTS:** Of the 778 patients (median age, 55 years [interquartile range, 48-61 years]), 204 were women and 574 were men. At a median follow-up of 23.6 months (interquartile range, 14.2-38.2 months), 131 patients (16.8%) experienced brain metastases. The rate of brain metastasis at 3 years in the TDRT group was significantly higher than in the ODRT group (26.0% vs 16.9%; hazard ratio, 1.55; 95% CI, 1.06-2.26; P = .03). Of the 338 matched patients (169 in the ODRT group vs 169 in the TDRT group), 60 (17.8%) experienced brain metastases, with a rate at 3 years of 14.9% in the ODRT group vs 26.0% in the TDRT group (hazard ratio, 1.71; 95% CI, 1.02-2.88; P = .04). Progression-free survival was similar in both the whole cohort and the matched cohort. Median overall survival in the ODRT group tended to be significantly longer than in the TDRT group after matching (47.2 vs 32.8 months; hazard ratio, 1.41; 95% CI, 0.99-2.01; P = .06). **CONCLUSIONS AND RELEVANCE:** In this study, patients with small cell lung cancer who received thoracic TDRT appeared to have a higher risk of brain metastases than those who received ODRT, which supports the need for further prospective randomized clinical trials, especially in China and other parts of Asia.

[Role of Immunotherapy in Small Cell Lung Cancer, Thymic Epithelial Tumors, and Mesothelioma.](#) Hann CL1, Scherpereel A2,3, Hellyer JA4, Wakelee HA4. Am Soc Clin Oncol Educ Book. 2019 Jan;39:543-552. doi: 10.1200/EDBK_237847. Epub 2019 May 17.

The introduction of programmed death receptor ligand-1 (PD-L1) and programmed death receptor-1 (PD-1) inhibitors into the field of non-small cell lung cancer (NSCLC) was practice changing. The pivotal trials consistently showed a clinically meaningful improvement in overall survival (OS) for patients with driver mutation-negative NSCLC, a field in which outcomes had been stagnant for decades. The success of immune checkpoint inhibitor (ICI) therapy in NSCLC has led to enthusiasm to expand the reach of these drugs into other thoracic malignancies such as thymic epithelial tumors (TETs), mesothelioma, and small cell lung cancer (SCLC). Unfortunately, the improvement in outcomes with ICI therapy in these rarer thoracic tumors has been somewhat modest, and in the case of thymoma, rates of adverse events are too high to routinely justify their use. Although the response rates seen in ICI therapy in these tumor types are similar to those seen with other available single-agent therapies for advanced disease, ICIs do present another option for clinicians treating patients with mesothelioma, small cell carcinoma, and thymic carcinoma (TC), diseases in which approved treatment options are limited. Here we review the latest trials of ICI therapy in mesothelioma, SCLC, and TETs.

[Immune Cell Infiltration May be a Key Determinant of Long-Term Survival in Small Cell Lung Cancer.](#) Muppa P1, Parrilha Terra SB1, et al. J Thorac Oncol. 2019 May 9. pii: S1556-0864(19)30356-9. doi: 10.1016/j.jtho.2019.03.028. [Epub ahead of print]

INTRODUCTION: While most small cell lung cancer (SCLC) patients die within a few months of diagnosis, a sub-group of patients survive for many years. Factors determining long-term survivorship remain largely unknown. We present the first comprehensive comparative genomic and tumor microenvironment analyses of small cell lung cancer (SCLC) between patients with long term (LTS) and expected (EXS) survival times. **METHODS:** We compared surgically resected tumors of 23 LTS (survival > 4 years) and 18 EXS (survival ≤ 2 years). There were no significant differences in clinical variables including TNM staging and curative versus non-curative intent surgery between the groups. Gene expression profiling was performed by microarrays and tumor microenvironment analyses were by IHC of prominent immune related markers. **RESULTS:** Immune related genes and pathways represented the majority of the differentially overexpressed genes in LTS compared to the EXS. The differences in the immunological tumor-microenvironment were confirmed by quantitative immuno-staining. Increased numbers of tumor infiltrating and associated lymphocytes were present throughout tumors of LTS. Several differentiating patterns of enhanced anti-tumor immunity were identified. While some areas of LTS tumors also harbored higher numbers of suppressive immune cells (monocytes, regulatory lymphocytes, and macrophages), ratios of these suppressive cells to CD3+ lymphocytes were generally lower in LTS tumors indicating a less tumor suppressive microenvironment. **CONCLUSIONS:** Our data demonstrate that long-term survivorship of SCLC patients is strongly influenced by the presence of the immune cells in the tumor microenvironment. Characterization of the anti-tumor immune responses may identify opportunities for individualized immunotherapies for SCLC.

[Malignant Pleural Effusion at Presentation in Patients with Small-Cell Lung Cancer.](#) Shojaee S1,2, Singh I3,4, Solsky I5,4, Nana-Sinkam P6. Respiration. 2019 May 23:1-5. doi: 10.1159/000499372. [Epub ahead of print]

BACKGROUND: Malignant pleural effusion (MPE) is commonly seen in patients with non-small cell lung cancer. However, the prevalence of MPE at presentation in small-cell lung cancer (SCLC) is not reported and the clinical impact of MPE at presentation on patients with SCLC remains largely unknown. **OBJECTIVE:** The objective of this study is to assess the occurrence rate of MPE and its prognostic implications at presentation in patients with SCLC. **METHOD:** We used the Surveillance Epidemiology and End Results (SEER) registry to extract data from patients with SCLC diagnosed between 2004 and 2014. The Kaplan-Meier method was used to estimate the overall survival and the Cox proportional hazard model was used to evaluate whether MPE was an independent risk for outcome. **RESULTS:** Among the 68,443 patients with SCLC, MPE was present in 7,639 (11.16%). The probability of MPE was higher in older patients with larger tumors and mediastinal lymph node involvement at presentation. Median overall survival (3 vs. 7 months), estimated 1-year survival (17 vs. 30%), and 2-year survival (6 vs. 14%) were significantly lower in patients with MPE than without MPE, respectively (hazard ratio [HR] 1.46, 95% confidence interval [CI] 1.41-1.50, p < 0.001). MPE was also an independent factor for worse survival in multivariate analysis (HR 1.36, 95% CI 1.32-1.41, p < 0.001). **CONCLUSIONS:** MPE is common at presentation (11%) in patients with SCLC and may be associated with decreased survival. Additional studies are required to assess the treatment-adjusted survival rate in the setting of MPE.

PALLIATIVE AND SUPPORTIVE CARE

[Frequency and imaging features of abdominal immune-related adverse events in metastatic lung cancer patients treated with PD-1 inhibitor.](#) Alessandrino F1,2, Sahu S2, Nishino M1,2, Adeni AE3,

Tirumani SH1,2, Shinagare AB4,5, Awad MM3. *Abdom Radiol (NY)*. 2019 May;44(5):1917-1927. doi: 10.1007/s00261-019-01935-2.

PURPOSE: To investigate the frequency and imaging features of radiographically evident abdominal immune-related adverse events (irAEs) in patients with metastatic non-small-cell lung cancer (NSCLC) treated with PD-1 inhibitors. **METHODS:** This retrospective study included 137 patients with metastatic NSCLC treated with PD-1 inhibitor nivolumab monotherapy (75 women; median age: 65 years), who had a baseline CT and at least one follow-up abdomen CT during therapy. Baseline and all follow-up abdominal CTs performed for monitoring of nivolumab therapy were reviewed to identify the organ-specific abdominal irAEs including colitis/enteritis, hepatitis, biliary toxicity, pancreatitis, nephritis, sarcoid-like reaction, and pancreatic and adrenal atrophy. Their frequency and imaging features were described. **RESULTS:** Eighteen (13%) patients had radiologically identified abdominal irAEs (median 2.1 months after starting nivolumab; interquartile range 1.17-5.83 months); 16 patients developed enteritis/colitis (12 pancolitis, two segmental colitis, one enterocolitis, one enteritis), two hepatitis, one adrenalitis. One patient with hepatitis also developed colitis/enteritis. Radiographic abdominal irAE occurred after nivolumab therapy was discontinued in six patients before any subsequent therapy was started. IrAEs prompted nivolumab interruption and treatment with steroids in four patients (three colitis/enteritis, one hepatitis). Most common CT features of colitis/enteritis included mesenteric hyperemia (n = 15), bowel wall thickening (n = 13), mucosal hyperenhancement (n = 10), and fluid-filled colon (n = 9). **CONCLUSION:** Abdominal irAEs were detected on CT in 13% of NSCLC patients treated with nivolumab, and colitis, in the pancolitis form, was the most common irAE. Given the expanding role of immunotherapy, radiologists should be aware of the frequency and imaging manifestations of abdominal irAEs and the impact on patient management.

[Stigma and Quality of Life in Patients With Advanced Lung Cancer.](#) Johnson LA1, Schreier AM1, Swanson M1, Moya JP2, Ridner S2. *Oncol Nurs Forum*. 2019 May 1;46(3):318-328. doi: 10.1188/19.ONF.318-328.

OBJECTIVES: To identify groups of participants with high and low levels of stigma and to examine the influence of stigma on social support, social constraints, symptom severity, symptom interference, and quality of life (QOL). **SAMPLE & SETTING:** 62 individuals with lung cancer were identified and recruited from a comprehensive cancer center in the southeastern United States. **METHODS & VARIABLES:** Participants completed a questionnaire that included demographic information and measures of stigma, symptom severity and interference, social support, social constraints, and QOL. IBM SPSS Statistics TwoStep Cluster Analysis was used to identify high- and low-stigma groups. Independent sample t tests were used to compare differences between the groups. **RESULTS:** 22 participants had a high level of stigma; they had significantly higher symptom severity on feeling distressed, problems remembering things, and feeling sad, and greater symptom interference related to mood, relations with others, and enjoyment of life. Participants also had significantly higher levels of social support and lower social constraints. Stigma was significantly related to lower levels of QOL. **IMPLICATIONS FOR NURSING:** Nurses should be aware that stigma may influence various factors throughout the disease trajectory; they can privately assess individuals with lung cancer for access to social supports, feelings of stigma, and QOL, and make appropriate referrals as needed.

[National Trends in End-of-Life Care for Veterans With Advanced Cancer in the Veterans Health Administration: 2009 to 2016.](#) Smith CEP1, Kamal AH1, Kluger M2, Coke P3, Kelley MJ1,4. *J Oncol Pract*. 2019 May 2;JOP1800559. doi: 10.1200/JOP.18.00559. [Epub ahead of print]

PURPOSE: It is imperative to provide quality end-of-life (EOL) care for patients with cancer. Although rates of hospice use within the Veterans Health Administration have improved, antineoplastic administration and intensive care unit (ICU) admission at the EOL, indicators of aggressive care, have not

clearly declined over recent years. **METHODS:** We identified 32,665 veterans diagnosed with stage IV lung, colorectal, or pancreatic cancer who died between 2009 and 2016 using a novel EOL Dashboard Tool created from Veterans Administration Cancer Registry data. This EOL tool reports the incidence of antineoplastic drug use in the last 14 days of life, ICU admission in the last 30 days of life, and hospice admission or consult. Change from 2009 to 2016 was assessed using a repeated measures one-way analysis of variance with post hoc test for linear trend of time for individual cancers and two-way analysis of variance for all cancers combined. **RESULTS:** Antineoplastic use in the last 14 days of life declined from 6.8% in 2009 to 4.4% in 2016 ($P = .03$). ICU admission in the last 30 days did not change significantly, from 13.3% in 2009 to 14.7% in 2016. The exception was patients with stage IV lung cancer, in whom ICU admissions increased from 12.9% to 16.2% ($P = .01$). Patients using hospice services increased from 32.4% to 52.6% ($P < .01$). **CONCLUSION:** Although antineoplastic administration at the EOL is declining for veterans with stage IV cancer, ICU admissions are unchanged and becoming more common in stage IV lung cancer despite increasing hospice use.

[Ten-Year Trends of Utilization of Palliative Care Services and Life-Sustaining Treatments and Hospital Costs Associated With Patients With Terminally Ill Lung Cancer in the United States](#)

[From 2005 to 2014.](#) Hwang J1,2, Shen J2, Kim SJ3, Chun SY2, Kioka M4, Sheraz F4, Kim P2, Byun D5, Yoo JW4. *Am J Hosp Palliat Care.* 2019 May 23;1049909119852082. doi: 10.1177/1049909119852082. [Epub ahead of print]

BACKGROUND: Palliative care services and life-sustaining treatments are provided to dying patients with lung cancer in the United States. However, data on the utilization trends of palliative care services and life-sustaining treatments of dying patients with lung cancer are not available. **METHODS:** This study was a retrospective analysis of the National Inpatient Sample data (2005-2014) and included patients with lung cancer, aged ≥ 18 years, who died in the hospitals. Claims data of palliative care services and life-sustaining treatments that contained systemic procedures, local procedures, or surgeries were extracted. Compound annual growth rates (CAGRs) using Rao-Scott correction for χ^2 tests were used to determine the statistical significance of temporal utilization trends of palliative care services and life-sustaining treatments and their hospital costs. Multilevel multivariate regressions were performed to identify factors associated with hospital costs. **RESULTS:** A total of 120 144 weighted patients with lung cancer died in the hospitals and 41.9% of them received palliative care services. The CAGRs of systemic procedures, local procedures, surgeries, palliative care services, and hospital cost were 3.42%, 3.48%, 6.08%, 18.5%, and 5.0% (all $P < .001$), respectively. Increased hospital cost was attributed to systemic procedures (50.6%), local procedures (74.4%), and surgeries (68.5%; all $P < .001$), respectively. Palliative care services were related to decreasing hospital costs by 28.6% ($P < .001$). **CONCLUSION:** The temporal trends of palliative care services indicate that their utilization has increased gradually. Palliative care services were associated with reduced hospital costs. However, life-sustaining treatments were associated with increased hospital costs.

[A randomized phase II study of nutritional and exercise treatment for elderly patients with advanced non-small cell lung or pancreatic cancer: the NEXTAC-TWO study protocol.](#)

Miura S1, Naito T2, Mitsunaga S3, et al. *BMC Cancer.* 2019 May 31;19(1):528. doi: 10.1186/s12885-019-5762-6.

BACKGROUND: Most advanced elderly cancer patients experience fatigue, anorexia, and declining physical function due to cancer cachexia, for which effective interventions have not been established. We performed a phase I study of a new nonpharmacological multimodal intervention called the nutritional and exercise treatment for advanced cancer (NEXTAC) program and reported the excellent feasibility of and compliance with this program in elderly patients with advanced cancer who were at risk for cancer cachexia. We report here the background, hypothesis, and design of the next-step multicenter, randomized

phase II study to evaluate the efficacy of the program, the NEXTAC-TWO study. **METHODS:** Patients with chemo-naïve advanced non-small cell lung cancer or pancreatic cancer, age ≥ 70 years, performance status ≤ 2 , with adequate organ function and without disability according to the modified Katz index will be eligible. In total, 130 participants will be recruited from 15 Japanese institutions and will be randomized into either the intervention group or a control group. Computer-generated random numbers are allocated to each participant. Stratification factors include performance status (0 to 1 vs. 2), site of primary cancer (lung vs. pancreas), stage (III vs. IV), and type of chemotherapy (cytotoxic vs. others). Interventions and assessment will be performed 4 times every 4 ± 2 weeks from the date of randomization. Interventions will consist of nutritional counseling, nutritional supplements (rich in branched-chain amino acids), and a home-based exercise program. The exercise program will include low-intensity daily muscle training and lifestyle education to promote physical activity. The primary endpoint is disability-free survival. It is defined as the period from the date of randomization to the date of developing disability or death due to any cause. This trial also plans to evaluate the improvements in nutritional status, physical condition, quality of life, activities of daily living, overall survival, and safety as secondary endpoints. Enrollment began in August 2017. The study results will demonstrate the efficacy of multimodal interventions for elderly cancer patients and their application for the maintenance of physical and nutritional conditions in patients with cancer cachexia. This work is supported by a grant-in-aid from the Japan Agency for Medical Research and Development. **DISCUSSION:** This is the first randomized trial to evaluate the efficacy and safety of a multimodal intervention specific for elderly patients with advanced cancer.

[Dispositional mindfulness, self-compassion, and compassion from others as moderators between stress and depression in caregivers of patients with lung cancer.](#) Hsieh CC1, Yu CJ2, Chen HJ3, Chen YW4, Chang NT1, Hsiao FH1,5. *Psychooncology*. 2019 May 13. doi: 10.1002/pon.5106. [Epub ahead of print]

OBJECTIVE: The present study aimed to identify the most important protective factors predicting caregivers' depressive symptoms among factors of caregivers' dispositional mindfulness, self-compassion, compassion from others, and patients' dispositional mindfulness and their moderator effects on the relationship between caregiving stress and depressive symptoms. **METHODS:** A total of 72 lung cancer outpatients and their family caregivers participated in this study. Family caregivers completed the Kingston Caregiver Stress Scale, Beck Depression Inventory-II (BDI-II), Five Facet Mindfulness Questionnaire (FFMQ), Self-Compassion Scale, and Compassion from Others Scale. Patients completed the EORTC Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), BDI-II, and FFMQ. **RESULTS:** After controlling for patients' factors (treatment status, symptom distress, and depressive symptoms) and caregivers' health status, caregivers' stress and dispositional mindfulness, the domain of mindful awareness, and self-compassionate action were significantly associated with their depressive symptoms. Further analysis indicated that mindful awareness or self-compassionate action could buffer the effect of caregiving stress on depressive symptoms. When the two moderators, mindful awareness and self-compassionate action, were tested simultaneously, only self-compassionate action remained as a significant moderating effect. **CONCLUSIONS:** Caregivers' mindful awareness and self-compassionate action were protective factors, which mitigate the impact of caregiving stress on their depressive symptoms. Therefore, the future supportive program aims at training the competencies of self-compassionate action with mindful awareness, which may enhance caregivers' coping resources.

Chinese Herbal Medicine (Xiaoaiping) Injections for Chemotherapy-Induced Thrombocytopenia: A Randomized, Controlled, Multicenter Clinical Trial. Qi S1,2,3,4, Li X1, Dong Q1, et al. *J Altern Complement Med.* 2019 Jun;25(6):648-655. doi: 10.1089/acm.2018.0470. Epub 2019 May 17.

OBJECTIVES: The study aims to evaluate the therapeutic efficacy and safety of Chinese herbal medicine (Xiaoaiping) injections for chemotherapy-induced thrombocytopenia (CIT) in nonsmall cell lung cancer (NSCLC) and gastric cancer. Design: A randomized, controlled, multicenter study from December 2013 to August 2015. Settings/Location: All patients are from China. **SUBJECTS:** One hundred forty patients with either NSCLC or gastric cancer were enrolled in this trial. Interventions: The intervention group (n = 70) was given Xiaoaiping injections (1 dose/day for 10 days) with chemotherapy, whereas the control group (n = 70) was given chemotherapy only. The follow up period was 11 days after the final injection. **OUTCOME MEASURES:** Platelet (PLT) count was tested at day 0, 7, 14, and 21 as the primary outcome for evaluation. Safety measurements, including red blood cells (RBC), hemoglobin (HGB), white blood cells (WBC), neutrophil (NE)#, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine kinase (CK), creatinine (Cr), and blood urea nitrogen (BUN) were tested at day 0 and 21 as the secondary outcomes. **RESULTS:** (1) Two patients in the intervention group and four patients in the control group were lost upon follow-up. (2) PLT count: there was no significant difference in PLT count between the two groups from baseline (day 0), day 7, and day 14. At day 21, the intervention group indicated an upward trend of PLT count with a statistically significant difference than that of the control group ($p < 0.05$). (3) NSCLC: there was significant difference in PLT count between the two groups on day 21 ($p < 0.01$). (4) Gastric cancer: there was no significant difference in PLT count between the two groups during this trial ($p > 0.05$). (5) There was no statistically significant difference between the intervention group and the control group with the safety figures (secondary outcomes) RBC, HGB, WBC, NE#, AST, ALT, LDH, CK, Cr, and BUN measured ($p > 0.05$). (6) Adverse events: one gastric cancer patient in the control group was diagnosed with gastrointestinal bleeding on day 3. **CONCLUSIONS:** In conclusion, Xiaoaiping injections may provide a safe and effective option for CIT in patients with NSCLC.

Yi-qi-yang-yin-tian-sui-fang enhances cisplatin-induced tumor eradication and inhibits interleukin-7 reduction in non-small cell lung cancer. Ke B1, Wu X1, Yang Q2, Huang Y3, Wang F4, Gong Y5, Liu J5, Shi L6. *Biosci Rep.* 2019 May 28. pii: BSR20190052. doi: 10.1042/BSR20190052. [Epub ahead of print]

Traditional Chinese Medicine (TCM) has been recognized to be conducive to enhancing the efficiency and reducing the side effects in the whole course of cancer treatment. The mechanisms of TCM/chemotherapy combination involved with interleukin-7 (IL-7) potentially enhance immune responses against tumor. In this study, we emphasized on an herbal formulation Yi-qi-yang-yin-tian-sui-fang or TCM for short, and investigated its roles in chemotherapy of non-small cell lung cancer (NSCLC). The mice bared with tumor were treated with cisplatin (DDP) and simultaneously administrated with/without low, medium and high doses of TCMS (effective content: 0.5 g, 2.0 g and 8.0 g/per mice) via oral gavage. The results indicated that combination of TCM further elevated the therapy efficiency of DDP in dose-dependent manner. The growth of tumor cells was estimated by Ki-67 stain and Tunel assay. The addition of TCM to the DDP treatment could significantly decrease the expression of Ki-67 and promote the apoptosis of tumor cells. In addition, the serum IL-7 level was down-regulated by DDP but restored by the treatment of TCM. The expression of IL-7 and its receptor IL-7R in tumor tissues was also recovered by TCM. Furthermore, the side effect that bone marrow suppression (myelosuppression) induced by DDP were assessed. TCM could abrogate DDP-induced apoptosis of bone marrow and also remarkably induced the expressions of IL-7 and hematopoietic growth factors including

G-CSF, GM-CSF, SCF, and SDF-1 in bone marrow. These data indicated that this TCM combined with DDP showed superior anti-tumor effects with reduced myelosuppression via up-regulating IL-7.

MISCELLANEOUS WORKS

[Analysis of time-to-treatment discontinuation of targeted therapy, immunotherapy, and chemotherapy in clinical trials of patients with non-small-cell lung cancer.](#) Blumenthal GM1,2, Gong Y1, Kehl K3, et al. *Ann Oncol.* 2019 May 1;30(5):830-838. doi: 10.1093/annonc/mdz060.

BACKGROUND: Pragmatic end points, such as time-to-treatment discontinuation (TTD), defined as the date of starting a medication to the date of treatment discontinuation or death has been proposed as a potential efficacy end point for real-world evidence (RWE) trials, where imaging evaluation is less structured and standardized. **PATIENTS AND METHODS:** We studied 18 randomized clinical trials of patients with metastatic non-small-cell lung cancer (mNSCLC), initiated after 2007 and submitted to U.S. Food and Drug Administration. TTD was calculated as date of randomization to date of discontinuation or death and compared to progression-free survival (PFS) and overall survival (OS) across all patients, as well as in treatment-defined subgroups [EGFR mutation-positive treated with tyrosine kinase inhibitor (TKI), EGFR wild-type treated with TKI, ALK-positive treated with TKI, immune checkpoint inhibitor (ICI), chemotherapy doublet with maintenance, chemotherapy monotherapy]. **RESULTS:** Overall across 8947 patients, TTD was more closely associated with PFS ($r = 0.87$, 95% CI 0.86-0.87) than with OS (0.68, 95% CI 0.67-0.69). Early TTD (PFS-TTD ≥ 3 months) occurred in 7.7% of patients overall, and was more common with chemo monotherapy (15.0%) while late TTD (TTD-PFS ≥ 3 months) occurred in 6.0% of patients overall, and was more common in EGFR-positive and ALK-positive patients (12.4% and 22.9%). In oncogene-targeted subgroups (EGFR positive and ALK positive), median TTDs (13.4 and 14.1 months) exceeded median PFS (11.4 and 11.3 months). **CONCLUSIONS:** At the patient level, TTD is associated with PFS across therapeutic classes. Median TTD exceeds median PFS for biomarker-selected patients receiving oncogene-targeted therapies. TTD should be prospectively studied further as an end point for pragmatic randomized RWE trials only for continuously administered therapies. Published by Oxford University Press on behalf of the European Society for Medical Oncology 2019. This work is written by US Government employees and is in the public domain in the US.

[Indoor Radon in EGFR- and BRAF-Mutated and ALK-Rearranged Non-Small-Cell Lung Cancer Patients.](#) Mezquita L1, Benito A2, Ruano-Raviña A3, et al. *Clin Lung Cancer.* 2019 May 3. pii: S1525-7304(19)30100-7. doi: 10.1016/j.clcc.2019.04.009. [Epub ahead of print]

BACKGROUND: Radon gas is the leading cause of lung cancer in the nonsmoking population. The World Health Organization (WHO) recommends indoor concentrations of < 100 Bq/m³. Several molecular alterations have been described in non-small-cell lung cancer (NSCLC), mainly in nonsmokers, with no risk factors identified. We studied the role of indoor radon in NSCLC patients harboring specific driver alterations. **PATIENTS AND METHODS:** We assessed the radon concentration from EGFR-, BRAF-mutated (m), and ALK-rearranged (r) NSCLC patients measured by an alpha-track detector placed in their homes between September 2014 and August 2015. Clinical characteristics were collected prospectively, and pathologic samples were reviewed retrospectively. **RESULTS:** Forty-eight patients were included (36 EGFRm, 10 ALKr, 2 BRAFm). Median radon concentration was 104 Bq/m³ (IQR 69-160) overall, and was 96 Bq/m³ (42-915) for EGFRm, 116 (64-852) for ALKr, and 125 for BRAFm, with no significant differences. Twenty-seven patients (56%) had indoor radon above WHO recommendations, 8 (80%) of 10 ALKr, 2 (100%) of 2 BRAFm, and 17 (47%) of 36 EGFRm. **CONCLUSION:** The median indoor radon concentration was above the WHO recommendations, with no differences between EGFR, ALK, and BRAF patients. Concentrations above the WHO recommendations were most common with ALKr and BRAFm. These findings should be validated in larger studies.

[Molecular links between COPD and lung cancer: new targets for drug discovery?](#) Caramori G1, Ruggeri P1, Mumby S2, et al. *Expert Opin Ther Targets*. 2019 Jun;23(6):539-553. doi: 10.1080/14728222.2019.1615884. Epub 2019 May 11.

COPD and lung cancer are leading causes of morbidity and mortality worldwide, and they share a common environmental risk factor in cigarette smoke exposure and a genetic predisposition represented by their incidence in only a fraction of smokers. This reflects the ability of cigarette smoke to induce an inflammatory response in the airways of susceptible smokers. Moreover, COPD could be a driving factor in lung cancer, by increasing oxidative stress and the resulting DNA damage and repression of the DNA repair mechanisms, chronic exposure to pro-inflammatory cytokines, repression of innate immunity and increased cellular proliferation. Areas covered: We have focused our review on the potential pathogenic molecular links between tobacco smoking-related COPD and lung cancer and the potential molecular targets for new drug development by understanding the common signaling pathways involved in COPD and lung cancer. Expert commentary: Research in this field is mostly limited to animal models or small clinical trials. Large clinical trials are needed but mostly combined models of COPD and lung cancer are necessary to investigate the processes caused by chronic inflammation, including genetic and epigenetic alteration, and the expression of inflammatory mediators that link COPD and lung cancer, to identify new molecular therapeutic targets.

[Advanced stage at diagnosis and elevated mortality among US patients with cancer infected with HIV in the National Cancer Data Base.](#) Coghill AE1,2, Han X3, Suneja G4, Lin CC3,5, Jemal A3, Shiels MS1. *Cancer*. 2019 May 3. doi: 10.1002/cncr.32158. [Epub ahead of print]

BACKGROUND: People living with HIV (PLWH) are at an increased risk of developing several cancers, but to the authors' knowledge less is known regarding how HIV impacts the rate of progression to advanced cancer or death. **METHODS:** The authors compared stage of disease at the time of presentation and mortality after diagnosis between 14,453 PLWH and 6,368,126 HIV-uninfected patients diagnosed with cancers of the oral cavity, stomach, colorectum, anus, liver, pancreas, lung, female breast, cervix, prostate, bladder, kidney, and thyroid and melanoma using data from the National Cancer Data Base (2004-2014). Polytomous logistic regression and Cox proportional hazards regression were used to evaluate the association between HIV, cancer stage, and stage-adjusted mortality after diagnosis, respectively. Regression models accounted for the type of health facility at which cancer treatment was administered and the type of individual health insurance. **RESULTS:** HIV-infected patients with cancer were found to be more likely to be uninsured (HIV-infected: 5.0% vs HIV-uninfected: 3.3%; $P < .0001$) and were less likely to have private health insurance (25.4% vs 44.7%; $P < .0001$). Compared with those not infected with HIV, the odds of being diagnosed at an advanced stage of disease were significantly elevated in PLWH for melanoma and cancers of the oral cavity, liver, female breast, prostate, and thyroid (odds ratio for stage IV vs stage I range, 1.24-2.06). PLWH who were diagnosed with stage I to stage III disease experienced elevated mortality after diagnosis across 13 of the 14 cancer sites evaluated, with hazard ratios ranging from 1.20 (95% CI, 1.14-1.26) for lung cancer to 1.85 (95% CI, 1.68-2.04), 1.85 (95% CI, 1.51-2.27), and 2.93 (95% CI, 2.08-4.13), respectively, for cancers of the female breast, cervix, and thyroid. **CONCLUSIONS:** PLWH were more likely to be diagnosed with advanced-stage cancers and to experience elevated mortality after a cancer diagnosis, even after accounting for health care-related factors.

[An Insurer's Program To Incentivize Generic Oncology Drugs Did Not Alter Treatment Patterns Or Spending On Care.](#) Yasaitis L1, Gupta A2, Newcomb C3, Kim E4, Newcomer L5, Bekelman J6. *Health Aff (Millwood)*. 2019 May;38(5):812-819. doi: 10.1377/hlthaff.2018.05083.

The high and rising costs of anticancer drugs have received national attention. The prices of brand-name anticancer drugs often dwarf those of established generic drugs with similar efficacy. In 2007-16 UnitedHealthcare sought to encourage the use of several common low-cost generic anticancer drugs by offering providers a voluntary incentivized fee schedule with substantially higher generic drug payments (and profit margins), thereby increasing financial equivalence for providers in the choice between generic and brand-name drugs and regimens. We evaluated how this voluntary payment intervention affected treatment patterns and health care spending among enrollees with breast, lung, or colorectal cancer. We found that the incentivized fee schedule had neither significant nor meaningful effects on the use of incentivized generic drugs or on spending. Practices that adopted the incentivized fee schedule already had higher rates of generic anticancer drug use before switching, which demonstrates selection bias in take-up. Our study provides cautionary evidence of the limitations of voluntary payment reform initiatives in meaningfully affecting health care practice and spending.