Caring Ambassadors Lung Cancer Program
Literature Review, February 2021

SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

Establishing a Cohort and a Biorepository to Identify Biomarkers for Early Detection of Lung Cancer: The Nashville Lung Cancer Screening Cohort Ann Am Thorac Soc. 2021 Jan 5. doi: 10.1513/AnnalsATS.202004-344OC. Online ahead of print. Dhairya A Lakhani 1 , Sheau-Chiann Chen 2 , et al.

RATIONALE: A prospective longitudinal cohort of individuals at high-risk of developing lung cancer was established to build a biorepository of carefully annotated biological specimens and low-dose computed tomography (LDCT) chest images for derivation and validation of candidate biomarkers for early detection of lung cancer. **OBJECTIVE:** The goal of this study is to characterize individuals with high-risk for lung cancer, accumulating valuable biospecimens and LDCT chest scan longitudinally over five years. **METHODS:** Participants 55-80 years of age and with a 5-year estimated risk of developing lung cancer greater than 1.5% were recruited and enrolled from clinics at Vanderbilt University Medical Center, the Veteran Affairs Medical Center, and Meharry Medical Center. Individual demographic characteristics were assessed via questionnaire at baseline. Participants underwent a LDCT scan, spirometry, sputum cytology, and research bronchoscopy at the time of enrollment. Participants will be followed yearly for five years. Positive LDCT scans are followed-up according to standard of care. The clinical, imaging and biospecimen data are collected prospectively and stored in a biorepository. Participants are offered smoking cessation counseling at each study visit. **RESULTS:** A total of 480 participants were enrolled at study baseline and consented to sharing of their data and biospecimens for research. Participants are followed with yearly clinic visits to collect imaging data and biospecimens. To date, a total of 19 cancers (13 adenocarcinomas, 4 squamous cell carcinoma, 1 large cell neuroendocrine and 1 small cell lung cancer) have been identified. **CONCLUSION:** We established a unique prospective cohort of individuals at high-risk for lung cancer, enrolled at three institutions for which full clinical data, well-annotated LDCT and biospecimens are being collected longitudinally. This repository will allow for the derivation of independent validation of clinical, imaging and molecular biomarkers of risk or diagnosis of lung cancer. Clinical trial registered with ClinicalTrials.gov (NCT01475500).

Major Pathologic Response in Patients Treated for Non-small Cell Carcinoma of the Lung: Is There a Magic Number in the Histologic Sections to be Evaluated? Adv Anat Pathol. 2021 Jan 4;Publish Ahead of Print. doi: 10.1097/PAP.0000000000000292. Online ahead of print.
Diana M Oramas 1 , Cesar A Moran
Over the last years, great advancements have taken place in the medical approach to lung non-small cell carcinomas. Currently, with the use of biomarkers and diagnostic molecular pathology, tumors that in the past were treated with conventional chemotherapy, radiation therapy, or both, now similar patients afflicted by non-small cell carcinoma may have other alternative treatments. More importantly, because of those advancements in treatment options, it has become imperative that pathologists not only become familiar with the pathologic response to those treatments but also attempt to provide a pathologic assessment of the different changes that may be present as a result of a particular treatment. Even though for pathologists the demonstration of tumor necrosis and other inflammatory responses because of therapy as well as residual tumor does not represent a difficult task to accomplish, the issue is not in the diagnostic histopathologic assessment but in providing an adequate assessment of tumor viability as well as tumor necrosis and other histopathologic changes. More interesting is to acknowledge that it is in this particular area in which there may be differences in the approach because of the lack of a universal approach regarding how much of a particular tumor needs to be examined. Needless to say, the number of histologic sections examined may at the end be used as a specific parameter for tumor response to a particular treatment. The current review, will highlight, the different methodologies that over the years have been used or employed in the assessment of what is now referred as major pathologic response.

Predictive biomarkers for response to immune checkpoint inhibitors in lung cancer: PD-L1 and beyond Virchows Arch. 2021 Jan 24. doi: 10.1007/s00428-021-03030-8. Online ahead of print.
Hironori Uruga 1 , Mari Mino-Kenudson 2
Immune checkpoint inhibitor (ICI) therapies, including the programmed cell death protein 1 (PD-1) axis blockade, are considered a major oncological breakthrough of the early twenty-first century and have led to remarkable response rates and survival in a subset of patients with non-small cell lung cancer (NSCLC). However, the available therapies work only for one in five unselected, advanced NSCLC patients; thus, patient selection needs to be performed with the use of efficient biomarkers. Although imperfect, programmed death-ligand 1 (PD-L1) expression by immunohistochemistry (IHC) on tumor cells and/or immune cells has been established as a predictive biomarker for response to the PD-1 axis blockade. There remain several pre-analytical, analytical, and post-analytical issues, however, before implementing a PD-L1 IHC assay(s) in the pathology laboratory. In addition, given the lack of robust sensitivity and specificity of PD-L1 IHC for predicting response to ICIs, other biomarkers including tumor mutation burden (TMB) are under investigation. In this review, issues associated with PD-L1 IHC and TMB estimations will be discussed, and other promising biomarkers for predicting response to ICIs will be briefly introduced.

Evaluation of Revised US Preventive Services Task Force Lung Cancer Screening Guideline Among Women and Racial/Ethnic Minority Populations JAMA Netw Open. 2021 Jan 4;4(1):e2033769. doi: 10.1001/jamanetworkopen.2020.33769.
IMPORTANCE: Lung cancer incidence and mortality disproportionately affect women and racial/ethnic minority populations, yet screening guidelines for the past several years were derived from clinical trials of predominantly White men. To reflect current evidence, the US Preventive Services Task Force (USPSTF) has revised the eligibility criteria, which may help to ameliorate sex- and race/ethnicity-related disparities in lung cancer screening. **OBJECTIVE:** To determine the changes associated with the revised USPSTF guideline for lung cancer screening eligibility among female, Black, and Hispanic populations using a large nationwide survey. **DESIGN, SETTING, AND PARTICIPANTS:** This cross-sectional

study included respondents to the Centers for Disease Control and Prevention's Behavioral Risk Factor Surveillance System who were 50 to 80 years of age with a smoking history in 19 states that used the optional lung cancer screening module. The change in eligibility among female, male, Black, Hispanic, and White participants was examined. Eligibility by sex and race/ethnicity was compared with a reference population. Data were collected from January 1, 2017, to December 31, 2018, and analyzed from May 8 to June 11, 2020. **EXPOSURES:** Self-reported sex, race/ethnicity, age, and smoking history. **MAIN OUTCOMES AND MEASURES:** Lung cancer screening eligibility using the revised USPSTF criteria. The previous criteria included current or past smokers (within 15 years) who were 55 to 80 years of age and had a smoking history of more than 30 pack-years. In the revised criteria, age was modified to 50 to 80 years; smoking history, to 20 pack-years. **RESULTS:** Among 40 869 respondents aged 50 to 80 years with a smoking history, 21 265 (52.0%) were women, 3430 (8.4%) were Black, and 1226 (30.0%) were Hispanic (mean [SD] age, 65.6 [7.9] years). The revised criteria increased eligibility for the following populations: men (29.4% to 38.3% [8.9% difference]; P < .001), women (25.9% to 36.4% [10.5% difference]; P < .001), White individuals (31.1% to 40.9% [9.8% difference]; P < .001), Black individuals (16.3% to 28.8% [12.5% difference]; P < .001), and Hispanic individuals (10.5% to 18.7% [8.2% difference]; P < .001). The odds of eligibility were lower for women compared with men (adjusted odds ratio [AOR], 0.88; 95% CI, 0.79-0.99; P = .04) and for Black (AOR, 0.43; 95% CI, 0.33-0.56; P < .001) and Hispanic populations (AOR, 0.70; 95% CI, 0.62-0.80; P < .001) compared with the White population. **CONCLUSIONS AND RELEVANCE:** The revised USPSTF guideline may likely increase lung cancer screening rates for female, Black, and Hispanic populations. However, despite these potential improvements, lung cancer screening inequities may persist without tailored eligibility criteria.

Current Status and Future Perspectives of Liquid Biopsy in Small Cell Lung Cancer Biomedicines. 2021 Jan 7;9(1):48. doi: 10.3390/biomedicines9010048. Patricia Mondelo-Macía 1 , Jorge García-González 2 3 4 , Luis León-Mateos 2 3 4 , et al.
Approximately 19% of all cancer-related deaths are due to lung cancer, which is the leading cause of mortality worldwide. Small cell lung cancer (SCLC) affects approximately 15% of patients diagnosed with lung cancer. SCLC is characterized by aggressiveness; the majority of SCLC patients present with metastatic disease, and less than 5% of patients are alive at 5 years. The gold standard of SCLC treatment is platinum and etoposide-based chemotherapy; however, its effects are short. In recent years, treatment for SCLC has changed; new drugs have been approved, and new biomarkers are needed for treatment selection. Liquid biopsy is a non-invasive, rapid, repeated and alternative tool to the traditional tumor biopsy that could allow the most personalized medicine into the management of SCLC patients. Circulating tumor cells (CTCs) and cell-free DNA (cfDNA) are the most commonly used liquid biopsy biomarkers. Some studies have reported the prognostic factors of CTCs and cfDNA in SCLC patients, independent of the stage. In this review, we summarize the recent SCLC studies of CTCs, cfDNA and other liquid biopsy biomarkers, and we discuss the future utility of liquid biopsy in the clinical management of SCLC.

Endobronchial Ultrasound Staging of Operable NSCLC: Do Triple Normal Lymph Nodes Require Routine Biopsy? Chest. 2021 Jan 9;S0012-3692(21)00027-1. doi: 10.1016/j.chest.2020.12.050. Online ahead of print. Danielle A Hylton 1 , Biniam Kidane 2 , Jonathan Spicer 3 , et al.
BACKGROUND: Staging guidelines for lung cancer recommend endobronchial ultrasound (EBUS) and systematic biopsy of at least 3 mediastinal lymph node (LN) stations for accurate staging. A 4-point ultrasonographic score (Canada Lymph Node Score- CLNS) was developed to determine the probability of malignancy in each LN. A LN with a CLNS<2 is considered low probability for malignancy. We hypothesized that, in patients with cN0 non-small cell lung cancer, LNs with CLNS<2 may not require routine biopsy because they represent true node negative disease. **RESEARCH QUESTION:** Do lymph

nodes considered triple normal on CT, PET, and CLNS require routine biopsy? **STUDY DESIGN AND METHODS:** LNs were evaluated for ultrasonographic features at the time of EBUS and the CLNS was applied. "Triple Normal" LNs were defined as cN0 on computed tomography (short axis <1cm), positron emission tomography (no hypermetabolic activity), and EBUS (CLNS<2). Specificity and negative predictive value (NPV) were calculated against the gold-standard pathological diagnosis from surgically excised specimens. **RESULTS:** In total, 143 LNs from 57 cN0 patients were assessed. Triple Normal LNs had a specificity and NPV of 60% (95%CI:51.2-68.3%) and 93.1% (95%CI:85.6-97.4%), respectively. After pathological assessment, only 5.6% (n=8/143) of Triple Normal nodes were proven to be malignant. **INTERPRETATION:** At the time of staging for lung cancer, combining CT, PET and CLNS criteria can identify Triple Normal LNs which have a high NPV for malignancy. This raises the question of whether Triple Normal LNs require routine sampling during EBUS-TBNA. A prospective trial is required to confirm these findings.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Robotic Pneumonectomy for Lung Cancer: Perioperative Outcomes and Factors Leading to Conversion to Thoracotomy Innovations (Phila). 2021 Jan 15;1556984520978227. doi: 10.1177/1556984520978227. Online ahead of print. Byron D Patton 1 , Daniel Zarif 1 , Donna M Bahroloomi 1 , Iam C Sarmiento 1 , Paul C Lee 1 , Richard S Lazzaro 1
OBJECTIVE: In the tide of robot-assisted minimally invasive surgery, few cases of robot-assisted pneumonectomy exist in the literature. This study evaluates the perioperative outcomes and risk factors for conversion to thoracotomy with an initial robotic approach to pneumonectomy for lung cancer. **METHODS:** This study is a single-center retrospective review of all pneumonectomies for lung cancer with an initial robotic approach between 2015 and 2019. Patients were divided into 2 groups: surgeries completed robotically and surgeries converted to thoracotomy. Patient demographics, preoperative clinical data, surgical pathology, and perioperative outcomes were compared for meaningful differences between the groups. **RESULTS:** Thirteen total patients underwent robotic pneumonectomy with 8 of them completed robotically and 5 converted to thoracotomy. There were no significant differences in patient characteristics between the groups. The Robotic group had a shorter operative time ($P < 0.01$) and less estimated blood loss ($P = 0.02$). There were more lymph nodes harvested in the Robotic group ($P = 0.08$) but without statistical significance. There were 2 major complications in the Robotic group and none in the Conversion group. Neither tumor size nor stage were predictive of conversion to thoracotomy. Conversions decreased over time with a majority occurring in the first 2 years. There were no conversions for bleeding and no mortalities. **CONCLUSIONS:** Robotic pneumonectomy for lung cancer is a safe procedure and a reasonable alternative to thoracotomy. With meticulous technique, major bleeding can be avoided and most procedures can be completed robotically. Larger studies are needed to elucidate any advantages of a robotic versus open approach.

Bias Against Complex Lung Cancer Surgery Ann Thorac Surg. 2021 Jan 4;S0003-4975(21)00009-6. doi: 10.1016/j.athoracsur.2020.12.019. Online ahead of print. Mark S Allen 1 , William S Harmsen 2 , Jay Mandrekar 2 , Gaetano Rocco 3
BACKGROUND: Lung cancer remains a major public health problem. There remain differences in mortality among socioeconomic and racial groups. Using the STS GTS database, we attempted to determine whether there were differences in treatment choices by thoracic surgeons based on patient's race or insurance. **METHODS:** Using data from 2012-2017, we analyzed the data from 75,774 patients with a diagnosis of lung cancer who had complete information on race and/or insurance was available and

underwent a pulmonary resection. We categorized 66,614 (87.9%) operations into "standard" (lobectomy, bilobectomy, or wedge excision) and 9,160 (12.1%) into complex (pneumonectomy, sleeve or bronchoplastic resection, segmentectomy, or Pancoast resection) operations. Univariate and multiple variable logistic regression models were used to assess associations with receipt of a complex operation. **RESULTS:** Patients with private insurance had a higher incidence of complex operations (14.4%) than patients with government insurance (11.6%) ($p<0.0001$). We also found a higher incidence of complex operations in white patients (12.2%) compared to non-white patients (11.3%) ($p=0.0054$). On multivariate analysis patients with private insurance were significantly more likely to have a complex operation (odds ratio 1.08, $p<0.03$) and non-Caucasian patients were less likely to have a complex operation (odds ratio 0.93, $p=0.04$) respectively. **CONCLUSIONS:** In this cohort of patients from the STS GTS database, white patients and those with private insurance had a higher incidence of complex operations. Many factors affect the decision to proceed with a complex thoracic surgical operation; type of medical insurance and race may represent two of them.

Prospective study of recurrence at the surgical margin after wedge resection of pulmonary metastases Gen Thorac Cardiovasc Surg. 2021 Jan 3. doi: 10.1007/s11748-020-01560-7. Online ahead of print.Satoshi Shiono 1 , Noriyuki Matsutani 2 , Hiroshi Hashimoto 3 , Yoshikane Yamauchi 2 , et al.
BACKGROUND: Pulmonary metastasectomy is a common treatment for selected patients with pulmonary metastases. Among pulmonary resections, wedge resection is considered sufficient for pulmonary metastases. However, a major problem with wedge resection is the risk of local recurrence, especially at the surgical margin. The aim of this prospective study was to explore the frequency of and the risk factors for recurrence at the surgical margin in patients who underwent wedge resection for pulmonary metastases. **METHODS:** Between September 2013 and March 2018, 177 patients (220 lesions) with pulmonary metastases from 15 institutions were enrolled. We studied 130 cases (169 lesions) to determine the frequency of and risk factors associated with recurrence at the surgical margin in patients who underwent wedge resection. Moreover, we evaluated the recurrence-free rate and disease-free survival after wedge resection. **RESULTS:** A total of 81 (62.3%) patients developed recurrence. Recurrence at the surgical margin was observed in 11 of 130 (8.5%) cases. The 5-year recurrence-free rate was 89.1%. Per patient, multivariable analysis revealed that the presence of multiple pulmonary metastases was a significant risk factor for recurrence. Per tumor, distance from the surgical margin and tumor/margin ratio were risk factors for local recurrence. The 5-year disease-free survival rate was 34.7%, and the presence of multiple pulmonary metastases and small surgical margin were risk factors for disease-free survival by univariable analysis. **CONCLUSIONS:** Among patients who undergo wedge resection for pulmonary metastasis, patients with multiple pulmonary metastases tend to develop recurrence at the surgical margin.

Lobectomy with artery reconstruction and pneumonectomy for NSCLC: a propensity score weighting study Ann Thorac Surg. 2021 Jan 9;S0003-4975(21)00045-X. doi: 10.1016/j.athoracsur.2020.12.029. Online ahead of print. Marco Schiavon 1 , Giovanni Maria Comacchio 2 , Marco Mammana 2 , et al.
BACKGROUND: The treatment of NSCLC is based, when suitable, on surgical resection. Pneumonectomy has been considered the standard surgical procedure for locally advanced lung cancers but it is associated with high mortality and morbidity rates. Reconstruction of the pulmonary artery, associated with parenchyma sparing techniques, is meant to be an alternative to pneumonectomy. **METHODS:** This retrospective single-centre study is based on a detailed and comprehensive analysis of the clinical and oncological data of patients treated between 2004 and 2016 through pneumonectomy or lobectomy with reconstruction of the pulmonary artery. A propensity score weighting approach, based on

the pre-operative characteristics of two groups of 124 patients each was performed. The subsequent statistical analysis evaluated long and short-term clinical outcomes together with risk factors analysis. **RESULTS:** The comparison between pneumonectomy and pulmonary artery reconstructions showed a higher 30-days (p=0.02) and 90-days (p=0.03) mortality rate in the pneumonectomy group, together with a higher incidence of major complications (p=0.004). Long term results have shown comparable outcomes, both in terms of 5-years disease free survival (52.2% in pneumonectomy vs 46.0% in pulmonary artery reconstructions, p=0.57) and overall 5-years survival (41.9% vs 35.6% respectively, p=0.57). Risk factors analysis showed that cancer specific survival was related to lymph node status (p<0.01) and absence of adjuvant therapy (p=0.04). Lymph node status also influenced the risk of recurrence (p<0.01). **CONCLUSIONS**: Lobectomy with reconstruction of the pulmonary artery is a valuable and oncologically safe alternative to pneumonectomy, with lower short-term mortality and morbidity, without affecting long-term oncological results.

NSCLC – Systemic Therapies (Chemotherapy, Targeted Therapy, and Immunotherapy)

Recent advances and future perspectives in adjuvant and neoadjuvant immunotherapies for lung cancer Jpn J Clin Oncol. 2021 Jan 1;51(1):28-36. doi: 10.1093/jjco/hyaa187. Masaya Yotsukura 1 , Kazuo Nakagawa 1 , Kenji Suzuki 2 , et al.
The superior efficacy of immune checkpoint inhibitors for the treatment of advanced non-small cell lung cancer has inspired many clinical trials to use immune checkpoint inhibitors in earlier stages of lung cancer worldwide. Based on the theoretical feasibility that neoantigens derived from a tumor tissue are present in vivo, some clinical trials have recently evaluated the neoadjuvant, rather than the adjuvant, use of immune checkpoint inhibitors. Some of these trials have already produced evidence on the safety and efficacy of immune checkpoint inhibitors in a neoadjuvant setting, with a favorable major pathologic response and few adverse events. In the most impactful report from Johns Hopkins University and the Memorial Sloan Kettering Cancer Center, the programed death-1 inhibitor nivolumab was administered to 21 patients in a neoadjuvant setting. The authors reported a major pathologic response rate of 45%, with no unexpected delay of surgery related to the adverse effects of nivolumab. The adjuvant as well as the neoadjuvant administration of immune checkpoint inhibitors has also been considered in various clinical trials, with or without the combined use of chemotherapy or radiotherapy. The development of appropriate biomarkers to predict the efficacy of immune checkpoint inhibitors is also underway. The expression of programed death ligand-1 and the tumor mutation burden are promising biomarkers that have been evaluated in many settings. To establish an appropriate method for using immune checkpoint inhibitors in combination with surgery, the Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group will manage clinical trials using a multimodality treatment, including immune checkpoint inhibitors and surgery.

First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial Lancet Oncol. 2021 Jan 18;S1470-2045(20)30641-0. doi: 10.1016/S1470-2045(20)30641-0. Online ahead of print. Luis Paz-Ares 1 , Tudor-Eliade Ciuleanu 2 , Manuel Cobo 3 , et al.
BACKGROUND: First-line nivolumab plus ipilimumab has shown improved overall survival in patients with advanced non-small-cell lung cancer (NSCLC). We aimed to investigate whether the addition of a limited course (two cycles) of chemotherapy to this combination would further enhance the clinical benefit. **METHODS:** This randomised, open-label, phase 3 trial was done at 103 hospitals in 19 countries. Eligible patients were aged 18 years or older with treatment-naive, histologically confirmed stage IV or recurrent NSCLC, and an Eastern Cooperative Oncology Group performance status of 0-1. Patients were randomly assigned (1:1) by an interactive web response system via permuted blocks (block

size of four) to nivolumab (360 mg intravenously every 3 weeks) plus ipilimumab (1 mg/kg intravenously every 6 weeks) combined with histology-based, platinum doublet chemotherapy (intravenously every 3 weeks for two cycles; experimental group), or chemotherapy alone (every 3 weeks for four cycles; control group). Randomisation was stratified by tumour histology, sex, and PD-L1 expression. The primary endpoint was overall survival in all randomly assigned patients. Safety was analysed in all treated patients. Results reported here are from a pre-planned interim analysis (when the study met its primary endpoint) and an exploratory longer-term follow-up analysis. This study is active but no longer recruiting patients, and is registered with ClinicalTrials.gov, number NCT03215706. **FINDINGS:** Between Aug 24, 2017, and Jan 30, 2019, 1150 patients were enrolled and 719 (62·5%) randomly assigned to nivolumab plus ipilimumab with two cycles of chemotherapy (n=361 [50%]) or four cycles of chemotherapy alone (n=358 [50%]). At the pre-planned interim analysis (median follow-up 9·7 months [IQR 6·4-12·8]), overall survival in all randomly assigned patients was significantly longer in the experimental group than in the control group (median 14·1 months [95% CI 13·2-16·2] vs 10·7 months [9·5-12·4]; hazard ratio [HR] 0·69 [96·71% CI 0·55-0·87]; p=0·00065). With 3·5 months longer median follow-up (median 13·2 months [IQR 6·4-17·0]), median overall survival was 15·6 months (95% CI 13·9-20·0) in the experimental group versus 10·9 months (9·5-12·6) in the control group (HR 0·66 [95% CI 0·55-0·80]). The most common grade 3-4 treatment-related adverse events were neutropenia (in 24 [7%] patients in the experimental group vs 32 [9%] in the control group), anaemia (21 [6%] vs 50 [14%]), diarrhoea (14 [4%] vs two [1%]), increased lipase (22 [6%] vs three [1%]), and asthenia (tjree [1%] vs eight [2%]). Serious treatment-related adverse events of any grade occurred in 106 (30%) patients in the experimental group and 62 (18%) in the control group. Seven (2%) deaths in the experimental group (acute kidney failure, diarrhoea, hepatotoxicity, hepatitis, pneumonitis, sepsis with acute renal insufficiency, and thrombocytopenia; one patient each) and six (2%) deaths in the control group (anaemia, febrile neutropenia, pancytopenia, pulmonary sepsis, respiratory failure, and sepsis; one patient each) were treatment related. **INTERPRETATION:** Nivolumab plus ipilimumab with two cycles of chemotherapy provided a significant improvement in overall survival versus chemotherapy alone and had a favourable risk-benefit profile. These data support this regimen as a new first-line treatment option for patients with advanced NSCLC.

Clinical utility of the C-reactive protein:albumin ratio in non-small cell lung cancer patients treated with nivolumab Thorac Cancer. 2021 Jan 12. doi: 10.1111/1759-7714.13788. Online ahead of print.
Taisuke Araki 1 , Kazunari Tateishi 1 , Kei Sonehara 1 , et al.
BACKGROUND: Nivolumab is a second-line chemotherapy for non-small cell lung cancer (NSCLC). This study explored the impact of clinical biomarkers such as neutrophil:lymphocyte ratio (NLR), C-reactive protein:albumin ratio (CAR), and modified Glasgow prognostic score on the efficacy and outcome of nivolumab monotherapy in previously treated NSCLC patients. **METHODS:** We retrospectively analyzed advanced or postoperative recurrence of NSCLC in 113 patients in two Japanese facilities from January 2015 to December 2019. Optimal cutoff values of NLR and CAR were assessed by the area under the receiver operating characteristic curves predicting death events to conduct regression analysis. Baseline values and values collected eight weeks after nivolumab treatment were measured to investigate time-series changes of these markers. **RESULTS:** The patients showed median overall survival (OS) and progression-free survival (PFS) of 14.0 months and 2.3 months, respectively, with both being significantly longer in patients with partial response (PR) than in patients with progressive disease (PD). Optimal cutoff levels for NLR and CAR were 5.8 and 0.83, with significant decrease in CAR (P = 0.002) from baseline levels in PR patients and significant increase in PD patients. Baseline CAR ≥0.83 was significantly associated with one-year mortality events and overall survival (OS), and multivariate analysis showed significant association of age ≤70 years, an Eastern Cooperative Oncology Group performance status score of 2 or 3, and a baseline CAR ≥0.83 with inferior OS. **CONCLUSIONS**: For

second-line nivolumab therapy, evaluation of baseline CAR and subsequent changes in CAR may be predictive of therapeutic response to nivolumab and long-term survival in NSCLC patients. **KEY POINTS:** Significant findings of the study The baseline value of C-reactive protein:albumin ratio was significantly associated with one-year mortality and overall survival in non-small cell lung cancer patients treated with nivolumab. What this study adds Time-series change of C-reactive protein:albumin ratio may be useful for predicting the treatment efficacy in patients treated with nivolumab.

Outcomes in patients with lung cancer treated with crizotinib and erlotinib in routine clinical practice: A post-authorization safety cohort study conducted in Europe and in the United States
Pharmacoepidemiol Drug Saf. 2021 Jan 11. doi: 10.1002/pds.5193. Online ahead of print. Vera Ehrenstein 1 , Kui Huang 2 , Johnny Kahlert 1 , et al.
PURPOSE: We examined safety outcomes of interest (SOI) and overall survival (OS) among lung cancer patients initiating crizotinib and erlotinib in routine clinical practice. **METHODS:** This descriptive cohort study used routinely collected health data in Denmark, Finland, Sweden, the Netherlands, and the United States (US) during 2011-2017, following crizotinib commercial availability in each country. Among crizotinib or erlotinib initiators, we reported baseline characteristics and incidence rates and cumulative incidences of the SOI - hepatotoxicity, pneumonitis/interstitial lung disease, QT interval prolongation-related events, bradycardia, vision disorders, renal cysts, edema, leukopenia, neuropathy, photosensitivity, malignant melanoma, gastrointestinal perforation, cardiac failure and OS. Results from the European Union (EU) countries were combined using meta-analysis; results from the US were reported separately. **RESULTS:** There were 456 patients in the crizotinib cohort and 2957 patients in the erlotinib cohort. Rates of the SOI per 1000 person-years in the crizotinib cohort ranged from 0 to 65 in the EU and from 0 to 374 in the US. Rates of the SOI per 1000 person-years in the erlotinib cohort ranged from 0 to 91 in the EU and from 3 to 394 in the US. In the crizotinib cohort, 2-year OS was ~50% in both EU and US. In the erlotinib cohort, 2-year OS was 21% in the EU and 35% in the US. **CONCLUSIONS:** This study describes clinical outcomes among lung cancer patients initiating crizotinib or erlotinib in routine clinical practice. Differences between SOI rates in EU and US may be partially attributable to differences in the underlying databases.

Improved survival and disease control following pembrolizumab-induced immune-related adverse events in high PD-L1 expressing non-small cell lung cancer with brain metastases
J Neurooncol. 2021 Jan 7. doi: 10.1007/s11060-020-03686-3. Online ahead of print.Michael Zhang 1 , Adrian J Rodrigues 1 , Erqi L Pollom 2 , et al.
INTRODUCTION: Immune checkpoint inhibitors have become standard of care for many patients with non-small cell lung cancer (NSCLC). These agents often cause immune-related adverse events (IRAEs), which have been associated with increased overall survival (OS). Intracranial disease control and OS for patients experiencing IRAEs with metastatic NSCLC and brain metastases have not yet been described. **METHODS:** We performed a single-institution, retrospective review of patients with NSCLC and existing diagnosis of brain metastasis, who underwent pembrolizumab treatment and developed any grade IRAE. The primary outcome of the study was intracranial time to treatment failure (TTF), defined from time of pembrolizumab initiation to new intracranial disease progression or death. Kaplan-Meier and Cox proportional hazard analyses were performed. **RESULTS:** A total of 63 patients with NSCLC brain metastasis were identified, and 24 developed IRAEs. Patients with any grade IRAEs had longer OS (21 vs. 10 months, $p = 0.004$), systemic TTF (15 vs. 4 months, $p < 0.001$) and intracranial TTF (14 vs. 5 months, $p = 0.001$), relative to patients without IRAEs. Presence of IRAEs and high PD-L1 ($\geq 50\%$), but not absent/moderate PD-L1 (0-49%), had a positive association for OS, systemic TTF, and intracranial TTF. Following multivariable analysis, IRAE experienced on pembrolizumab was an independent predictor of OS, systemic TTF, and intracranial TTF. **CONCLUSIONS:** In our series of patients with

NSCLC and brain metastases treated with pembrolizumab, IRAE presence was associated with a significant increase in OS, systemic TTF, and intracranial TTF. Future studies with increased cohorts will clarify how IRAEs should be interpreted among molecular subtypes.

Brief report: Four-year survival with durvalumab after chemoradiotherapy in Stage III NSCLC - an update from the PACIFIC trial J Thorac Oncol. 2021 Jan 18;S1556-0864(21)00022-8. doi: 10.1016/j.jtho.2020.12.015. Online ahead of print.Corinne Faivre-Finn 1 , David Vicente 2 , Takayasu Kurata 3 , et al.
BACKGROUND: In the phase-3, placebo-controlled PACIFIC trial of patients with unresectable, stage III non-small-cell lung cancer (NSCLC) without disease progression after concurrent chemoradiotherapy (CRT), consolidative durvalumab was associated with significant improvements in the primary endpoints of overall survival (OS) (HR, 0.68; 95% CI, 0.53-0.87; P=0.00251; data-cutoff, 22-March-2018) and progression-free survival (PFS; blinded-independent-central-review; RECIST-v1.1) (HR, 0.52; 95% CI, 0.42-65; P<0.0001; 13-February-2017) with manageable safety. We report updated analyses of OS and PFS, approximately 4 years after the last patient was randomized. **METHODS:** Patients with WHO PS 0/1 (any tumor PD-L1 status) were randomized (2:1) to intravenous durvalumab (10 mg/kg), or placebo, every-2-weeks (≤12 months), stratified by age, sex, and smoking history. OS/PFS were analyzed using a stratified log-rank test in the intent-to-treat population. Medians and 4-year OS/PFS rates were estimated by Kaplan-Meier method. **RESULTS:** Overall, 709/713 randomized patients received durvalumab (n/N=473/476) or placebo (n/N=236/237). As of 20-March-2020 (median follow-up, 34.2 months; range, 0.2-64.9), updated OS (HR, 0.71; 95% CI, 0.57-0.88) and PFS (HR, 0.55; 95% CI, 0.44-0.67) remained consistent with the primary analyses. Median OS for durvalumab was reached (47.5 months; placebo, 29.1 months). Estimated 4-year OS rates were 49.6% versus 36.3% for durvalumab versus placebo, and 4-year PFS rates were 35.3% versus 19.5% respectively. **CONCLUSIONS:** These updated, exploratory analyses demonstrate durable PFS and sustained OS benefit with durvalumab following CRT. An estimated 49.6% of patients randomized to durvalumab remain alive at 4 years (placebo, 36.3%), and 35.3% remain alive and progression free (placebo, 19.5%).

Efficacy of Osimertinib Plus Bevacizumab vs Osimertinib in Patients With EGFR T790M-Mutated Non-Small Cell Lung Cancer Previously Treated With Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor: West Japan Oncology Group 8715L Phase 2 Randomized Clinical Trial JAMA Oncol. 2021 Jan 7;e206758. doi: 10.1001/jamaoncol.2020.6758. Online ahead of print.
Hiroaki Akamatsu 1 , Yukihiro Toi 2 , Hidetoshi Hayashi 3 , et al.
IMPORTANCE: Although treatment with first-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) plus antiangiogenic inhibitor has shown promising efficacies in patients with EGFR-mutated lung adenocarcinoma, recent single-arm studies have suggested that osimertinib plus antiangiogenic inhibitor might not work synergistically. **OBJECTIVE:** To explore the efficacy and safety of osimertinib plus bevacizumab compared with osimertinib alone in patients with lung adenocarcinoma with EGFR T790M mutation. **DESIGN, SETTING, AND PARTICIPANTS:** Patients with advanced lung adenocarcinoma that progressed with prior EGFR-TKI treatment (other than third-generation TKI) and acquired EGFR T790M mutation were enrolled. This study comprises a lead-in part with 6 patients and a subsequent phase 2 part. In phase 2, patients were randomized to osimertinib plus bevacizumab or osimertinib alone in a 1:1 ratio. **INTERVENTIONS:** The combination arm received oral osimertinib (80 mg, every day) plus intravenous bevacizumab (15 mg/kg, every 3 weeks) until progression or unacceptable toxic effects. The control arm received osimertinib monotherapy. **MAIN OUTCOMES AND MEASURES:** The primary end point was progression-free survival (PFS) assessed by investigators. Secondary end points consisted of overall response rate, time to treatment failure, overall survival, and safety. **RESULTS:** From August 2017 through September 2018, a total of 87 patients were

registered (6 in the lead-in part and 81 in the phase 2 part [intention-to-treat population]). Among those randomized, the median (range) age was 68 (41-82) years; 33 (41%) were male; 37 (46%) had an Eastern Cooperative Oncology Group performance status of 0; and 21 (26%) had brain metastasis. Although the overall response rate was better with osimertinib plus bevacizumab than osimertinib alone (68% vs 54%), median PFS was not longer with osimertinib plus bevacizumab (9.4 months vs 13.5 months; adjusted hazard ratio, 1.44; 80% CI, 1.00 to 2.08; P = .20). Median time to treatment failure was also shorter in the combination arm vs the osimertinib arm (8.4 months vs 11.2 months; P = .12). Median overall survival was not different in the combination arm vs osimertinib arm (not reached vs 22.1 months; P = .96). In the combination arm, common adverse events of grade 3 or higher were proteinuria (n = 9; 23%), hypertension (n = 8; 20%). **CONCLUSIONS AND RELEVANCE:** In this randomized clinical trial comparing osimertinib plus bevacizumab vs osimertinib alone, the combination arm failed to show prolongation of PFS in patients with advanced lung adenocarcinoma with EGFR T790M mutation.

NSCLC - RADIOTHERAPY

The Role of Radiation Therapy in the Older Patient Curr Oncol Rep. 2021 Jan 2;23(1):11. doi: 10.1007/s11912-020-01000-y. Ammoren Dohm 1 , Roberto Diaz 1 , Ronica H Nanda 2
PURPOSE OF REVIEW: Older patients represent a unique subgroup of the cancer patient population for which the role of radiation therapy (RT) requires special consideration. This review will discuss many of these considerations as well as various radiation treatment techniques in the context of a variety of disease sites. **RECENT FINDINGS:** Several recent studies give insight into the management of older cancer patients considering their age, performance status, comorbid conditions, quality of life, genetics, cost, and individual goals. RT plays an evolving and pivotal role in providing optimal care for this population. Recent advances in RT technique allow for more precise treatment delivery and reduced toxicity. Studies evaluating the use of radiation therapy in breast, brain, lung, prostate, rectal, pancreatic, esophageal, and oligometastatic cancer are summarized and discussed in the context of treating the older patient population. Individual age, performance and functional status, comorbid conditions, and patients' objectives and goals should all be considered when presenting treatment options for older patients and age alone should not disqualify patients from curative intent treatments. When possible, hypofractionated courses should be utilized as outcomes are often equivalent and toxicities are reduced. In many cases, RT may be preferable to other treatment options due to decreased toxicity profile and acceptable disease control.

Differences in patterns of recurrence of squamous cell carcinoma and adenocarcinoma after radiotherapy for stage III non-small cell lung cancer Jpn J Radiol. 2021 Jan 23. doi: 10.1007/s11604-021-01091-y. Online ahead of print. Yu Katagiri 1 , Keiichi Jingu 2 , Takaya Yamamoto 1 , et al.
PURPOSE: To evaluate the differences in patterns of recurrence and treatment results by histology after definitive radiotherapy for stage III non-small cell lung cancer (NSCLC) in Japan. **MATERIALS AND METHODS:** Patients with stage III NSCLC who underwent definitive radiotherapy between 2000 and 2016 in our institution were included. A total of 217 patients were enrolled. Propensity score matching was used to exclude the following confounding factors: (1) age (≥70 years or <70 years), (2) gender, (3) T factor, (4) N factor, (5) Eastern Cooperative Oncology Group performance status score and (6) smoking status (Brinkman index ≥400 or <400). **RESULTS:** The median observation period for survivors was 55.1 months. After propensity score matching, the Sqcc and adenocarcinoma groups each included 62 paired patients. There was no significant difference in OS or PFS between the adenocarcinoma and Sqcc groups. However, rates of recurrence in the GTV-primary site (p = 0.009) and GTV-lymph node site (p = 0.037) were significantly higher in patients with Sqcc than in patients with adenocarcinoma. New metastatic recurrence was more frequent in patients with adenocarcinoma than in patients with Sqcc (p =

0.025). **CONCLUSION:** There were significant differences in patterns of recurrence after definitive (chemo)radiotherapy between patients with Sqcc and patients with adenocarcinoma.

The Impact of Radiotherapy on the Incidence of Secondary Malignancies: A Pan-Cancer Study in the US SEER Cancer Registries Curr Oncol. 2021 Jan 8;28(1):301-316. doi: 10.3390/curroncol28010035. Wei Li 1 , Haitao Xiao 1 , Xuewen Xu 1 , Yange Zhang 1
The population of cancer patients with second primary malignancies (SPMs) is rapidly growing. The relationship between radiotherapy and SPMs for some types of tumors is unknown or debated. In this study, we identify 24 types of first primary malignancies (FPMs) between 2004 and 2015 in the Surveillance, Epidemiology, and End Results (SEER) database. Patients in the radiotherapy group were matched to those in the no radiotherapy group with a matching ratio of 1:1. After propensity-score matching (PSM), additional competing risk regression analyses were performed to calculate the efficacy of radiotherapy to SPMs in the PSM-adjusted population. In addition, the Fine and Gray model was utilized in the primary cohorts, and stratified analyses were performed based on surgery. This study includes a total of 2,831,789 eligible patients with tumors diagnosed from 2004 to 2015 in the SEER 18 database, amongst whom 100,194 (3.5%) patients developed SPMs. We observe higher risks of SPMs associated with radiotherapy in several types of tumors in the PSM-adjusted populations (small bowel adenocarcinoma, small cell lung carcinoma, prostate adenocarcinoma, urinary bladder transitional cell carcinoma, invasive ductal breast carcinoma, invasive lobular breast carcinoma, and Hodgkin lymphoma). The results in the PSM-adjusted populations were consistent with outcomes in the multivariable competing risk models. Meanwhile, in subgroup analyses stratified by surgery, some other types of tumor (except for those with positive results in the PSM-adjusted cohorts) with radiotherapy were also associated with a higher prevalence of SPMs in the subgroups of surgical treatment (pancreatic adenocarcinoma, rectal adenocarcinoma, lung adenocarcinoma and follicular thyroid carcinoma in the surgery subgroups). The impact of radiotherapy on the incidence of secondary malignancies is distinct in different types of cancer. These findings merit further investigation and may ultimately impact treatment decision-making for tumor management.

Safety of radiosurgery concurrent with systemic therapy (chemotherapy, targeted therapy, and/or immunotherapy) in brain metastases: a systematic review Cancer Metastasis Rev. 2021 Jan 4. doi: 10.1007/s10555-020-09949-9. Online ahead of print. Pierre-Yves Borius 1 , Jean Régis 2 , Alexandre Carpentier 3 , Michel Kalamarides 3 , Charles Ambroise Valery 3 , Igor Latorzeff 4
Stereotactic radiosurgery (SRS) is a standard option for brain metastases (BM). There is lack of consensus when patients have a systemic treatment, if a washout is necessary. The aim of this review is to analyze the toxicity of SRS when it is concurrent with chemotherapies, immunotherapy, and/or targeted therapies. From Medline and Embase databases, we searched for English literature published up to April 2020 according to the PRISMA guidelines, using for key words the list of the main systemic therapies currently in use And "radiosurgery," "SRS," "GKRS," "Gamma Knife," "toxicity," "ARE," "radiation necrosis," "safety," "brain metastases." Studies reporting safety or toxicity with SRS concurrent with systemic treatment for BM were included. Of 852 abstracts recorded, 77 were included. The main cancers were melanoma, lung, breast, and renal carcinoma. These studies cumulate 6384 patients. The median SRS dose prescription was 20 Gy [12-30] .For some, they compared a concurrent arm with a non-concurrent or a SRS-alone arm. There were no skin toxicities, no clearly increased rate of bleeding, or radiation necrosis with significant clinical impact. SRS combined with systemic therapy appears to be safe, allowing the continuation of treatment when brain SRS is considered.

A comparison of mixture cure fraction models to traditional parametric survival models in estimation of the cost-effectiveness of nivolumab for relapsed small cell lung cancer J Med Econ. Jan-Dec 2021;24(1):79-86. doi: 10.1080/13696998.2020.1857960. Joshua A Roth 1 , Yong Yuan 2 , Megan Othus 1 , Mark Danese 3 , Samuel Wagner 2 , John R Penrod 2 , Scott D Ramsey 1
BACKGROUND: In August 2018, the US FDA granted accelerated approval for nivolumab in small cell lung cancer (SCLC) that has progressed after platinum-based chemotherapy and at least one other line of therapy. The objective of this study was to evaluate the cost-effectiveness of nivolumab vs. usual care as third-line (3 L) therapy for patients with recurrent SCLC (rSCLC) from the health payer perspective. Given the potential for a meaningful fraction of treated patients to achieve long-term response to nivolumab, we also assessed the impact of using mixture cure modeling (MCM) vs. parametric survival modeling on survival estimates and cost-effectiveness from the US Medicare payer perspective. **METHODS:** We created a partitioned survival decision model to assess the cost-effectiveness of 3 L nivolumab vs. usual care in rSCLC, based on observed US treatment patterns. Using this approach, we assessed the impact of extrapolating long-term survival from the CheckMate 032 trial, using both MCM and standard parametric curve fits. Nivolumab survival, resource use, and Grade 3/4 adverse event rates were derived from CheckMate 032. Usual care survival, resource use, and costs were derived from an analysis of patients receiving 3 L treatment for rSCLC in the SEER-Medicare registry. We applied 2020 Wholesale Acquisition Cost for drugs and 2020 CMS reimbursement for procedures. Utilities were derived from the literature. We estimated life years (LY), quality-adjusted life years (QALYs), and costs over a lifetime horizon. **RESULTS:** MCM and parametric survival model extrapolations resulted in 0.43 versus 0.38 more LYs, 0.34 versus 0.30 more QALYs, and $69,308 versus $61,336 more expenditure for nivolumab vs. usual care, respectively. The costs per QALY gained using mixture cure versus parametric survival modeling were $204,386 and $207,431, respectively. **CONCLUSIONS:** Mixture cure modeling was equivalent compared to parametric modeling in estimating the cost-effectiveness of nivolumab-based therapy due to the small fraction of patients achieving a long-term response with nivolumab (12.9%).

Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133) Clin Oncol. 2021 Jan 13;JCO2001055. doi: 10.1200/JCO.20.01055. Online ahead of print. Stephen V Liu 1 , Martin Reck 2 , Aaron S Mansfield 3 , et al.
PURPOSE: IMpower133 (ClinicalTrials.gov identifier: NCT02763579), a randomized, double-blind, phase I/III study, demonstrated that adding atezolizumab (anti-programmed death-ligand 1 [PD-L1]) to carboplatin plus etoposide (CP/ET) for first-line (1L) treatment of extensive-stage small-cell lung cancer (ES-SCLC) resulted in significant improvement in overall survival (OS) and progression-free survival (PFS) versus placebo plus CP/ET. Updated OS, disease progression patterns, safety, and exploratory biomarkers (PD-L1, blood-based tumor mutational burden [bTMB]) are reported. **PATIENTS AND METHODS:** Patients with untreated ES-SCLC were randomly assigned 1:1 to receive four 21-day cycles of CP (area under the curve 5 mg per mL/min intravenously [IV], day 1) plus ET (100 mg/m2 IV, days 1-3) with atezolizumab (1,200 mg IV, day 1) or placebo, and then maintenance atezolizumab or placebo until unacceptable toxicity, disease progression, or loss of clinical benefit. Tumor specimens were collected; PD-L1 testing was not required for enrollment. The two primary end points, investigator-assessed PFS and OS, were statistically significant at the interim analysis. Updated OS and PFS and exploratory biomarker analyses were conducted. **RESULTS:** Patients received atezolizumab plus CP/ET (n = 201) or placebo plus CP/ET (n = 202). At the updated analysis, median follow-up for OS was 22.9 months; 302 deaths had occurred. Median OS was 12.3 and 10.3 months with atezolizumab plus CP/ET and placebo plus CP/ET, respectively (hazard ratio, 0.76; 95% CI, 0.60 to 0.95; descriptive P = .0154). At

18 months, 34.0% and 21.0% of patients were alive in atezolizumab plus CP/ET and placebo plus CP/ET arms, respectively. Patients derived benefit from the addition of atezolizumab, regardless of PD-L1 immunohistochemistry or bTMB status. **CONCLUSION:** Adding atezolizumab to CP/ET as 1L treatment for ES-SCLC continued to demonstrate improved OS and a tolerable safety profile at the updated analysis, confirming the regimen as a new standard of care. Exploratory analyses demonstrated treatment benefit independent of biomarker status.

Small-cell lung cancer Nat Rev Dis Primers. 2021 Jan 14;7(1):3. doi: 10.1038/s41572-020-00235-0. Charles M Rudin 1 2 , Elisabeth Brambilla 3 , Corinne Faivre-Finn 4 5 , Julien Sage 6 7
Small-cell lung cancer (SCLC) represents about 15% of all lung cancers and is marked by an exceptionally high proliferative rate, strong predilection for early metastasis and poor prognosis. SCLC is strongly associated with exposure to tobacco carcinogens. Most patients have metastatic disease at diagnosis, with only one-third having earlier-stage disease that is amenable to potentially curative multimodality therapy. Genomic profiling of SCLC reveals extensive chromosomal rearrangements and a high mutation burden, almost always including functional inactivation of the tumour suppressor genes TP53 and RB1. Analyses of both human SCLC and murine models have defined subtypes of disease based on the relative expression of dominant transcriptional regulators and have also revealed substantial intratumoural heterogeneity. Aspects of this heterogeneity have been implicated in tumour evolution, metastasis and acquired therapeutic resistance. Although clinical progress in SCLC treatment has been notoriously slow, a better understanding of the biology of disease has uncovered novel vulnerabilities that might be amenable to targeted therapeutic approaches. The recent introduction of immune checkpoint blockade into the treatment of patients with SCLC is offering new hope, with a small subset of patients deriving prolonged benefit. Strategies to direct targeted therapies to those patients who are most likely to respond and to extend the durable benefit of effective antitumour immunity to a greater fraction of patients are urgently needed and are now being actively explored.

PALLIATIVE AND SUPPORTIVE CARE

End-of-life patterns of symptom management and cancer-directed care among Medicare beneficiaries with lung cancer: a claims-based analysis Support Care Cancer. 2021 Jan 3. doi: 10.1007/s00520-020-05964-2. Online ahead of print.
BACKGROUND: Rather than early hospice enrollment, most Medicare beneficiaries receive "usual care" in the last months of life, outside of the hospice setting. While care intensity during the last weeks of life has been studied extensively, patterns of symptom management services (SMS) and/or cancer-directed therapies (CDT) received over a 6-month end-of-life period have not. **METHODS:** This retrospective study used the Surveillance, Epidemiology, and End Results (SEER)-Medicare database to identify decedents diagnosed with lung cancer at age ≥ 66 years between January 2007 and December 2013 who survived ≥ 6 months from diagnosis. Medicare claims identified receipt of SMS and/or CDT. We created monthly indicators for care content (SMS-only, CDT-only, or both; otherwise full-month hospice or inpatient/skilled nursing). Multinomial logistic regression estimated associations between sociodemographics and comorbidity, with care content in the final month. **RESULTS:** Between 6 and 1 months before death, full-month hospice and inpatient/skilled nursing increased; CDT decreased from 31.9 to 18.5%; SMS increased from 86.6 to 97.7%. Relative to full-month hospice, the percentage of patients receiving SMS-only was higher for males, unmarried, younger age, and higher comorbidity; the percentage receiving CDT was also higher for males, unmarried, and younger age, but decreased with increasing comorbidity and over calendar time. **CONCLUSION:** Among lung cancer decedents observed in the outpatient, nonhospice setting, SMS receipt increased and was nearly universal as death approached. CDT diminished dramatically over the end-of-life period. Associations between

sociodemographic characteristics and care setting suggest differences in care preferences or access barriers. Claims represent an important resource for characterizing end-of-life care patterns.

Cost Savings Associated With Palliative Care Among Older Adults With Advanced Cancer Am J Hosp Palliat Care. 2021 Jan 11;1049909120986800. doi: 10.1177/1049909120986800. Online ahead of print. Paige E Sheridan 1 , Wendi G LeBrett 1 , Daniel P Triplett 1 , Eric J Roeland 2 , Andrew R Bruggeman 1 , Heidi N Yeung 3 , James D Murphy 1

BACKGROUND: There is inconsistent evidence that palliative care intervention decreases total healthcare expenditure at end-of-life for oncology patients. This inconsistent evidence may result from small sample sizes at single institution studies and disparate characterization of costs across studies. Comprehensive studies in population-based datasets are needed to fully understand the impact of palliative care on total healthcare costs. This study analyzed the impact of palliative care on total healthcare costs in a nationally representative sample of advanced cancer patients. **METHODS:** We conducted a matched cohort study among Medicare patients with metastatic lung, colorectal, breast and prostate cancers. We matched patients who received a palliative care consultation to similar patients who did not receive a palliative care consultation on factors related to both the receipt of palliative care and end of life costs. We compared direct costs between matched patients to determine the per-patient economic impact of a palliative care consultation. **RESULTS:** Patients who received a palliative care consultation experienced an average per patient cost of $5,834 compared to $7,784 for usual care patients (25% decrease; $p < 0.0001$). Palliative care consultation within 7 days of death decreased healthcare costs by $451, while palliative care consultation more than 4 weeks from death decreased costs by $4,643. **CONCLUSION:** This study demonstrates that palliative care has the capacity to substantially reduce healthcare expenditure among advanced cancer patients. Earlier palliative care consultation results in greater cost reductions than consultation in the last week of life.

Examination of individual and multiple comorbid conditions and health-related quality of life in older cancer survivors Qual Life Res. 2021 Jan 14;1-11. doi: 10.1007/s11136-020-02713-0. Online ahead of print. Elizabeth J Siembida 1 2 3 , Ashley Wilder Smith 4 , Arnold L Potosky 5 , Kristi D Graves 5 , Roxanne E Jensen 4

PURPOSE: Older cancer survivors (≥ 65 years at diagnosis) are at high-risk for multimorbidity (2 + comorbid conditions). However, few studies have utilized a generalizable sample of older cancer survivors to understand how individual comorbid conditions, as opposed to total comorbidity burden, are associated with health-related quality of life (HRQOL). We examined associations between HRQOL outcomes (pain, fatigue, physical function), individual comorbidities (cardiovascular disease [CVD], lung disease, diabetes, arthritis) and total comorbidity (cancer-only, cancer + 1 condition, cancer + 2 or more conditions). **METHODS:** Utilizing a population-based sample of 2019 older cancer survivors, we tested associations between comorbid conditions and the HRQOL outcomes using generalized linear models. HRQOL domains were assessed using Patient-Reported Outcome Measurement Information System® (PROMIS®) measures. Comorbidity was assessed via self-report. **RESULTS:** Cancer survivors with lung disease reported significantly worse physical functioning ($\beta = -4.96$, $p < 0.001$), survivors with arthritis reported significantly higher pain ($\beta = 4.37$, $p < 0.001$), and survivors with CVD reported significantly higher fatigue ($\beta = 3.45$, $p < 0.001$) compared to survivors without each condition. Having cancer + 1 condition was not as strongly associated with all outcomes as when individual conditions were tested (e.g. pain: $\beta = 3.09$, $p < 0.001$). Having 2+ comorbidities had a stronger association with all outcomes (e.g. physical function: $\beta = -7.51$, $p < 0.001$) than examining conditions individually. **CONCLUSIONS:** Knowing the specific comorbid condition profile of an older cancer survivor provides insight into specific HRQOL outcomes that may be impaired in cancer survivorship, but understanding total comorbidity

burden, regardless of the specific conditions, sheds light on survivors at-risk for multiple impairments in HRQOL. This information, taken together, can inform risk-stratified survivorship care.

Physiologic and psychologic adaptation to exercise interventions in lung cancer patients undergoing chemotherapy: a systematic review and meta-analysis of randomized controlled trials Support Care Cancer. 2021 Jan 6. doi: 10.1007/s00520-020-05939-3. Online ahead of print. Junga Lee 1
OBJECTIVE: The purpose of this meta-analysis is to investigate the effectiveness of exercise interventions in patients with lung cancer (LC) during chemotherapy regarding physiological and psychological outcomes. **METHODS:** Databases including MEDLINE and EMBASE were used to find relevant randomized controlled trails that explored outcomes of exercise interventions for patients with LC during chemotherapy up to June 2020. Effect sizes were calculated by standardized mean difference statistics. **RESULTS:** Six studies were included that involved 244 participants with average age of 65 years. Patients with LC participating in exercise interventions during chemotherapy had significantly increased strength, forced expired volume, and quality of life as well as significantly decreased pain. Effective exercise intervention characteristics were combined aerobic and resistance exercise, performance more than 5 times a week, moderate to vigorous intensity, and 1-h sessions. **CONCLUSION:** Supervised participation in exercise improves strength, forced expired volume, and quality of life and relieves pain and depression during chemotherapy.

COMPLEMENTARY & ALTERNATIVE THERAPY

Herbal medicines for anorexia in lung cancer: A protocol for systematic review and meta-analysis Medicine (Baltimore). 2020 Dec 24;99(52):e23913. doi: 10.1097/MD.0000000000023913. Ju Ah Lee 1 , Kyun Ha Kim 2 , Geum Young Ko 2 , Hwa-Seung Yoo 3 , Jun-Yong Choi 2 4 5
INTRODUCTION: Lung cancer is the leading cause of cancer-related death worldwide. Anorexia is the most common cause of malnutrition in lung cancer patients as well as an independent prognostic factor for cancer survival. This review will deal with the clinical evidence of herbal medicine use for reducing anorexia in lung cancer patients. **METHODS AND ANALYSIS:** Fourteen electronic databases will be searched from inception until October 2020. We will include randomized controlled trials (RCTs) assessing herbal medicines for anorexia in lung cancer patients. Interventions of any herbal medicines will be included. The methodological qualities of the included RCTs will be assessed via the Cochrane Collaboration tool for assessing the risk of bias. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) instrument will be used to evaluate the confidence in the cumulative evidence. **ETHICS AND DISSEMINATION:** This systematic literature review does not require an ethics review. This review will be published in a peer-reviewed journal and disseminated electronically and in print. The review will be updated to inform and guide healthcare practices.

Efficacy and safety of Shengjiang Xiexin decoction in prophylaxis of chemotherapy-related diarrhea in small cell lung cancer patients: study protocol for a multicenter randomized controlled trial Trials. 2020 May 1;21(1):370. doi: 10.1186/s13063-020-04275-5. Chao Deng 1 , Yanni Lou 1 , Yu Gao 1 2 , Bo Deng 1 , Fei Su 1 , Liqun Jia 3
BACKGROUND: Diarrhea is a common adverse reaction in patients with cancer receiving chemotherapy, for which there is currently no effective method of treatment. Shengjiang Xiexin decoction (SXD), a classic traditional Chinese medicine (TCM) formula, has shown efficacy in alleviating irinotecan-induced diarrhea in preliminary clinical studies. The current study is designed to assess the efficacy and safety of SXD for prophylaxis against irinotecan-induced diarrhea. Additionally, we employ a new approach to analyze and evaluate the data based on the patients' uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) genotype, which predicts the risk of diarrhea. **METHODS AND**

DESIGN: A prospective, double-blind, randomized, placebo-controlled trial will be conducted in patients with small cell lung cancer (SCLC) from five hospitals in China. For this study, 100 irinotecan-naïve patients will be randomly allocated to either the SXD or placebo arms in a 1:1 ratio. Stratified randomization will be used to divide subjects by UGT1A1 genotype into groups with differing risk of diarrhea. The trial will consist of two cycles of chemotherapy with 14 days of oral administration of SXD or placebo administered beginning between 3 days before and up to 11 days after initiation of each chemotherapy cycle. The primary study outcome is the incidence of diarrhea. Secondary outcomes include the degree of diarrhea, the degree of neutropenia, the rate of alterations in chemotherapy regimens, the amount of antidiarrheal drug taken, the rate of hospitalization, and evaluation of chemotherapy efficacy. **DISCUSSION:** This study is the first to use the UGT1A1 genotype to stratify patients into groups based on their risk of diarrhea, and to provide a complete assessment of chemotherapy-related diarrhea (CRD), including records of diarrhea duration, grading the severity of diarrhea, and evaluating concomitant symptoms. Study results will provide high-level clinical evidence on the use of SXD as prophylaxis for CRD.

MISCELLANEOUS WORKS

A Systematic Review and Meta-Analysis of Clinical Characteristics and Outcomes in Patients With Lung Cancer with Coronavirus Disease 2019 JTO Clin Res Rep. 2021 Mar;2(3):100141. doi: 10.1016/j.jtocrr.2020.100141. Epub 2021 Jan 7. Monica Peravali 1 , Ishani Joshi 2 , Jaeil Ahn 3 , Chul Kim 4

Cancer is considered to be an independent risk factor for severe illness and higher mortality in patients with coronavirus disease 2019 (COVID-19). These adverse outcomes have been suspected to be more severe in patients with lung cancer. The objective of this systematic review and meta-analysis is to outline patient characteristics, challenges in diagnosis and treatment, and outcomes of patients with lung cancer with COVID-19. A comprehensive search was conducted using EMBASE and PubMed databases using the terms "COVID" and "cancer." Studies that reported clinical characteristics or outcomes of patients with lung cancer with COVID-19 were then systematically identified. Meta-analysis for COVID-19 related mortality associated with lung cancer compared with other cancer types was conducted. The results were reported as OR and confidence intervals using the mixed-effects logistic regression model. The most frequently reported clinical findings in patients with lung cancer with COVID-19 were fever and cough, with 68% and 61%, respectively. Laboratory and radiographic findings were consistent with broadly reported data. The meta-analysis noted a statistically significant increase in mortality rate in patients with lung cancer compared with other patients with cancer, with an OR of 1.62 (95% confidence interval: 1.06-2.48). Patients with lung cancer with COVID-19 also reflected greater severity of illness and higher rates of intensive care unit admissions and mechanical ventilation. COVID-19 in patients with lung cancer is associated with severe disease and increased mortality relative to patients with other malignancies and the general population. There is conflicting evidence on the effect of specific lung cancer treatments on outcomes. Until more definitive data is available, lung cancer-directed treatment should be continued or restarted as early as possible in mild to moderate cases to prevent worsening and cancer-related mortality.

Lung Cancer Pre-Diagnostic Pathways from First Presentation to Specialist Referral Curr Oncol. 2021 Jan 11;28(1):378-389. doi: 10.3390/curroncol28010040.Satya Rashi Khare 1 , Sreenath Arekunnath Madathil 2 , Gerald Batist 3 , Peter Brojde Lung Cancer Group 4 , Isabelle Vedel 1 5

BACKGROUND: Lung cancer is often diagnosed at a late stage with high associated mortality. Timely diagnosis depends on timely referral to a respiratory specialist; however, in Canada, little is known about how patients move through primary care to get to a respiratory specialist. Accordingly, we aimed to

identify and describe lung cancer pre-diagnostic pathways in primary care from first presentation to referral. **METHODS:** In this retrospective cohort study, patients with primary lung cancer were recruited using consecutive sampling (n = 50) from a lung cancer center in Montréal, Québec. Data on healthcare service utilization in primary care were collected from chart reviews and structured patient interviews and analyzed using latent class analysis to identify groups of patients with similar pre-diagnostic pathways. Each group was described based on patient- and tumor-related characteristics and the sequence of utilization activities. **RESULTS:** 68% of the patients followed a pathway where family physician (FP) visits were dominant ("FP-centric") and 32% followed a pathway where walk-in clinic and emergency department (ED) visits were dominant ("ED-centric"). Time to referral in the FP group was double that of the ED group (45 days (IQR: 12-111) vs. 22 (IQR: 5-69)) with more advanced disease (65% vs. 50%). In the FP group, 29% of the patients saw their FP three times or more before being referred and 41% had an ED visit. **CONCLUSIONS:** Our findings may reflect the challenge of diagnosing lung cancer in primary care, missed opportunities for earlier diagnosis, and a lack of integration between primary and specialist care.

Epigenetic underpinnings of inflammation: Connecting the dots between pulmonary diseases, lung cancer and COVID-19 Semin Cancer Biol. 2021 Jan 20;S1044-579X(21)00008-0. doi: 10.1016/j.semcancer.2021.01.003. Online ahead of print. Shama Ahmad 1 , Shajer Manzoor 1 , Simmone Siddiqui 1 , Nithya Mariappan 1 , Iram Zafar 1 , Aamir Ahmad 1 , Aftab Ahmad 2
Inflammation is an essential component of several respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma and acute respiratory distress syndrome (ARDS). It is central to lung cancer, the leading cancer in terms of associated mortality that has affected millions of individuals worldwide. Inflammation and pulmonary manifestations are also the major causes of COVID-19 related deaths. Acute hyperinflammation plays an important role in the COVID-19 disease progression and severity, and development of protective immunity against the virus is greatly sought. Further, the severity of COVID-19 is greatly enhanced in lung cancer patients, probably due to the genes such as ACE2, TMPRSS2, PAI-1 and furin that are commonly involved in cancer progression as well as SAR-CoV-2 infection. The importance of inflammation in pulmonary manifestations, cancer and COVID-19 calls for a closer look at the underlying processes, particularly the associated increase in IL-6 and other cytokines, the dysregulation of immune cells and the coagulation pathway. Towards this end, several reports have identified epigenetic regulation of inflammation at different levels. Expression of several key inflammation-related cytokines, chemokines and other genes is affected by methylation and acetylation while non-coding RNAs, including microRNAs as well as long non-coding RNAs, also affect the overall inflammatory responses. Select miRNAs can regulate inflammation in COVID-19 infection, lung cancer as well as other inflammatory lung diseases, and can serve as epigenetic links that can be therapeutically targeted. Furthermore, epigenetic changes also mediate the environmental factors-induced inflammation. Therefore, a better understanding of epigenetic regulation of inflammation can potentially help develop novel strategies to prevent, diagnose and treat chronic pulmonary diseases, lung cancer and COVID-19.

Social Media and Your Cancer Patient Semin Thorac Cardiovasc Surg. 2021 Jan 9;S1043-0679(21)00008-3. doi: 10.1053/j.semtcvs.2020.12.014. Online ahead of print. Brendon M Stiles 1 , J Nathan Mynard 2
In an increasingly connected world, healthcare is rapidly evolving to meet the needs of a growing patient population seeking information online. In the past few years, social media has erupted as a means of dissemination of health-related information between patients and healthcare providers alike. Patients online have access to communities and expert-opinion previously inaccessible. Cancer patients especially are empowered through online knowledge acquisition and interactions with support groups or advocacy groups. As patients continue seeking information online, social media has increasingly been recognized as

an important potential physician-patient interface. Healthcare provider's presence on social media is growing to meet this need. Providers can utilize social media to easily reach patients to promote health-related information, guide important conversations like the importance of cancer screening and even improve health-related behaviors. Social media can also aid in conducting research through cultivation of networking, patient recruitment, and promotion of rapid dissemination of new results. Whether through "Tweet chats" or conference hashtags, the most up to date information is easily accessible and rapidly transmissible. Social media is positioned to bridge a gap of communication and accessibility between 21st century patients and physicians.

Lung adenocarcinoma patients have higher risk of SARS-CoV-2 infection Aging (Albany NY). 2021 Jan 10;12. doi: 10.18632/aging.202375. Online ahead of print.Long Chen 1 , Yue Liu 1 , Jiamin Wu 2 , Chao Deng 3 , Jianjun Tan 3 , Huawen Liu 3 , Li Zhong 1
Both lung adenocarcinoma and coronavirus disease 2019 would cause pulmonary inflammation. Angiotensin-converting enzyme 2, the functional receptor of SARS-CoV-2, also plays a key role in lung adenocarcinoma. To study the risk of SARS-CoV-2 infection in lung adenocarcinoma patients, mRNA and microRNA profiles were obtained from The Cancer Genome Atlas and Gene Expression Omnibus followed by bioinformatics analysis. A network which regards angiotensin-converting enzyme 2 as the center was structured. In addition, via immunological analysis to explore the essential mechanism of SARS-CoV-2 susceptibility in lung adenocarcinoma. Compared with normal tissue, angiotensin-converting enzyme 2 was increased in lung adenocarcinoma patients. Furthermore, a total of 7 correlated differently expressed mRNAs (ACE2, CXCL9, MMP12, IL6, AZU1, FCN3, HYAL1 and IRAK3) and 5 correlated differently expressed microRNAs (miR-125b-5p, miR-9-5p, miR-130b-5p, miR-381-3p and miR-421) were screened. Interestingly, the most frequent toll-like receptor signaling pathway was enriched by mRNA (interlukin 6) and miRNA (miR-125b-5p) sets simultaneously. In conclusion, it was assumed that miR-125b-5p-ACE2-IL6 axis could alter the risk of SARS-CoV-2 infection in lung adenocarcinoma patients.

Recent updates on biomarkers of exposure and systemic toxicity in e-cigarette users and EVALI Am J Physiol Lung Cell Mol Physiol. 2021 Jan 27. doi: 10.1152/ajplung.00520.2020. Online ahead of print. Samantha R McDonough 1 , Irfan Rahman 1 , Isaac Kirubakaran Sundar 2
Electronic nicotine delivery systems (ENDS), or e-cigarettes, are emerging tobacco products that produce aerosols by heating e-liquids, which most often consist of propylene glycol and vegetable glycerin along with various flavoring compounds, bypassing the combustion that occurs in the use of traditional tobacco cigarettes. These products have seen a drastic increase in popularity in recent years both as smoking cessation devices as well as among younger generations, due in large part to the widespread perception among consumers that e-cigs are significantly less harmful for health than traditional tobacco cigarettes. Due to the novelty of ENDS as well as their rapidly increasing use, research into biomarkers of e-cig exposure and toxicity have lagged behind their popularity, leaving important questions about their potential toxicity unanswered. Research into potential biomarkers of acute, chronic e-cig use and E-cigarette- or Vaping-Associated Lung Injury is necessary for informing both clinical and regulatory decision-making. We aim to provide an updated review of recent research into potential circulating, genomic, transcriptomic and epigenetic biomarkers of exposure to and toxicity of e-cigs. We additionally highlight research areas that warrant additional study to gain better understanding of health risks associated with ENDS use, as well as to provide validation of existing data and methods for measuring and analyzing e-cig-associated biomarkers in human and animal biofluids, tissues and cells. This review also highlights ongoing efforts within the WNY Center for Research on Flavored Tobacco for research into novel biomarkers in extracellular vesicles that may be associated with short- and long-term ENDS use.

Role of vitamin D in regulating COVID-19 severity-An immunological perspective J Leukoc Biol. 2021 Jan 19. doi: 10.1002/JLB.4COVR1020-698R. Online ahead of print.
Vandana Kalia 1 2 , George P Studzinski 3 , Surojit Sarkar 1 2 4
Vitamin D, a key nutrient/prohormone classically associated with skeletal health, is also an important immunomodulator, with pleotropic effects on innate and adaptive immune cells. Outcomes of several chronic, autoimmune, and infectious diseases are linked to vitamin D. Emergent correlations of vitamin D insufficiency with coronavirus-induced disease 2019 (COVID-19) severity, alongside empirical and clinical evidence of immunoregulation by vitamin D in other pulmonary diseases, have prompted proposals of vitamin D supplementation to curb the COVID-19 public health toll. In this review paper, we engage an immunological lens to discuss potential mechanisms by which vitamin D signals might regulate respiratory disease severity in severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infections, vis a vis other pulmonary infections. It is proposed that vitamin D signals temper lung inflammatory cascades during SARS-CoV2 infection, and insufficiency of vitamin D causes increased inflammatory cytokine storm, thus leading to exacerbated respiratory disease. Additionally, analogous to studies of reduced cancer incidence, the dosage of vitamin D compounds administered to patients near the upper limit of safety may serve to maximize immune health benefits and mitigate inflammation and disease severity in SARS-CoV2 infections. We further deliberate on the importance of statistically powered clinical correlative and interventional studies, and the need for in-depth basic research into vitamin D-dependent host determinants of respiratory disease severity.

Determination of disease severity in COVID-19 patients using deep learning in chest X-ray images Diagn Interv Radiol. 2021 Jan;27(1):20-27. doi: 10.5152/dir.2020.20205. Maxime Blain 1 , Michael T Kassin 1 , et al.
PURPOSE: Chest X-ray plays a key role in diagnosis and management of COVID-19 patients and imaging features associated with clinical elements may assist with the development or validation of automated image analysis tools. We aimed to identify associations between clinical and radiographic features as well as to assess the feasibility of deep learning applied to chest X-rays in the setting of an acute COVID-19 outbreak. **METHODS:** A retrospective study of X-rays, clinical, and laboratory data was performed from 48 SARS-CoV-2 RT-PCR positive patients (age 60±17 years, 15 women) between February 22 and March 6, 2020 from a tertiary care hospital in Milan, Italy. Sixty-five chest X-rays were reviewed by two radiologists for alveolar and interstitial opacities and classified by severity on a scale from 0 to 3. Clinical factors (age, symptoms, comorbidities) were investigated for association with opacity severity and also with placement of central line or endotracheal tube. Deep learning models were then trained for two tasks: lung segmentation and opacity detection. Imaging characteristics were compared to clinical datapoints using the unpaired student's t-test or Mann-Whitney U test. Cohen's kappa analysis was used to evaluate the concordance of deep learning to conventional radiologist interpretation. **RESULTS:** Fifty-six percent of patients presented with alveolar opacities, 73% had interstitial opacities, and 23% had normal X-rays. The presence of alveolar or interstitial opacities was statistically correlated with age ($P = 0.008$) and comorbidities ($P = 0.005$). The extent of alveolar or interstitial opacities on baseline X-ray was significantly associated with the presence of endotracheal tube ($P = 0.0008$ and $P = 0.049$) or central line ($P = 0.003$ and $P = 0.007$). In comparison to human interpretation, the deep learning model achieved a kappa concordance of 0.51 for alveolar opacities and 0.71 for interstitial opacities. **CONCLUSION:** Chest X-ray analysis in an acute COVID-19 outbreak showed that the severity of opacities was associated with advanced age, comorbidities, as well as acuity of care. Artificial intelligence tools based upon deep learning of COVID-19 chest X-rays are feasible in the acute outbreak setting.