Caring Ambassadors Lung Cancer Program
Literature Review, March 2021

SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

Provision of Smoking Cessation Resources in the Context of in-person Shared Decision Making for Lung Cancer Screening Chest. 2021 Mar 18;S0012-3692(21)00493-1. doi: 10.1016/j.chest.2021.03.016. Online ahead of print. Jolie Shen 1 , Kristina Crothers 2 , Erin K Kross 3 , Kaylee Petersen 4 , Anne C Melzer 5 , Matthew Triplette 6

BACKGROUND: Lung cancer screening (LCS) is effective at reducing mortality for high-risk smokers. Mortality benefits go beyond early cancer detection, as shared-decision making (SDM) may present a "teachable moment" to reinforce cessation and provide resources. **RESEARCH QUESTION:** How well is smoking cessation performed during LCS SDM encounters and what patient and provider characteristics associated with smoking cessation assistance? **STUDY DESIGN AND METHODS:** This is a retrospective cohort study of current smokers participating in initial LCS SDM through a multisite program in Seattle, Washington between 2015-2018. The LCS tracking database and EHR were reviewed for demographics, comorbidity data and clinical encounter information. The primary outcome was provision of a smoking cessation resource, defined as: referral to cessation resources, recommendation for nicotine replacement and/or prescription for cessation medication. Participant and provider factor associations with the outcome were evaluated using χ2 testing and multivariable logistic regression. **RESULTS:** The majority of the 423 study participants were men (70%), with a median age of 61 (IQR 58-66) years and median of 50 (41-72) pack-years of smoking. Only 26% of encounters had documentation consistent with SDM. Thirty-nine percent of participants received at least one smoking cessation resource, and only 5% received both counseling referrals and medication. In a multivariable model, the provision of any smoking cessation resource was half as likely in participants with higher levels of comorbidity (Charlson Index >2, OR 0.53, 95% CI: 0.31-0.81), and half as likely if the ordering provider was not the patient's PCP or their specialist (OR 0.55, 95% CI 0.32-0.96). **INTERPRETATION:** Overall provision of smoking cessation resources was moderate during SDM encounters for LCS, and lower in patients with more comorbidities and when not performed by the patient's PCP or specialist. Interventions are needed to improve smoking cessation counseling and resource utilization at the time of LCS encounters.

[A Machine Learning Model Based on PET/CT Radiomics and Clinical Characteristics Predicts ALK Rearrangement Status in Lung Adenocarcinoma](#) Front Oncol. 2021 Mar 2;11:603882. doi: 10.3389/fonc.2021.603882. eCollection 2021. Cheng Chang 1 2 , Xiaoyan Sun 1 2 , Gang Wang 3 , et al. **OBJECTIVES:** Anaplastic lymphoma kinase (ALK) rearrangement status examination has been widely used in clinic for non-small cell lung cancer (NSCLC) patients in order to find patients that can be treated with targeted ALK inhibitors. This study intended to non-invasively predict the ALK rearrangement status in lung adenocarcinomas by developing a machine learning model that combines PET/CT radiomic features and clinical characteristics. **METHODS**: Five hundred twenty-six patients of lung adenocarcinoma with PET/CT scan examination were enrolled, including 109 positive and 417 negative patients for ALK rearrangements from February 2016 to March 2019. The Artificial Intelligence Kit software was used to extract radiomic features of PET/CT images. The maximum relevance minimum redundancy (mRMR) and least absolute shrinkage and selection operator (LASSO) logistic regression were further employed to select the most distinguishable radiomic features to construct predictive models. The mRMR is a feature selection method, which selects the features with high correlation to the pathological results (maximum correlation), meanwhile retain the features with minimum correlation between them (minimum redundancy). LASSO is a statistical formula whose main purpose is the feature selection and regularization of data model. LASSO method regularizes model parameters by shrinking the regression coefficients, reducing some of them to zero. The feature selection phase occurs after the shrinkage, where every non-zero value is selected to be used in the model. Receiver operating characteristic (ROC) analysis was used to evaluate the performance of the models, and the performance of different models was compared by the DeLong test. **RESULTS:** A total of 22 radiomic features were extracted from PET/CT images for constructing the PET/CT radiomic model, and majority of these features used were based on CT features (20 out of 22), only 2 PET features were included (PET percentile 10 and PET difference entropy). Moreover, three clinical features associated with ALK mutation (age, burr and pleural effusion) were also employed to construct a combined model of PET/CT and clinical model. We found that this combined model PET/CT-clinical model has a significant advantage to predict the ALK mutation status in the training group (AUC = 0.87) and the testing group (AUC = 0.88) compared with the clinical model alone in the training group (AUC = 0.76) and the testing group (AUC = 0.74) respectively. However, there is no significant difference between the combined model and PET/CT radiomic model. **CONCLUSIONS:** This study demonstrated that PET/CT radiomics-based machine learning model has potential to be used as a non-invasive diagnostic method to help diagnose ALK mutation status for lung adenocarcinoma patients in the clinic.

[Next Generation Sequencing for liquid biopsy based testing in Non-Small Cell Lung Cancer in 2021](#) Crit Rev Oncol Hematol. 2021 Mar 26;103311. doi: 10.1016/j.critrevonc.2021.103311. Online ahead of print. Pasquale Pisapia 1 , José Luis Costa 2 , Francesco Pepe 1 , et al. Lung cancer is the leading cause of cancer death worldwide, with non-small cell lung cancer (NSCLC) representing its most commonly diagnosed sub-type. Despite the significant improvements in lung cancer biomarkers knowledge, accompanied by substantial technological advances in molecular tumor profiling, a considerable fraction (up to 30%) of advanced NSCLC patient presents with major testing challenges or tissue unavailability for molecular analysis. In this context, liquid biopsy is on the rise, currently gaining considerable interest within the molecular pathology and oncology community. Molecular profiling of liquid biopsy specimens using next generation molecular biology methodologies is a rapidly evolving field with promising applications not exclusively limited to advanced stages but also more recently expanding to early stages cancer patients. Here, we offer an overview of some of the most consolidated and emerging applications of next generation sequencing technologies for liquid biopsy testing in NSCLC.

[**Patient Perspectives on the Risk-Based NLST Outcomes Tool for Lung Cancer Screening**](#) J Cancer Educ. 2021 Mar 9. doi: 10.1007/s13187-021-01977-5. Online ahead of print. Megan C Roberts 1 , Elizabeth L Seaman 2 , William M P Klein 2 , Rebecca A Ferrer 2 , Paul K J Han 3 , Hormuzd A Katki 2 , Stephanie R Land 2 , Robert A Liotta 4   5 , Joel A Nations 6   7 , P Gabriel Peterson 4   5

Researchers at the NCI have developed the Risk-Based NLST Outcomes Tool (RNOT), an online tool that calculates risk of lung cancer diagnosis and death with and without lung cancer screening, and false-positive risk estimates. This tool has the potential to facilitate shared decision making for screening. The objective of this study was to examine how current heavy and former smokers understand and respond to personalized risk estimates from the RNOT. Individuals who were eligible for lung cancer screening and were visiting Walter Reed National Military Medical Center were invited to participate in a semi-structured interview to assess their experiences with and perceptions of the RNOT. Results were analyzed using template analysis. Participants found their risk of lung cancer death to be lower than anticipated and were confused by changes in risk for lung cancer diagnosis with and without screening. Most participants indicated that the RNOT would be helpful in making screening decisions, despite reporting that there was no maximum risk for a false positive that would lead them to forgo lung cancer screening. Participants provided actionable needs and recommendations to optimize this tool. Risk-based screening tools may enhance shared decision making. The RNOT is being updated to incorporate these findings.

[**Expanding TNM for lung cancer through machine learning**](#) Thorac Cancer. 2021 Mar 13. doi: 10.1111/1759-7714.13926. Online ahead of print. Matthew Hueman 1 , Huan Wang 2 , Zhenqiu Liu 3 , Donald Henson 4 , Cuong Nguyen 5 , Dean Park 6 , Li Sheng 7 , Dechang Chen 4

BACKGROUND: Expanding the tumor, lymph node, metastasis (TNM) staging system by accommodating new prognostic and predictive factors for cancer will improve patient stratification and survival prediction. Here, we introduce machine learning for incorporating additional prognostic factors into the conventional TNM for stratifying patients with lung cancer and evaluating survival. **METHODS:** Data were extracted from SEER. A total of 77 953 patients were analyzed using factors including primary tumor (T), regional lymph node (N), distant metastasis (M), age, and histology type. Ensemble algorithm for clustering cancer data (EACCD) and C-index were applied to generate prognostic groups and expand the current staging system. **RESULTS:** With T, N, and M, EACCD stratified patients into 11 groups, resulting in a significantly higher accuracy in survival prediction than the 10 AJCC stages (C-index = 0.7346 vs. 0.7247, increase in C-index = 0.0099, 95% CI: 0.0091-0.0106, p-value = 9.2×10^{-147}). There nevertheless remained a strong association between the EACCD grouping and AJCC staging (rank correlation = 0.9289; p-value = 6.7×10^{-22}). A further analysis demonstrated that age and histological tumor could be integrated with the TNM. Data were stratified into 12 prognostic groups with an even higher prediction accuracy (C-index = 0.7468 vs. 0.7247, increase in C-index = 0.0221, 95% CI: 0.0212-0.0231, p-value $< 5 \times 10^{-324}$). **CONCLUSIONS:** EACCD can be successfully applied to integrate additional factors with T, N, M for lung cancer patients.

[**Suitability of Bronchoscopic Biopsy Tissue Samples for Next-Generation Sequencing**](#) Diagnostics (Basel). 2021 Feb 25;11(3):391. doi: 10.3390/diagnostics11030391. Shuji Murakami 1 , Tomoyuki Yokose 2 , Daiji Nemoto 3 , et al.

A sufficiently large tissue sample is required to perform next-generation sequencing (NGS) with a high success rate, but the majority of patients with advanced non-small-cell lung cancer (NSCLC) are diagnosed with small biopsy specimens. Biopsy samples were collected from 184 patients with bronchoscopically diagnosed NSCLC. The tissue surface area, tumor cell count, and tumor content rate of each biopsy sample were evaluated. The impact of the cut-off criteria for the tissue surface area (≥1 mm2) and tumor content rate (≥30%) on the success rate of the Oncomine Dx Target Test (ODxTT) was

evaluated. The mean tissue surface area of the transbronchial biopsies was 1.23 ± 0.85 mm2 when small endobronchial ultrasonography with a guide sheath (EBUS-GS) was used, 2.16 ± 1.49 mm2 with large EBUS-GS, and 1.81 ± 0.75 mm2 with endobronchial biopsy (EBB). The proportion of samples with a tissue surface area of ≥1 mm2 was 48.8% for small EBUS-GS, 79.2% for large EBUS-GS, and 78.6% for EBB. Sixty-nine patients underwent ODxTT. The success rate of DNA sequencing was 84.1% and that of RNA sequencing was 92.7% over all patients. The success rate of DNA (RNA) sequencing was 57.1% (71.4%) for small EBUS-GS (n = 14), 93.4% (96.9%) for large EBUS-GS (n = 32), 62.5% (100%) for EBB (n = 8), and 100% (100%) for endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) (n = 15). Regardless of the device used, a tissue surface area of ≥ 1 mm2 is adequate for samples to be tested with NGS.

[Safety and Diagnostic Yield of Transthoracic Needle Aspiration of the Lung in Elderly Patients](#)
Lung. 2021 Mar 12. doi: 10.1007/s00408-021-00429-7. Online ahead of print. Drew Willey 1 , Juan Garcia-Saucedo 2 , Fernando Stancampiano 1 , et al.
BACKGROUND: Pulmonary nodules in elderly patients are commonly encountered in clinical practice. Tissue sampling with image guided transthoracic needle aspiration is often performed but may be complicated by pneumothorax or bleeding. To understand the outcomes of transthoracic needle aspiration in the elderly, we retrospectively reviewed outcomes of patients age 75 or greater in a single tertiary center. **METHODS:** Four-hundred eleven patients age 75 or greater with a pulmonary nodule identified on computed tomography who underwent needle aspiration of the lung were studied. Diagnostic yield and procedural complications were assessed for each patient and subgroups analysis of those age 85 or greater was performed. **RESULTS:** Malignancy was confirmed in 70% of subjects and a benign diagnosis identified in 9%. Of the 411 patents, 203 (49.4%) experienced a complication; 150 patients (36.5%) developed a pneumothorax and 79 (19.2%) had bleeding. No patient required transfusion, experienced persistent air leak or massive hemoptysis, air embolism or death. Post procedural hospitalization was required in 36 patients (8.8%) with a median hospital stay of 2 days. No factors were identified to be associated with occurrence of a complication (all p ≥ 0.16) and complications were not increased in those 85 or greater. **CONCLUSION:** Our results suggest that in an elderly population, image guided needle aspiration of a pulmonary nodule provides diagnostic findings in most patients. Procedural complications following are not uncommon but the severity and long-term impact are limited. The occurrence of complications is similar in those age 75-84 and age 85 and older.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[Segmental resection is associated with decreased survival in patients with stage IA non-small cell lung cancer with a tumor size of 21-30 mm](#) Transl Lung Cancer Res. 2021 Feb;10(2):900-913. doi: 10.21037/tlcr-20-1217.
BACKGROUND: The feasibility of segmental resection for early-stage non-small cell lung cancer (NSCLC) is still controversial. This study aimed to compare survival outcomes following lobectomy and segmental resection in patients with pathological T1cN0M0 (tumor size 21-30 mm) NSCLC.
METHODS: Patients diagnosed between 1998 and 2016 with pathological stage IA NSCLC and with tumors measuring 21-30 mm were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. The observational outcomes were cancer-specific survival (CSS) and overall survival (OS) at 5 years. Univariate survival analysis was carried out to identify potential prognostic factors of prolonged survival. Cox proportional hazards model was used to adjust for confounding factors. Additionally, pairwise comparisons were conducted between lobectomy and segmental resection for CSS

and OS, and forest plots were drawn. **RESULTS:** Of the 9,580 patients analyzed, 400 patients (4.2%) underwent segmental resections. Patients with older age (P<0.001), smaller tumors (P<0.001), and left-sided tumors (P=0.002) were more likely to receive segmental resection. No difference was found in the operative mortality rates between the segmental resection group and the lobectomy group (1.0% vs. 1.2%, P=0.707). The CSS (HR, 1.429; 95% CI, 1.166-1.752; P=0.001) and OS (HR, 1.348; 95% CI, 1.176-1.544; P<0.001) in the segmental resection group were significantly worse than those in the lobectomy group. Subgroup analyses by age, year of diagnosis, sex, tumor size, histology, grade, and the number of dissected lymph nodes also confirmed that lobectomy was associated with improved CSS and OS. **CONCLUSIONS:** Lobectomy and thorough removal of lymph nodes should continue to be the recommended standard of care for patients with surgically resectable stage IA NSCLC with tumor size of 21-30 mm.

[Correlation between smoking status and short-term outcome of thoracoscopic surgery for lung cancer](#) Ann Thorac Surg. 2021 Mar 2;S0003-4975(21)00350-7. doi: 10.1016/j.athoracsur.2021.01.063. Online ahead of print. Takashi Yamamichi 1 , Junji Ichinose 2 , Naoya Iwamoto 1 , Kenshiro Omura 1 , Hiroki Ozawa 1 , Yasuto Kondo 1 , Kohei Hashimoto 1 , Yosuke Matsuura 1 , Masayuki Nakao 1 , Sakae Okumura 1 , Mingyon Mun 1
BACKGROUND: Smoking has a major role in the risk of postoperative pulmonary complications. We aimed to elucidate the correlation between smoking status and pulmonary complications following thoracoscopic surgery for lung cancer. **METHODS:** A total of 1,751 patients who underwent thoracoscopic lobectomy or segmentectomy for lung cancer between April 2011 and March 2020 were assessed. The rate of pulmonary complications was evaluated according to smoking status and preoperative duration of smoking cessation. Univariate and multivariate logistic regression analyses were performed. **RESULTS:** Pulmonary complications were observed in 50 patients (2.9%), while 3 (0.2%) died within 90 days of surgery. The rate of pulmonary complications was higher in smokers than in nonsmokers (4.6% vs. 0.9%, p < 0.001), and smoking history was an independent risk factor of pulmonary complications (odds ratio = 3.31, p = 0.007). The complication rate in patients with a cessation period of > 2 months was significantly lower than that in those who ceased smoking within 2 months (4.0% vs. 8.5%, p = 0.043), but it was still higher than that in nonsmokers (4.0% vs. 0.9%, p < 0.001). In the multivariable analysis for smokers, preoperative short-term smoking cessation within 2 months, male sex, histology, tumor size, and cardiopulmonary comorbidities were associated with pulmonary complications instead of pack-year smoking history. **CONCLUSIONS:** Smoking habits and preoperative smoking cessation were independently associated with pulmonary complications after thoracoscopic surgery for lung cancer. A preoperative smoking cessation period of 2 months or more is preferable for reducing the risk of such complications.

[Influence of enhanced recovery after surgery (ERAS) on patients receiving lung resection: a retrospective study of 1749 cases](#) BMC Surg. 2021 Mar 6;21(1):115. doi: 10.1186/s12893-020-00960-z. Chunmei Wang # 1 , Yutian Lai # 2 , Pengfei Li 1 , Jianhuan Su 3 , Guowei Che 4
BACKGROUND: The study aimed to evaluate the outcomes following the implementation of enhanced recovery after surgery (ERAS) for patients undergoing lung cancer surgery. **METHOD:** A retrospective cohort study involving 1749 patients with lung cancer undergoing pulmonary resection was conducted. The patients were divided into two time period groups for analysis (routine pathway and ERAS pathway). Logistic regression analysis was performed to assess the risks of developing postoperative pulmonary complications. **RESULTS:** Among the 1749 patients, 691 were stratified into the ERAS group, and 1058 in to the routine group. The ERAS group presented with shorter postoperative in-hospital length of stay (LOS) (4.0 vs 6.0, P < 0.001), total LOS (10.0 vs. 13.0 days, P < 0.001), and lower total in-hospital costs (P < 0.001), including material (P < 0.001) and drug expenses (P < 0.001). Furthermore, the ERAS group

also presented with a lower occurrence of postoperative pulmonary complications (PPCs) than the routine group (15.2% vs. 19.5%, P = 0.022). Likewise, a significantly lower occurrence of pneumonia (8.4% vs. 14.2%, P < 0.001) and atelectasis (5.9% vs. 9.8%, P = 0.004) was found in the ERAS group. Regarding the binary logistic regression, the ERAS intervention was the sole independent factor for the occurrence of PPCs (OR: 0.601, 95% CI 0.434-0.824, P = 0.002). In addition, age (OR: 1.032, 95% CI 1.018-1.046), COPD (OR: 1.792, 95% CI 1.196-2.686), and FEV1 (OR: 0.205, 95% CI 0.125-0.339) were also independent predictors of PPCs. **CONCLUSION:** Implementation of an ERAS pathway shows improved postoperative outcomes, including shortened LOS, lower in-hospital costs, and reduced occurrence of PPCs, providing benefits to the postoperative recovery of patients with lung cancer undergoing surgical treatment.

[The significance of systematic lymph node dissection in surgery for early-stage non-small cell lung cancer patients aged ≤40 years](#) J Thorac Dis. 2021 Feb;13(2):1196-1204. doi: 10.21037/jtd-21-190. Zhi-Yi Guo 1 , Jiang-Hao Ren 1 , Yuan-Yuan Xu 1 , Rui-Jun Liu 1 , Hui Tao 1 , Jia Huang 1 , Qiang Tan 1
BACKGROUND: Surgery remains the best option for treating early-stage non-small cell lung cancer (NSCLC), and lymph node dissection (LND) is an important step in this approach. However, the extent of LND in the general age population, especially in young patients, is controversial. This retrospective study aimed to investigate the correlation between systematic lymph node dissection (SLND) and prognosis in young (≤40 years) patients with stage IA NSCLC. **METHODS:** Clinicopathological data of 191 patients aged ≤40 years who underwent surgical pulmonary resection for stage IA NSCLC between January 2010 and December 2016 were retrospectively collected. Of the patients, 104 received SLND (SLND group), while the other 87 patients underwent sampling or no LND (non-SLND group). The disease-free survival (DFS) and overall survival (OS) curves of the patients from each group were plotted using the Kaplan-Meier method, and the correlations of the patients' clinical factors with prognosis were also analyzed. **RESULTS:** The median follow-up period was 55 months. During follow-up, 7 patients died, and recurrence or metastasis was detected in 16 patients. Kaplan-Meier analysis revealed no difference in DFS (P=0.132) between the SLND and non-SLND group, but a significant difference was found between the groups in OS (P=0.022). Additionally, there was no statistically pronounced difference in OS or DFS between male and female patients. Multivariate survival analysis showed that the type of SLND, as well as tumor size, is an independent prognostic factor for DFS (HR, 3.530; 95% CI, 1.120-11.119; P=0.031) and OS (HR, 13.076; 95% CI, 1.209-141.443; P=0.034). **CONCLUSIONS:** For young (age ≤40) stage IA NSCLC patients with pathological invasive adenocarcinoma, intraoperative SLND can improve the DFS and OS. Further studies are needed to verify the most optimal degree of LND in young patients.

[Differential impacts of postoperative complications on patients' survival in completely resected non-small-cell lung cancer](#) Gen Thorac Cardiovasc Surg. 2021 Mar 9. doi: 10.1007/s11748-021-01619-z. Online ahead of print. Yuka Kadomatsu 1 , Hideki Tsubouchi 2 , Keita Nakanishi 2 , et al.
OBJECTIVE: The aim of this study was to investigate the effects of inflammatory respiratory complications on long-term survival in patients with resected non-small cell lung cancer. We defined inflammatory respiratory complications to include the following six conditions: pneumonia, empyema, bronchial fistula, respiratory dysfunction, acute interstitial pneumonia, and atelectasis. **METHODS:** Part of the National Clinical Database was linked to our prospective database from 2014 to 2017. Linkage was achieved for 866 patients. The Kaplan-Meier method was used to evaluate the overall, relapse-free, and cancer-related survival. The Cox proportional hazard model was used to analyze the impact of each complication. **RESULTS:** Of the 736 patients included in the study, 149 had complications. The 5-year overall and cancer-specific survival rates were significantly lower in patients with inflammatory respiratory complications. The Cox proportional hazard model showed that the inflammatory respiratory

complications had a significant impact on overall survival (hazard ratio 2.48, 95% confidence interval 1.41-4.38) but not air leak (hazard ratio 1.38, 95% confidence interval 0.70-2.70). **CONCLUSIONS:** Our study shows the differential impact of each complication on the survival of patients with non-small cell lung cancer. The presence of inflammatory respiratory complications was the only predictor of poor overall survival.

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

Next-Generation Immunotherapies for Brain Metastatic Cancers Trends Cancer. 2021 Mar 12;S2405-8033(21)00045-5. doi: 10.1016/j.trecan.2021.02.003. Online ahead of print.
María López Vázquez 1 , Wanlu Du 2 , Nobuhiko Kanaya 1 , Yohei Kitamura 1 , Khalid Shah 3
Patients with extracranial tumors, like lung, breast, and skin cancers, often develop brain metastases (BM) during the course of their diseases and BM commonly represent the terminal stage of cancer progression. Recent insights in the immune biology of BM and the increasing focus of immunotherapy as a therapeutic option for cancer has prompted testing of promising biological immunotherapies, including immune cell-targeting, virotherapy, vaccines, and different cell-based therapies. Here, we review the pathobiology of BM progression and evaluate the potential of next-generation immunotherapies for BM tumors. We also provide future perspectives on the development and implementation of such therapies for brain metastatic cancer patients.

Afatinib therapy in case of EGFR G724S emergence as resistance mechanism to osimertinib
Anticancer Drugs. 2021 Mar 5. doi: 10.1097/CAD.0000000000001064. Online ahead of print.
Roberta Minari 1 , Alessandro Leonetti, Letizia Gnetti, et al.
Osimertinib is a third-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) used both as the first-line treatment of EGFR-mutated non-small cell lung cancer patients and in second-line after T790M-positive disease progression to first- or second-generation TKIs. Unfortunately, patients unavoidably experience disease progression to osimertinib and the current research is focused on resistance mechanisms and the relative therapeutic strategy. We report the case of a patient with advanced EGFR-mutated (exon 19 deletion and T790M-positive) non-small cell lung cancer who developed disease progression to osimertinib characterized by the loss of T790M concurrently with the emergence of G724S EGFR mutation, which was tackled by subsequent afatinib treatment. Next-generation sequencing molecular study of rebiopsy at time of progression to osimertinib revealed the persistence of EGFR exon 19 deletion, loss of T790M with a new G724S EGFR mutation; other concomitant mechanisms were excluded. Retrospective analysis of cell-free DNA revealed the emergence of G724S EGFR mutation four months before the radiologically-proven disease progression. The patient, after chemotherapy, was treated with afatinib with clinical and radiological benefit. Our case report contributes to increase the knowledge on acquired resistance mechanisms to osimertinib treatment, and it shows, for the first time, the efficacy of afatinib in the case of T790M loss and emergence of G724S EGFR mutation.

Neoadjuvant immunotherapy for non-small cell lung cancer: State of the art Cancer Commun (Lond). 2021 Mar 10. doi: 10.1002/cac2.12153. Online ahead of print. Jin Kang 1 , Chao Zhang 1 , Wen-Zhao Zhong 1 2
Lung cancer mortality has decreased over the past decade and can be partly attributed to advances in targeted therapy and immunotherapy. Immune checkpoint inhibitors (ICIs) have rapidly evolved from investigational drugs to standard of care for the treatment of metastatic non-small cell lung cancer (NSCLC). In particular, antibodies that block inhibitory immune checkpoints, such as programmed cell death protein 1 (PD-1) and programmed cell death 1 ligand 1 (PD-L1), have revolutionized the treatment of advanced NSCLC, when administered alone or in combination with chemotherapy. Immunotherapy is

associated with higher response rates, improved overall survival (OS), and increased tolerability compared with conventional cytotoxic chemotherapy. These benefits may increase the utility of immunotherapy and its combinational use with chemotherapy in the neoadjuvant treatment of patients with NSCLC. Early findings from various ongoing clinical trials suggest that neoadjuvant ICIs alone or combined with chemotherapy may significantly reduce systemic recurrence and improve long-term OS or cure rates in resectable NSCLC. Here we further summarize the safety and efficacy of various neoadjuvant treatment regimens including immunotherapy from ongoing clinical trials and elaborate the role of neoadjuvant immunotherapy in patients with resectable NSCLC. In addition, we discuss several unresolved challenges, including the evaluations to assess neoadjuvant immunotherapy response, the role of adjuvant treatment after neoadjuvant immunotherapy, the efficacy of treatment for oncogenic-addicted tumors, and predictive biomarkers. We also provide our perspective on ways to overcome current obstacles and establish neoadjuvant immunotherapy as a standard of care.

[Early plasma circulating tumor DNA (ctDNA) changes predict response to first-line pembrolizumab-based therapy in non-small cell lung cancer (NSCLC)](#) J Immunother Cancer. 2021 Mar;9(3):e001504. doi: 10.1136/jitc-2020-001504. Biagio Ricciuti 1 , Greg Jones 2 , Mariano Severgnini 1   3 , Joao V Alessi 1 , Gonzalo Recondo 1 , Marissa Lawrence 1 , Tim Forshew 2 , Christine Lydon 1 , Mizuki Nishino 4   5 , Michael Cheng 1 , Mark Awad 6

BACKGROUND: Currently available biomarkers are imperfect in their ability to predict responses to the multiple first-line treatment options available for patients with advanced non-small cell lung cancer (NSCLC). Having an early pharmacodynamic marker of treatment resistance may help redirect patients onto more effective alternative therapies. We sought to determine if changes in circulating tumor DNA (ctDNA) levels after initiation of first-line pembrolizumab±chemotherapy in NSCLC would enable early prediction of response prior to radiological assessment. **METHODS:** Plasma collected from patients with advanced NSCLC prior to and serially after starting first-line pembrolizumab±platinum doublet chemotherapy was analyzed by next-generation sequencing using enhanced tagged-amplicon sequencing of hotspots and coding regions from 36 genes. Early change in ctDNA allele fraction (AF) was correlated with radiographic responses and long-term clinical outcomes. **RESULTS:** Among 62 patients who received first-line pembrolizumab±platinum/pemetrexed and underwent ctDNA assessment, 45 had detectable ctDNA alterations at baseline. The median change in AF at the first follow-up (at a median of 21 days after treatment initiation) was -90.1% (range -100% to +65%) among patients who subsequently had a radiologic response (n=18), -19.9% (range: -100% to +1884%) among stable disease cases (n=15), and +28.8% (range: -100% to +410%) among progressive disease cases (n=12); p=0.003. In addition, there was a significant correlation between the percent change in ctDNA at the first follow-up and the percent change in tumor target lesions from baseline (R=0.66, p<0.001). AF decrease between the pretreatment and first on-treatment blood draw was associated with significantly higher response rate (60.7% vs 5.8%, p=0.0003), and significantly longer median progression-free survival (8.3 vs 3.4 months, HR: 0.29 (95% CI: 0.14 to 0.60), p=0.0007) and median overall survival (26.2 vs 13.2 months, HR: 0.34 (95% CI: 0.15 to 0.75), p=0.008) compared with cases with an AF increase. **CONCLUSION:** In patients with advanced NSCLC, rapid decreases in ctDNA prior to radiological assessment correlated with clinical benefit. These results suggest a potential role for ctDNA as an early pharmacodynamic biomarker of response or resistance to immunotherapies.

[Real-world outcomes of patients with advanced non-small cell lung cancer treated with anti-PD1 therapy on the basis of PD-L1 Results in EBUS-TBNA vs. histological specimens](#) Chest. 2021 Mar 3;S0012-3692(21)00453-0. doi: 10.1016/j.chest.2021.02.053. Online ahead of print. Pattraporn Tajarernmuang 1 , Linda Ofiara 2 , Stéphane Beaudoin 2, Hangjun Wang 3 , Andrea Benedetti 4 , Anne V Gonzalez 5

BACKGROUND: PD-L1 testing is feasible in a majority of specimens acquired using endobronchial ultrasound-guided needle aspiration (EBUS-TBNA). **RESEARCH QUESTION:** Are the outcomes of patients with advanced NSCLC treated with immune checkpoint inhibitors (ICI) on the basis of PD-L1 expression in EBUS-TBNA samples significantly different from those of patients who are treated on the basis of PD-L1 expression in histological samples? **STUDY DESIGN AND METHODS:** Patients treated with pembrolizumab or nivolumab between June 2016 and 2019 were included. Patient characteristics, PD-L1 expression, line of treatment, response (RECIST criteria) and vital status (14 May, 2020) were recorded. Progression-free survival (PFS) and overall survival (OS) were assessed, and hazard ratios (HR) estimated. **RESULTS:** A total of 145 patients were treated with pembrolizumab or nivolumab on the basis of PD-L1 expression in EBUS-TBNA (31.7%) or histological (68.3%) samples. The majority had metastatic disease, with a predominance of adenocarcinomas (64.1%). First-line pembrolizumab was administered to 61 patients with tumor proportion score $\geq$ 50% in EBUS-TBNA (16) or histology samples (45). Median OS and PFS of patients who received first-line pembrolizumab on the basis of PD-L1 Results in EBUS-TBNA vs. histology samples were not significantly different (OS 25.8 months vs. not reached, respectively, HR 0.82 [95% CI, 0.34-1.95], p=0.651). Similarly, the median OS and PFS of patients who received subsequent lines of treatment on the basis of PD-L1 results in EBUS-TBNA vs. histological samples were not significantly different (including after adjustment for PD-L1 expression). **INTERPRETATION:** These findings suggest that PD-L1 Results in EBUS-TBNA samples can guide ICI therapy, with treatment outcomes being comparable to those of patients in whom PD-L1 expression was assessed in histological specimens.

[Spectrum of Mechanisms of Resistance to Crizotinib and Lorlatinib in ROS1 Fusion-Positive Lung Cancer](#) Clin Cancer Res. 2021 Mar 8. doi: 10.1158/1078-0432.CCR-21-0032. Online ahead of print.
Jessica J Lin # 1 2 , Noura J Choudhury # 3 , Satoshi Yoda # 1 2 , et al.

PURPOSE: Current standard initial therapy for advanced, ROS proto-oncogene 1, receptor tyrosine kinase fusion (ROS1)-positive (ROS1+) non-small cell lung cancer (NSCLC) is crizotinib or entrectinib. Lorlatinib, a next-generation anaplastic lymphoma kinase/ROS1 inhibitor, recently demonstrated efficacy in ROS1+ NSCLC, including in crizotinib-pretreated patients. However, mechanisms of lorlatinib resistance in ROS1+ disease remain poorly understood. Here, we assessed mechanisms of resistance to crizotinib and lorlatinib. **EXPERIMENTAL DESIGN:** Biopsies from patients with ROS1 + NSCLC progressing on crizotinib or lorlatinib were profiled by genetic sequencing. **RESULTS:** From 55 patients, 47 post-crizotinib and 32 post-lorlatinib biopsies were assessed. Among 42 post-crizotinib and 28 post-lorlatinib biopsies analyzed at distinct timepoints, ROS1 mutations were identified in 38% and 46%, respectively. ROS1 G2032R was the most commonly occurring mutation in approximately one third of cases. Additional ROS1 mutations included D2033N (2.4%) and S1986F (2.4%) post-crizotinib and L2086F (3.6%), G2032R/L2086F (3.6%), G2032R/S1986F/L2086F (3.6%), and S1986F/L2000V (3.6%) post-lorlatinib. Structural modeling predicted ROS1L2086F causes steric interference to lorlatinib, crizotinib, and entrectinib, while it may accommodate cabozantinib. In Ba/F3 models, ROS1L2086F, ROS1G2032R/L2086F, and ROS1S1986F/G2032R/L2086F were refractory to lorlatinib but sensitive to cabozantinib. A patient with disease progression on crizotinib and lorlatinib and ROS1 L2086F received cabozantinib for nearly 11 months with disease control. Among lorlatinib-resistant biopsies, we also identified MET amplification (4%), KRAS G12C (4%), KRAS amplification (4%), NRAS mutation (4%), and MAP2K1 mutation (4%). **CONCLUSIONS:** ROS1 mutations mediate resistance to crizotinib and lorlatinib in more than one third of cases, underscoring the importance of developing next-generation ROS1 inhibitors with potency against these mutations, including G2032R and L2086F. Continued efforts are needed to elucidate ROS1-independent resistance mechanisms.

[Barriers to Prescribing Targeted Therapies for Patients With NSCLC With Highly Actionable Gene Variants in the Veterans Affairs National Precision Oncology Program](#) JCO Oncol Pract. 2021 Mar 29;OP2000703. doi: 10.1200/OP.20.00703. Online ahead of print. Vishal Vashistha 1 2 , Jenna Armstrong 3 4 , David Winski 5 , et al.

PURPOSE: Next-generation sequencing (NGS) gene panels are frequently completed for patients with advanced non-small-cell lung cancer (NSCLC). Patients with highly actionable gene variants have improved outcomes and reduced toxicities with the use of corresponding targeted agents. We sought to identify barriers to targeted agent use within the Veterans Health Affairs' National Precision Oncology Program (NPOP). **METHODS:** A retrospective evaluation of patients with NSCLC who underwent NGS multigene panels through NPOP between July 2015 and February 2019 was conducted. Patients who were assigned level 1 or 2A evidence for oncogenic gene variants by an artificial intelligence offering (IBM Watson for Genomics [WfG]) and NPOP staff were selected. Antineoplastic drug prescriptions and provider notes were reviewed. Reasons for withholding targeted treatments were categorized. **RESULTS:** Of 1,749 patients with NSCLC who successfully underwent NGS gene panel testing, 112 (6.4%) patients were assigned level 1 and/or 2A evidence for available targeted treatments by WfG and NPOP staff. All highly actionable gene variants were within ALK, BRAF, EGFR, ERBB2, MET, RET, and ROS1. Of these, 36 (32.1%) patients were not prescribed targeted agents. The three most common reasons were (1) patient did not carry a diagnosis of metastatic disease (33.3%), (2) treating provider did not comment on the NGS results (25.0%), and (3) provider felt that patient could not tolerate therapy (19.4%). No patients were denied access to level 1 or 2A targeted drugs because of rejection of a nonformulary drug request. **CONCLUSION:** A substantial minority of patients with NSCLC bearing highly actionable gene variants are not prescribed targeted agents. Further provider- and pathologist-directed educational efforts and implementation of health informatics systems to provide real-time decision support for test ordering and interpretation are needed.

[Comparing survival and subsequent treatment of first-line tyrosine kinase inhibitors in patients of advanced lung adenocarcinoma with epidermal growth factor receptor mutation](#) J Formos Med Assoc. 2021 Mar 9;S0929-6646(21)00076-0. doi: 10.1016/j.jfma.2021.02.012. Online ahead of print. Ming-Yi Huang 1 , Kun-Pin Hsieh 2 , Ru-Yu Huang 3 , Jen-Yu Hung 4 , Li-Tzong Chen 5 , Ming-Ju Tsai 6 , Yi-Hsin Yang 7

BACKGROUND/PURPOSE: Three first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are widely available to treat advanced lung adenocarcinoma harboring EGFR mutation. However, studies comparing efficacy or effectiveness of these EGFR TKIs came out with inconclusive results. **METHODS:** In this real-world data analysis with a nationwide retrospective cohort design, adult patients with newly diagnosed advanced lung adenocarcinoma with EGFR mutation between 2011 and 2016, who received a first-line EGFR TKI, were included. Overall survival (OS) and time to next treatment (TTNT) were compared between patients receiving different EGFR TKIs after overlap weighting. **RESULTS:** We enrolled 10,431 patients, including 6,230, 2,359, and 1842 in gefitinib, erlotinib, and afatinib groups, respectively. The median (95% confidence interval [CI]) OS were 24.2 (22.9-26.2), 25.7 (24.0-27.9), and 29.1 (25.8-32.1) months for those receiving gefitinib, erlotinib, and afatinib, respectively (p = 0.001). The hazard ratios (95% CI) for the afatinib group were 0.85 (0.74-0.98) and 0.91 (0.79-1.05) comparing with the gefitinib and erlotinib groups, respectively. The median (95% CI) TTNT were 10.9 (10.4-11.2), 11.7 (11.3-12.1), 13.4 (12.5-14.3) months for those receiving gefitinib, erlotinib, and afatinib, respectively (p < 0.001). The hazard ratios (95% CI) for the afatinib group were 0.79 (0.70-0.88) and 0.89 (0.79-1.00) comparing with the gefitinib and erlotinib groups, respectively. There were 6111 (59%) patients receiving subsequent therapies, and the majority of them received a second-line chemotherapy, particularly platinum-based chemotherapy. **CONCLUSIONS:** Afatinib,

compared with gefitinib, might provide better effectiveness as the first-line targeted therapy for patients of advanced lung adenocarcinoma with EGFR mutation.

[The International Association for the Study of Lung Cancer Global Survey on Programmed Death-Ligand 1 Testing for NSCLC](#) J Thorac Oncol. 2021 Apr;16(4):686-696. doi: 10.1016/j.jtho.2020.12.026. Epub 2021 Mar 2. Mari Mino-Kenudson 1 , Nolwenn Le Stang 2 , Jillian B Daigneault 3 , et al. **INTRODUCTION:** Programmed death-ligand 1 (PD-L1) immunohistochemistry (IHC) is required to determine the eligibility for pembrolizumab monotherapy in advanced NSCLC worldwide and for several other indications depending on the country. Four assays have been approved/ Communauté Européene-In vitro Diagnostic (CV-IVD)-marked, but PD-L1 IHC seems diversely implemented across regions and laboratories with the application of laboratory-developed tests (LDTs). **METHOD:** To assess the practice of PD-L1 IHC and identify issues and disparities, the International Association for the Study of Lung Cancer Pathology Committee conducted a global survey for pathologists from January to May 2019, comprising multiple questions on preanalytical, analytical, and postanalytical conditions. **RESULT:** A total of 344 pathologists from 64 countries participated with 41% from Europe, 24% from North America, and 18% from Asia. Besides biopsies and resections, cellblocks were used by 75% of the participants and smears by 11%. The clone 22C3 was most often used (69%) followed by SP263 (51%). They were applied as an LDT by 40% and 30% of the users, respectively, and 76% of the participants developed at least one LDT. Half of the participants reported a turnaround time of less than or equal to 2 days, whereas 13% reported that of greater than or equal to 5 days. In addition, quality assurance (QA), formal training for scoring, and standardized reporting were not implemented by 18%, 16%, and 14% of the participants, respectively. **CONCLUSIONS:** Heterogeneity in PD-L1 testing is marked across regions and laboratories in terms of antibody clones, IHC assays, samples, turnaround times, and QA measures. The lack of QA, formal training, and standardized reporting stated by a considerable minority identifies a need for additional QA measures and training opportunities.

[Long-term efficacy of immune checkpoint inhibitors in non-small cell lung cancer patients harboring MET exon 14 skipping mutations](#) Int J Clin Oncol. 2021 Mar 3. doi: 10.1007/s10147-021-01893-0. Online ahead of print. Yasuhiro Kato 1 2, Gou Yamamoto 3, Yasutaka Watanabe 4 **INTRODUCTION:** MET exon 14 skipping mutation, observed in 3-4% of non-small cell lung cancer (NSCLC), is emerging as a targetable alteration. In recent years, immune checkpoint inhibitors (ICI) have been effective in treating several NSCLCs. Our research aimed to investigate the characteristics of patients with NSCLCs harboring MET exon 14 mutations and their response to ICI in Japan. **METHODS**: Among the 1954 consecutive NSCLCs diagnosed at Saitama Cancer Center between 2010 and 2019, MET exon 14 skipping mutations were detected in 68 (3.5%) NSCLCs. We evaluated their characteristics such as programmed cell death ligand 1 (PD-L1) expression. **RESULTS:** Median age of patients with NSCLCs harboring MET exon 14 skipping mutations was 73 years. PD-L1 was highly expressed in 17 (70.8%) of the 24 patients examined. Seven patients received ICI monotherapy, and three out of seven had a remarkable treatment response, resulted in objective response rate (ORR) of 42.9% and progression-free survival of 24.7 months. Three patients with donor splice-site mutations showed a long-term treatment response, despite the fact that two with acceptor splice-site mutations demonstrated no response and experienced early disease progression with ICI monotherapy. **CONCLUSION:** Our results indicated that patients with NSCLCs harboring MET exon 14 mutations presented with a high rate of positive PD-L1 expression. ICI treatment showed a high ORR and long-term efficacy for NSCLCs harboring MET exon 14 mutations. Variants of MET exon 14 splice-site mutations may be associated with ICI response.

Association of tumor mutation burden and epidermal growth factor receptor inhibitor history with survival in patients with metastatic stage III/IV non-small-cell lung cancer: A retrospective study

Yan Lan 1 , Shuo Zhou 2 , Weihong Feng 3 , Ying Qiao 1 , Xueming Du 3 , Fenge Li 3 4

OBJECTIVES: Lung cancer is the leading cause of cancer-related deaths worldwide. However, factors associated with the survival of patients with advanced non-small-cell lung cancer (NSCLC) who received only hospice care are largely unclear. In this study, we aimed to determine the prognostic factors correlated with survival in patients with advanced NSCLC who had undergone hospice care only. **METHODS:** A total of 102 patients with recurrent stage III/IV NSCLC after traditional treatment failure were investigated. Survival was measured from the date of enrollment to December 2019 or the time of death. Tumor tissues were collected, and DNA sequencing was performed to identify somatic mutations. Data on clinical factors of patients were collected and analyzed by univariate and multivariate analyses. Overall survival analysis was conducted using the Kaplan-Meier method. **RESULTS:** The 6-month, 1-year, and 2-year overall survival rates of the 102 patients with metastatic NSCLC were 17.65%, 3.92%, and 0.98%, respectively. The median overall survival of the 102 patients was 3.15 months. Tumor location in the peripheral lung, epidermal growth factor receptor (EGFR) inhibitor history, low tumor mutation load, adenocarcinoma, and poor performance status score were associated with prolonged survival compared with tumor location in the central lung, no EGFR inhibitor history, high tumor mutation load, squamous cell carcinoma, and good performance status score (p=0.045, p=0.003, p=0.045, p=0.021, and p=0.0003, respectively). **CONCLUSIONS**: EGFR inhibitor treatment history and tumor mutation load are risk factors for the overall survival of patients with stage III/IV NSCLC who have undergone only hospice care. These results provide a critical clinical basis for further study of nontraditional anti-tumor responses induced by EGFR inhibitors.

Crizotinib in Patients With MET-Amplified NSCLC D Ross Camidge 1 , Gregory A Otterson 2 , Jeffrey W Clark 3 , et al.

INTRODUCTION: MET amplification is a rare, potentially actionable, primary oncogenic driver in patients with NSCLC. **METHODS:** The influence of MET amplification on the clinical activity of the ALK/ROS1/MET inhibitor, crizotinib (250 mg twice daily), was examined in patients with NSCLC (NCT00585195) who were enrolled into high (≥4 MET-to-CEP7 ratio), medium (>2.2 to <4 MET-to-CEP7 ratio), or low (≥1.8 to ≤2.2 MET-to-CEP7 ratio) amplification categories. Retrospective next-generation sequencing profiling was performed on archival tumor tissue. End points included objective response rate (ORR), duration of response, and progression-free survival. **RESULTS:** A total of 88 patients with a MET-to-CEP7 ratio greater than or equal to 1.8 by local fluorescence in situ hybridization testing received crizotinib. All patients were response-assessable, among whom 21, 14, and 3 had high, medium, and low MET amplification, respectively. ORRs of 8 of 21 (38.1%), 2 of 14 (14.3%), and 1 of 3 (33.3%), median duration of response of 5.2, 3.8, and 12.2 months, and median progression-free survival values of 6.7, 1.9, and 1.8 months were observed for those with high, medium, and low MET amplification, respectively. MET amplification gene copy number greater than or equal to 6 was detected by next-generation sequencing in 15 of 19 (78.9%) analyzable patients. Of these 15 patients, objective responses were observed in six (40%), two of whom had concurrent MET exon 14 alterations. No responses were observed among five patients with concurrent KRAS, BRAF, or EGFR mutations. **CONCLUSIONS:** Patients with high-level, MET-amplified NSCLC responded to crizotinib with the highest ORR. Use of combined diagnostics for MET and other oncogenes may potentially identify patients most likely to respond to crizotinib.

An early look at selective RET inhibitor resistance: new challenges and opportunities Br J Cancer. 2021 Mar 23. doi: 10.1038/s41416-021-01344-7. Online ahead of print. Jessica J Lin 1, Justin F Gainor 2 Two RET inhibitors, selpercatinib and pralsetinib, recently received approval for the treatment of advanced RET fusion-positive lung cancer. Acquired resistance to these inhibitors will be a major challenge. We have shown that resistance can emerge due to recurrent RET kinase domain mutations and, in most cases, due to RET-independent mechanisms.

Afatinib as First-Line Treatment in Asian Patients with EGFR Mutation-Positive NSCLC: A Narrative Review of Real-World Evidence Adv Ther. 2021 Mar 17. doi: 10.1007/s12325-021-01696-9. Online ahead of print. Shun Lu 1, Jin-Yuan Shih 2, Tae-Won Jang 3, Chong-Kin Liam 4, Yongfeng Yu 5

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) are a standard of care in the first-line treatment of patients with EGFR mutation-positive metastatic non-small-cell lung cancer (NSCLC). EGFR mutations are relatively common in Asian patients with NSCLC, and there is an increasing number of studies supporting the effectiveness of the second-generation TKI afatinib in routine clinical practice in Asia. This article reviews these real-world studies investigating afatinib as first-line treatment for EGFR mutation-positive NSCLC in Asian patients. Evidence from real-world studies with afatinib in this patient population supports findings from randomized controlled trials (RCTs) showing that afatinib is associated with more favorable outcomes compared with the first-generation EGFR TKIs. The effectiveness of afatinib has also been shown in real-world studies in Asian patients with poor prognostic factors, who are often under-represented or excluded from RCTs, such as those with uncommon EGFR mutations, brain metastases, or poor performance status, and elderly patients. The tolerability profile of afatinib in the real-world setting reflects that seen in RCTs, with no new safety signals reported in real-world studies in Asian patients with EGFR mutation-positive NSCLC. Dose-modification strategies also seem to be effective in the real world, with results of the RealGido study, which included 44% Asian patients, confirming findings from prospective clinical trials showing that tolerability-guided afatinib dose modifications can reduce the incidence of adverse events without adversely affecting clinical outcomes. While further research, including clinical trial data, is needed, real-world data have also demonstrated the feasibility of sequential afatinib followed by the third-generation TKI osimertinib in T790M-positive EGFR mutation-positive patients, which showed longer overall survival. Together, these real-world results demonstrate the real-world clinical effectiveness of afatinib as first-line treatment for patients with EGFR mutation-positive NSCLC. **PLAIN LANGUAGE SUMMARY:** Some patients with non-small-cell lung cancer (NSCLC) have a mutation in the EGFR gene, whose normal function is to regulate cell division. The proportion of NSCLC patients with these EGFR mutations is particularly high in Asian populations. Treatment of patients with EGFR mutation-positive NSCLC has changed markedly in recent years following the development of drugs called EGFR tyrosine kinase inhibitors (TKIs). Several EGFR TKIs have been developed, and clinical trial data have shown that the second-generation TKI afatinib and the third-generation TKI osimertinib are more effective than the first-generation TKIs erlotinib and gefitinib. However, these clinical trials, known as randomized controlled trials (RCTs), are highly selective, and many patients, such as elderly patients or those in poor health and/or with underlying diseases, are excluded. Consequently, less is known about how well TKIs work in these patients. Therefore, other less-selective studies, known as observational or 'real-world' studies, are used to provide information on the safety and effectiveness of EGFR TKIs across all patient groups seen in the clinic, not just those included in RCTs. In this article, we review the real-world evidence for the TKI afatinib as a treatment for Asian patients with EGFR mutation-positive NSCLC. Evidence from these real-world studies confirms that afatinib is more effective than erlotinib and gefitinib in real-world patients in Asia. Importantly, the efficacy and safety of afatinib is seen in groups of Asian patients often excluded from clinical trials including the elderly, those with brain metastases, and

frail patients or those with other underlying diseases. Importantly, the safety profile of afatinib was similar to that seen in RCTs, and no additional side effects were identified in real-world patients. Also, importantly, real-world studies show that side effects can be effectively controlled by reducing the dose of afatinib. Real-world studies have also been used to demonstrate the feasibility and effectiveness of the sequential use of EGFR TKIs, particularly in Asian patients.

[Final survival results for the LURET phase II study of vandetanib in previously treated patients with RET-rearranged advanced non-small cell lung cancer](#) Lung Cancer. 2021 Mar 10;155:40-45. doi: 10.1016/j.lungcan.2021.03.002. Online ahead of print. Kiyotaka Yoh 1 , Takashi Seto 2 , Miyako Satouchi 3 , et al.

OBJECTIVES: The LURET phase II study evaluated the efficacy and safety of the multikinase inhibitor vandetanib in patients with previously treatedRET-rearranged advanced non-small cell lung cancer (NSCLC). Among the eligible patients included in the primary analysis, the objective response rate met the primary endpoint (53 %, 90 % confidence interval [CI]: 31-74). Here, we report final survival outcomes of the LURET study. **MATERIALS AND METHODS:** Nineteen patients with previously treated RET-rearranged advanced NSCLC continuously received 300 mg of oral vandetanib daily. This final analysis provides updated data on progression-free survival (PFS), overall survival (OS) and safety. This study was registered with UMIN-CTR (number UMIN 000010095). **RESULTS:** Among the 19 patients in the intention-to-treat population, 42 % had been heavily treated with 3 or more prior chemotherapy regimens. The median PFS was 6.5 months (95 % CI, 3.9-9.3) as determined by an independent radiology review committee. The median OS was 13.5 months (95 % CI, 9.8-28.1) and the overall survival rate at 12 months was 52.6 % (95 % CI 28.7-71.9). The most common adverse events were hypertension (84.2 %), diarrhea (78.9 %), and rash acneiform (63.2 %). Overall, 11 patients (57.9 %) had adverse events leading to a dose reduction, although the safety profile was consistent with that reported in previous studies. **CONCLUSION:** Our results indicated that vandetanib enabled a prolonged and clinically meaningful PFS and OS in patients with previously treatedRET-rearranged advanced NSCLC at the updated final analysis. The safety profile was consistent with that reported in previous studies, although most of the patients experienced off-target adverse events besides RET.

NSCLC - RADIOTHERAPY

[Does Dissemination of Guidelines Alone Increase the Use of Palliative Single-Fraction Radiotherapy? Initial Report of a Longitudinal Change Management Campaign at a Provincial Cancer Program](#) urr Oncol. 2020 Aug 1;27(4):190-197. doi: 10.3747/co.27.6193. J O Kim 1 , N Hanumanthappa 1 , Y T Chung 2 , et al.

BACKGROUND: Despite level 1 evidence demonstrating the equivalence of single-fraction radiotherapy (SFRT) and multiple-fraction radiotherapy (MFRT) for the palliation of painful bone metastases, SFRT remains underused. In 2015, to encourage the sustainable use of palliative radiation oncology resources, CancerCare Manitoba disseminated, to each radiation oncologist in Manitoba, guidelines from Choosing Wisely Canada (CWC) that recommend SFRT. We assessed whether dissemination of the guidelines influenced SFRT use in Manitoba in 2016, and we identified factors associated with MFRT. **METHODS:** All patients treated with palliative radiotherapy for bone metastasis in Manitoba from 1 January 2016 to 31 December 2016 were identified from the provincial radiotherapy database. Patient, treatment, and disease characteristics were extracted from the electronic medical record and tabulated by fractionation schedule. Univariable and multivariable logistic regression analyses were performed to identify risk factors associated with MFRT. **RESULTS:** In 2016, 807 patients (mean age: 70 years; range: 35-96 years) received palliative radiotherapy for bone metastasis, with 69% of the patients having uncomplicated bone metastasis. The most common primary malignancies were prostate

(27.1%), lung (20.6%), and breast cancer (15.9%). In 62% of cases, MFRT was used-a proportion that was unchanged from 2015. On multivariable analysis, a gastrointestinal [odds ratio (OR): 5.3] or lung primary (OR: 3.3), complicated bone metastasis (OR: 4.3), and treatment at a subsidiary site (or: 4.4) increased the odds of MFRT use. **CONCLUSIONS:** Dissemination of cwc recommendations alone did not increase SFRT use by radiation oncologists in 2016. A more comprehensive knowledge translation effort is therefore warranted and is now underway to encourage increased uptake of SFRT in Manitoba.

[Impact of EGFR mutation on outcomes following SRS for brain metastases in non-small cell lung cancer](#) Lung Cancer. 2021 Mar 2;155:34-39. doi: 10.1016/j.lungcan.2021.02.036. Online ahead of print. Fabio Y Moraes 1 , Alireza Mansouri 2 , Archya Dasgupta 3 , et al.

INTRODUCTION: Patients with EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC) are at particularly high risk of developing brain metastases (BrM). In addition to EGFR targeting tyrosine kinase inhibitors (TKI), radiosurgery (SRS) has an important role in the management of EGFRm BrM. However, data specific to the response and toxicity of EGFRm BrM to SRS are sparse. We evaluated the incidence of local failure (LF) and toxicity of EGFRm and EGFR-wild-type (EGFRwt) BrM treated with SRS. **METHODS:** We analyzed a prospective registry of BrM patients treated at our centre between 2008 and 2017 and identified EGFRm and EGFRwt NSCLC patients treated with SRS ± systemic therapy for BrM. Incidences of local failure (LF) and radionecrosis (RN) were determined, and Cox regression was performed for univariate and multivariate analyses (MVAs). **RESULTS:** We analyzed data from 218 patients (615 lesions - 225 EGFRm and 390 EGFRwt). Median imaging follow-up per patient was 14.5 months (0.5-96.3). Prior to or concomitant with SRS, 62 % of EGFRm patients received TKI and 93 % received TKI post SRS. The 24-month incidence of LF was 6% and 16 % for EGFRm BrM and EGFRwt, respectively (0.43(0.19-0.95); p = 0.037). The 24-month incidence of RN was 4% and 6% for EGFRm and EGFRwt BrM, respectively (0.8(0.32-1.98) p = 0.63). On MVA, BrM size and prescription dose (PD) significantly correlated with a higher risk of LF and BrM size correlated with a higher risk of RN. **CONCLUSION:** We observed excellent rates of response and toxicity following SRS in EGFRm compared to EGFRwt NSCLC, suggesting that EGFRm BrM have a favourable risk benefit ratio compared to EGFRwt NSCLC

[Improved Survival Outcomes in Medically Fit Patients With Early-Stage Non-Small-Cell Lung Cancer Undergoing Stereotactic Body Radiotherapy](#) Clin Lung Cancer. 2021 Jan 19;S1525-7304(21)00006-1. doi: 10.1016/j.cllc.2021.01.003. Online ahead of print. Jason Liu 1 , Caressa Hui 2 , Colton Ladbury 1 , et al.

INTRODUCTION: Stereotactic body radiotherapy (SBRT) has been shown to result in excellent disease control rates for early-stage non-small-cell lung cancer (NSCLC). It remains unknown which patients would most benefit from SBRT in treating NSCLC. **PATIENTS AND METHODS:** We conducted a retrospective analysis of 346 patients treated with SBRT for early-stage NSCLC at 2 institutions (86 patients from City of Hope National Medical Center and 260 patients from The Newport Beach Radiosurgery Center/Hoag Hospital) from February 2010 to July 2019. The primary endpoint was overall survival (OS). The omnibus test of model coefficients was performed to study the associations between clinical factors and OS. Survival analyses were performed by the log-rank test and Cox proportional hazards regression. **RESULTS:** Under the univariate analysis, variables associated with a decreased likelihood of death included age < 65 years (P = .040) and being a surgical candidate (P = .010). Multivariate analysis found that surgical candidates still had a significantly decreased likelihood of death compared to nonsurgical candidates (Hazard ratio 0.360, 95% confidence interval 0.153-0.848, P = .019). Median OS was significantly increased for surgical candidates versus nonsurgical candidates (83 vs 53 months, P = .017). The local failure rate was 9.1%, the locoregional failure rate was 12.7%, and the distant failure rate was 10.7%. **CONCLUSION:** Patients who are deemed to be candidates for surgery

have improved OS compared to those who are not when treated with SBRT. This raises the question of selection bias in trials comparing surgery with SBRT in NSCLC, as patients who are deemed to be surgical candidates and then go on to undergo surgery may have an inherent OS benefit.

[**Whole-Brain Radiation Therapy With Simultaneous Integrated Boost Versus Whole-Brain Radiation Therapy Plus Stereotactic Radiosurgery for the Treatment of Brain Metastasis From Lung Cancer**](#) Front Oncol. 2021 Mar 5;11:631422. doi: 10.3389/fonc.2021.631422. eCollection 2021. Binwei Lin 1 , Dan Huang 2 , Huan Du 1   3 , Jinjia Fan 1   3 , Yu Zhang 1 , Gang Feng 1 , Feng Gao 1 , Xiao Bo Du 1

Radiotherapy is one of the most important treatments for brain metastasis (BM). This study aimed to assess whether whole-brain radiation therapy (WBRT) with simultaneous integrated boost (SIB) provided any therapeutic benefit compared to WBRT followed by stereotactic radiosurgery (SRS). Seventy-two consecutive cases of lung cancer with BM treated from January 2014 to June 2020 were analyzed retrospectively. Thirty-seven patients were treated with WBRT (30 Gy in 10 fractions) and SIB (45 Gy in 10 fractions), and 35 patients were treated with WBRT (30 Gy in ten fractions) followed by SRS (16-24 Gy according to the maximum tumor diameter). The primary endpoint was intracranial progression-free survival (PFS). The secondary endpoints were intracranial objective response (partial and complete responses), pattern of intracranial progression, overall survival (OS), and toxicity. The WBRT + SIB group had a significantly longer median intracranial PFS (9.1 vs. 5.9 months, P = 0.001) than the WBRT + SRS group. The intracranial objective response rate was 67.6% and 62.9% in the WBRT + SIB and in WBRT + SRS groups, respectively (P = 0.675). The incidence of progression outside the P-GTV in the WBRT + SIB group was significantly lower than that in the WBRT + SRS group (39.4% vs. 75.0%, P = 0.004). The median OS was 24.3 and 20.3 months in the WBRT + SIB and WBRT + SRS groups, respectively (P = 0.205). There was no significant difference in the incidence of grade 3 or worse adverse reactions between the two groups. Compared to treatment with WBRT + SRS, that with WBRT + SIB for BM appeared to contribute to local control.

[**Patient individual phase gating for stereotactic radiation therapy of early stage non-small cell lung cancer (NSCLC)**](#) Sci Rep. 2021 Mar 12;11(1):5870. doi: 10.1038/s41598-021-85031-w. K M Kraus 1 , M Oechsner 2 , J J Wilkens 2 , K A Kessel 2   3   4 , S Münch 2 , S E Combs 2   3   4

Stereotactic body radiotherapy (SBRT) applies high doses and requires advanced techniques to spare surrounding tissue in the presence of organ motion. In this work patient individual phase gating is investigated. We studied peripheral and central primary lung tumors. The internal target volume (ITV) was defined including different numbers of phases picked from a 4D Computed tomography (CT) defining the gating window (gw). Planning target volume (PTV) reductions depending on the gw were analyzed. A treatment plan was calculated on a reference phase CT (rCT) and the dose for each breathing phase was calculated and accumulated on the rCT. We compared the dosimetric results with the dose calculated when all breathing phases were included for ITV definition. GWs including 1 to 10 breathing phases were analyzed. We found PTV reductions up to 38.4%. The mean reduction of the lung volume receiving 20 Gy due to gating was found to be 25.7% for peripheral tumors and 16.7% for central tumors. Gating considerably reduced esophageal doses. However, we found that simple reduction of the gw does not necessarily influence the dose in a clinically relevant range. Thus, we suggest a patient individual definition of the breathing phases included within the gw.

[**Predicting Survival Duration With MRI Radiomics of Brain Metastases From Non-small Cell Lung Cancer**](#) Front Oncol. 2021 Mar 5;11:621088. doi: 10.3389/fonc.2021.621088. eCollection 2021. Bihong T Chen 1 , Taihao Jin 1 , Ningrong Ye 1 , et al.

BACKGROUND: Brain metastases are associated with poor survival. Molecular genetic testing informs on targeted therapy and survival. The purpose of this study was to perform a MR imaging-based radiomic analysis of brain metastases from non-small cell lung cancer (NSCLC) to identify radiomic features that were important for predicting survival duration. **METHODS:** We retrospectively identified our study cohort via an institutional database search for patients with brain metastases from EGFR, ALK, and/or KRAS mutation-positive NSCLC. We segmented the brain metastatic tumors on the brain MR images, extracted radiomic features, constructed radiomic scores from significant radiomic features based on multivariate Cox regression analysis ($p < 0.05$), and built predictive models for survival duration. **RESULT:** Of the 110 patients in the cohort (mean age 57.51 ± 12.32 years; range: 22-85 years, M:F = 37:73), 75, 26, and 15 had NSCLC with EGFR, ALK, and KRAS mutations, respectively. Predictive modeling of survival duration using both clinical and radiomic features yielded areas under the receiver operative characteristic curve of 0.977, 0.905, and 0.947 for the EGFR, ALK, and KRAS mutation-positive groups, respectively. Radiomic scores enabled the separation of each mutation-positive group into two subgroups with significantly different survival durations, i.e., shorter vs. longer duration when comparing to the median survival duration of the group. **CONCLUSION:** Our data supports the use of radiomic scores, based on MR imaging of brain metastases from NSCLC, as non-invasive biomarkers for survival duration. Future research with a larger sample size and external cohorts is needed to validate our results.

[**Risk of cardiac-related mortality in stage IIIA-N2 non-small cell lung cancer: Analysis of the Surveillance, Epidemiology, and End Results (SEER) database**](#) Thorac Cancer. 2021 Mar 16. doi: 10.1111/1759-7714.13908. Online ahead of print. Xin Sun 1 , Yu Men 1   2 , Jianyang Wang 1 , Yongxing Bao 1 , Xu Yang 1 , Maoyuan Zhao 1 , Shuang Sun 1 , Meng Yuan 1 , Zeliang Ma 1 , Zhouguang Hui 1   2

BACKGROUND: In this study, we aimed to investigate the association between postoperative radiotherapy (PORT) and cardiac-related mortality in patients with stage IIIA-N2 non-small cell lung cancer (NSCLC) using the Surveillance, Epidemiology, and End Results (SEER) database. **METHODS:** The United States (US) population based on the SEER database was searched for cardiac-related mortality among patients with stage IIIA-N2 NSCLC. Cardiac-related mortality was compared between the PORT and Non-PORT groups. Accounting for mortality from other causes, Fine and Gray's test compared cumulative incidences of cardiac-related mortality between both groups. Univariate and multivariate analysis were performed using the competing risk model. **RESULTS:** From 1988 to 2016, 7290 patients met the inclusion criteria: 3386 patients were treated with PORT and 3904 patients with Non-PORT. The five-year overall incidence of cardiac-related mortality was 3.01% in the PORT group and 3.26% in the Non-PORT group. Older age, male sex, squamous cell lung cancer, earlier year of diagnosis and earlier T stage were independent adverse factors for cardiac-related mortality. However, PORT use was not associated with an increase in the hazard for cardiac-related mortality (subdistribution hazard ratio [SHR] = 0.99, 95% confidence interval [CI]: 0.78-1.24, p = 0.91). When evaluating cardiac-related mortality in each time period, the overall incidence of cardiac-related mortality was decreased over time. There were no statistically significant differences based on PORT use in all time periods. **CONCLUSIONS:** With a median follow-up of 25 months, no significant differences were found in cardiac-related mortality between the PORT and Non-PORT groups in stage IIIA-N2 NSCLC patients.

[**Prognosis of severe lymphopenia after postoperative radiotherapy in non-small cell lung cancer: Results of a long-term follow up study**](#) Clin Transl Radiat Oncol. 2021 Mar 12;28:54-61. doi: 10.1016/j.ctro.2021.02.011. eCollection 2021 May. Wang Jing 1   2 , Yufei Liu 1 , Hui Zhu 2 , et al.

PURPOSE: To investigate the incidence and prognosis of severe radiation-induced lymphopenia (sRIL) after postoperative radiotherapy (PORT) for resected NSCLC. **PATIENTS AND METHODS:** Between

1998 and 2017, 170 patients treated with PORT for NSCLC were retrospectively reviewed. Lymphopenia was divided into tertiles with severe lymphopenia defined as absolute lymphocyte counts (ALC) < 0.37 × 103/ul. **RESULTS:** sRIL was observed in 32.3% of patients. Multivariable logistic regression analysis indicated sRIL was associated with planning target volume radiation fraction numbers (OR 1.09, p = 0.005) and total lung mean dose (OR 1.12, p = 0.006). With a median follow-up time of 12.2 years, the median progression-free survival and overall survival were 14.8 months and 28.4 months respectively in patients with sRIL, vs. 21.7 months (p = 0.008) and 48.3 months (p = 0.01) respectively in patients without sRIL. Multivariable analyses indicated sRIL significantly decreased OS (HR 1.95, p < 0.01). Since PORT for stage I-II NSCLC was done largely for positive margins, which may confound the contribution of severe RIL, we analyzed stage III separately and found that sRIL also significantly decreased OS (HR 1.88, p = 0.004) in multivariable analysis. **CONCLUSION:** For this long-term outcome study, severe RIL correlated with total lung mean dose and radiation fractionation numbers, and was a strong prognostic factor for poor survival in PORT patients, particularly in patients with stage III NSCLC, highlighting the importance of an intact immune system for post-radiation immunologic disease surveillance.

SMALL CELL LUNG CANCER - SCLC

Intrinsic immunogenicity of small cell lung carcinoma revealed by its cellular plasticity Cancer Discov. 2021 Mar 11;candisc.0913.2020. doi: 10.1158/2159-8290.CD-20-0913. Online ahead of print. Navin R Mahadevan [1], Erik H Knelson [1], Jacquelyn O Wolff [2], et al.

Small cell lung carcinoma (SCLC) is highly mutated, yet durable response to immune checkpoint blockade (ICB) is rare. SCLC also exhibits cellular plasticity, which could influence its immunobiology. Here we discover that a distinct subset of SCLC uniquely upregulates MHC I, enriching for durable ICB benefit. In vitro modeling confirms epigenetic recovery of MHC I in SCLC following loss of neuroendocrine differentiation, which tracks with de-repression of STING. Transient EZH2 inhibition expands these non-neuroendocrine cells, which display intrinsic innate immune signaling and basally restored antigen presentation. Consistent with these findings, murine non-neuroendocrine SCLC tumors are rejected in a syngeneic model, with clonal expansion of immunodominant effector CD8 T cells. Therapeutically, EZH2 inhibition followed by STING agonism enhances T cell recognition and rejection of SCLC in mice. Together, these data identify MHC I as a novel biomarker of SCLC immune responsiveness and suggest novel immunotherapeutic approaches to co-opt SCLC's intrinsic immunogenicity.

FDA Approval Summary: Atezolizumab and Durvalumab in Combination with Platinum-Based Chemotherapy in Extensive Stage Small Cell Lung Cancer Oncologist. 2021 Mar 9. doi: 10.1002/onco.13752. Online ahead of print. Luckson Mathieu [1], Sujay Shah [1], Lee Pai-Scherf [1], Erin Larkins [1], Jonathon Vallejo [1], Xiaoxue Li [1], et al.

The U.S. Food and Drug Administration (FDA) granted approval to atezolizumab and durvalumab in March of 2019 and 2020, respectively, for use in combination with chemotherapy for first-line treatment of patients with extensive stage small cell lung cancer. These approvals were based on data from two randomized controlled trials, IMpower133 (atezolizumab) and CASPIAN (durvalumab). Both trials demonstrated an improvement in overall survival (OS) with anti-programmed death ligand 1 antibodies when added to platinum-based chemotherapy as compared with chemotherapy alone. In IMpower133, patients receiving atezolizumab with etoposide and carboplatin demonstrated improved OS (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.54-0.91; p = .0069), with median OS of 12.3 months compared with 10.3 months in patients receiving etoposide and carboplatin. In CASPIAN, patients receiving durvalumab with etoposide and either cisplatin or carboplatin also demonstrated improved OS

(HR, 0.73; 95% CI, 0.59-0.91; p = .0047) with median OS of 13.0 months compared with 10.3 months in patients receiving etoposide and either cisplatin or carboplatin. The safety profiles of both drugs were generally consistent with known toxicities of immune-checkpoint inhibitor therapies. This review summarizes the FDA perspective and data supporting the approval of these two agents.

IMPLICATIONS FOR PRACTICE: Effective therapeutic options for small cell lung cancer (SCLC) are limited, and there has been modest improvement in the overall survival (OS) of patients with SCLC over the past 3 decades. The approvals of atezolizumab and of durvalumab in combination with chemotherapy for first-line treatment of patients with extensive stage SCLC represent the first approved therapies with OS benefit for this patient population since the approval of etoposide in combination with other approved chemotherapeutic agents. Additionally, the efficacy results from IMpower133 and CASPIAN lay the groundwork for possible further evaluation in other treatment settings in this disease.

[Successful bronchial arterial infusion chemotherapy combined with radiotherapy for an endobronchial metastasis after resection of small cell lung cancer](#) Respirol Case Rep. 2021 Mar 4;9(4):e00728. doi: 10.1002/rcr2.728. eCollection 2021 Apr. Yoshitsugu Horio 1   2 , Yozo Sato 3 , Hiroyuki Tachibana 4 , Waki Hosoda 5 , Junichi Shimizu 2 , Toyoaki Hida 2
Bronchial arterial infusion (BAI) chemotherapy has been reported to be an effective treatment option for centrally located early-stage squamous cell lung cancer (SCC) and has a favourable response rates for patients with stage III or IV or recurrent non-small cell lung cancer (NSCLC) without distant metastases who cannot tolerate standard chemotherapy. Here, we report a case of an 83-year-old male with a solitary polypoid endobronchial metastatic tumour in the left main bronchus one year and 10 months after video-assisted thoracoscopic surgery (VATS) combined segmentectomy (left S6 + S8a) for small cell lung cancer (SCLC), pT1bN0. He was treated with BAI of 100 mg of cis-Diamminedichloroplatinum/cisplatin (CDDP), followed by thoracic radiotherapy (56 Gy in 28 fractions). There was no recurrence for 2.5 years. BAI chemotherapy combined with radiotherapy seemed to be an effective salvage option for the treatment of solitary endobronchial metastases of SCLC in patients unfit for standard chemoradiotherapy.

[Risk Factors for Venous Thromboembolism in Patients With Small Cell Lung Cancer](#) Anticancer Res. 2021 Mar;41(3):1523-1528. doi: 10.21873/anticanres.14911. Evangelos Dimakakos 1 , Konstantinos Livanios 2 , Ioannis Vathiotis 2 , Georgia Gomatou 2 , Ioannis Gkiozos 2 , Elias Kotteas 2 , Elias Kainis 2 , Konstantinos Syrigos 2
BACKGROUND/AIM: Small cell lung cancer (SCLC) accounts for 13% of all lung cancers. Venous thromboembolism (VTE) is a frequent complication. The purpose of this study was to investigate the incidence and risk factors for VTE in SCLC patients. **PATIENTS AND METHODS:** Retrospective analysis of patients with histologically confirmed SCLC treated between January 2015 and June 2018 at Sotiria General Hospital, Athens, Greece. **RESULTS:** Two hundred and seventeen patients were included in the analysis. The incidence of VTE was 4.1%. Increased body mass index (BMI) was correlated with the development of VTE. Moreover, VTE appeared more frequently in patients with major vessel infiltration and with poor Eastern Cooperative Oncology Group Performance Status. Other factors, including gender, age, stage, presence of metastasis, treatment, immobilization, anticoagulation, comorbidities, and laboratory values did not correlate with the development of VTE. **CONCLUSION:** Factors associated with the development of VTE were BMI, major vessel infiltration and PS. Identifying factors that predispose to VTE could help physicians detect high-risk patients who would benefit from prophylactic anticoagulation therapy.

[**Best Supportive Care Versus Whole-Brain Irradiation, Chemotherapy Alone, or WBRT Plus Chemotherapy in Patients With Brain Metastases From Small-Cell Lung Cancer: A Case-Controlled Analysis**](#) Front Oncol. 2021 Mar 1;11:568568. doi: 10.3389/fonc.2021.568568. eCollection 2021. Hongwei Li 1 , Ruiqi Xue 1 , Xiaotang Yang 2 , et al.

BACKGROUND: WBRT and systemic chemotherapy are the mainstay treatments for small-cell lung cancer (SCLC) brain metastases (BM). However, current recommendations are mainly based on evidence from retrospective analyses. A recent randomized trial found no benefits from WBRT compared with best supportive care (BSC) in patients with more than three BM from non-small-cell lung cancer (NSCLC). Herein, we aimed to evaluate the roles of WBRT and chemotherapy further in the management of BM from SCLC. **MATERIALS AND METHODS**: There were 698 patients with BM from SCLC included. Of these, 580 received anti cancer treatment (Group 1), including 178 who received WBRT only (Group 1a), 129 who received chemotherapy only (Group 1b), and 273 who received WBRT plus chemotherapy (Group 1c). The other 118 received BSC (Group 2). Propensity score matching (PSM) analysis was used to compare Group 2 with each of the other groups. **RESULTS**: After PSM, compared with Group 2 (n = 118), patients in Group 1 (n = 440) had a prolonged overall survival (OS) in both univariate and multivariate tests, with a median survival time of 10 months (95% CI = 9-11) in Group 1 and 3.5 months (95% CI = 2-7) in Group 2 (p < 0.001). In subgroup analyses, patients who received WBRT plus chemotherapy were more likely to benefit from treatment (p < 0.001). Chemotherapy alone or WBRT alone did not show survival benefits. **CONCLUSION:** WBRT plus chemotherapy improved OS in patients with BM from SCLC as compared to BSC. Chemotherapy alone and WBRT alone did not show survival benefits. This retrospective study suggests that SCLC patients with BM who receive WBRT combined with chemotherapy have a better outcome than those receiving BSC alone.

[**Efficacy and safety of lurbinectedin and doxorubicin in relapsed small cell lung cancer. Results from an expansion cohort of a phase I study**](#) Invest New Drugs. 2021 Mar 11. doi: 10.1007/s10637-020-01025-x. Online ahead of print. María Eugenia Olmedo 1 , Martin Forster 2 , Victor Moreno 3 , et al.

BACKGROUND: A phase I study found remarkable activity and manageable toxicity for doxorubicin (bolus) plus lurbinectedin (1-h intravenous [i.v.] infusion) on Day 1 every three weeks (q3wk) as second-line therapy in relapsed small cell lung cancer (SCLC). An expansion cohort further evaluated this combination. **PATIENTS AND METHODS:** Twenty-eight patients with relapsed SCLC after no more than one line of cytotoxic-containing chemotherapy were treated: 18 (64%) with sensitive disease (chemotherapy-free interval [CTFI] ≥90 days) and ten (36%) with resistant disease (CTFI <90 days; including six with refractory disease [CTFI ≤30 days]). **RESULTS:** Ten patients showed confirmed response (overall response rate [ORR] = 36%); median progression-free survival (PFS) = 3.3 months; median overall survival (OS) = 7.9 months. ORR was 50% in sensitive disease (median PFS = 5.7 months; median OS = 11.5 months) and 10% in resistant disease (median PFS = 1.3 months; median OS = 4.6 months). The main toxicity was transient and reversible myelosuppression. Treatment-related non-hematological events (fatigue, nausea, decreased appetite, vomiting, alopecia) were mostly mild or moderate. **CONCLUSION:** Doxorubicin 40 mg/m2 and lurbinectedin 2.0 mg/m2 on Day 1 q3wk has shown noteworthy activity in relapsed SCLC and a manageable safety profile. The combination is being evaluated as second-line therapy for SCLC in an ongoing, randomized phase III trial.

[**Clinical outcomes of extensive-stage small cell lung cancer patients treated with thoracic radiotherapy at different times and fractionations**](#) Radiat Oncol. 2021 Mar 4;16(1):47. doi: 10.1186/s13014-021-01773-x. Jinmin Han # 1   2 , Chengrui Fu # 2   3 , Baosheng Li 4

OBJECTIVE: The purpose of this study was to assess whether thoracic radiotherapy (TRT) combined with chemotherapy (CHT) showed promising anti-tumour activity in extensive-stage small cell lung

cancer (ES-SCLC), to explore practice patterns for the radiation time and dose/fractionation and to identify prognostic factors for patients who would benefit from CHT/TRT. **METHODS:** A total of 492 ES-SCLC patients were included from January 2010 to March 2019, 244 of whom received CHT/TRT. Propensity score matching was performed to minimize bias between the CHT/TRT and CHT-alone groups. Patients in the CHT/TRT group were categorized into four subgroups based on the number of induction CHT cycles. For effective dose fractionation calculations, we introduced the time-adjusted biological effective dose (tBED). Categorical variables were analysed with chi-square tests and Fisher's exact tests. Kaplan-Meier curves were generated to estimate survival rates using the R-project. Multivariate prognostic analysis was performed with Cox proportional hazards models. **RESULTS:** Patients who received CHT/TRT experienced improved overall survival (OS) (18.1 vs 10.8 months), progression-free survival (PFS) (9.3 vs 6.0 months) and local recurrence-free survival (LRFS) (12.0 vs 6.6 months) before matching, with similar results after matching. In the CHT/TRT group, the median LRFS times for the groups based on the radiation time were 12.7, 12.0, 12.0, and 9.0 months, respectively. Early TRT had a tendency to prolong PFS (median 10.6 vs 9.8 vs 9.0 vs 7.7 months, respectively, $p = 0.091$) but not OS (median 17.6 vs 19.5 vs 17.2 vs 19.0 months, respectively, $p = 0.622$). Notably, patients who received TRT within 6 cycles of CHT experienced prolonged LRFS ($p = 0.001$). Regarding the radiation dose, patients in the high-dose group (tBED > 50 Gy) who achieved complete response and partial response (CR and PR) to systemic therapy had relatively short OS (median 27.1 vs 22.7, $p = 0.026$) and PFS (median 11.4 vs 11.2, $p = 0.032$), but the abovementioned results were not obtained after the exclusion of patients who received hyperfractionated radiotherapy (all $p > 0.05$). **CONCLUSION:** CHT/TRT could improve survival for ES-SCLC patients. TRT performed within 6 cycles of CHT and hyperfractionated radiotherapy (45 Gy in 30 fractions) may be a feasible treatment scheme for ES-SCLC patients.

[Detection of Genetic Mutations by Next-Generation Sequencing for Predicting Prognosis of Extensive-Stage Small-Cell Lung Cancer](#) J Oncol. 2020 Nov 19;2020:8811487. doi: 10.1155/2020/8811487. eCollection 2020.Dongfang Chen 1 , Jianlin Xu 1 , Rong Qiao 1 , Yizhuo Zhao 1, Tianqing Chu 1 , Baohui Han 1 , Runbo Zhong 1
Some studies have revealed that specific genetic mutations could be associated with chemotherapy response or even survival in small-cell lung cancer (SCLC). Our retrospective study aimed to identify the correlation between genetic mutations and progression-free survival (PFS) in extensive-stage SCLC after first-line chemotherapy. A total of 75 patients with extensive-stage SCLC confirmed by histopathology from February 2018 to February 2019 were retrospectively analyzed. The biopsy specimens of all patients were analyzed by Next-Generation Sequencing (NGS). All patients received first-line chemotherapy and follow-up at Shanghai Chest Hospital. Eleven genes were mutated in, at least, 10% of the 75 patients, including TP53 (96%), RB1 (77%), SMAD4 (32%), NOTCH1 (21%), PTEN (16%), FGFR1 (16%), KDR (15%), PIK3CA (15%), ROS1 (15%), BRCA2 (13%), and ERBB4 (10%). The median number of mutated genes among all patients was 5. Patients with more than 5 mutated genes (PFS = 6.7 months, P=0.004), mutant TP53 (PFS = 5.0 months, P=0.011), and mutant BRCA2 (PFS = 6.7 months, P=0.046) had better PFS after first-line chemotherapy than other patients. Multivariate Cox regression analysis showed that patients who achieved a PR (HR 3.729, 95% CI 2.038-6.822), had more than 5 mutated genes (HR 1.929, 95% CI 1.096-3.396), had BRCA2 mutations (HR 4.581, 95% CI 1.721-12.195), and had no liver metastasis (HR 0.415, 95% CI 0.181-0.951) showed improvements in PFS after first-line chemotherapy. **In conclusion**, the number of mutated genes and BRCA2 mutation status in extensive-stage SCLC were significantly related to PFS after first-line chemotherapy.

[**Efficacy of concurrent chemoradiotherapy for patients with limited-disease small-cell lung cancer: a retrospective, nationwide, population-based cohort study**](#) BMC Cancer. 2021 Mar 31;21(1):340. doi: 10.1186/s12885-021-08082-2.

Seo Ree Kim 1 , Ji Hyung Hong 1 , Soo-Yoon Sung 2 , Yeo Hyung Kim 3 , Sang Hoon Chun 1 , Hyun Woo Lee 4 , Jung Soo Lee 3 , Yoon Ho Ko 5 6

BACKGROUND: Small-cell lung cancer (SCLC) is a highly proliferative, rapidly growing tumor with a poor prognosis, even in cases of limited disease (LD). Timely and accurate high-intensity therapy is necessary. For concurrent chemoradiotherapy (CCRT), etoposide/platinum (EP)-based regimens are recommended, although irinotecan/platinum (IP)-based regimens are also effective with radiotherapy. This large-scale, retrospective, nationwide cohort study aimed to analyze the efficacy of CCRT in patients with LD-SCLC. **METHODS:** Population data registered between January 2008 and December 2018 was extracted from the Health Insurance Review and Assessment Service of Korea database. Survival outcomes of 4446 LD-SCLC patients who received CCRT were analyzed. **RESULTS:** Patients who received EP-CCRT (n = 4187) showed better time to first subsequent therapy (TFST: 11.2 months) and overall survival (OS: 22.2 months) than those who received IP-CCRT (n = 259; TFST: 9.6 months, P = 0.0477; OS: 16.4 months, P < 0.0001). When CCRT failed, dual-agent chemotherapy (n = 925; OS: 9.1 months) provided a better survival benefit than single-agent chemotherapy (n = 815; OS: 7.5 months). IP-based chemotherapy resulted in better OS (9.6 months) than EP-based chemotherapy (7.1 months, P = 0.017) in platinum-resistant relapsed patients; the opposite was observed for platinum-sensitive relapsed patients (OS: EP, 17.2 months; IP, 6.6 months; P < 0.0001). Poisson regression analysis demonstrated that age, EP-CCRT, and hypercholesterolemia retained significant associations with OS after adjustment for all variables. **CONCLUSION:** In the Korean population, the effects of EP-CCRT on OS and TFST are significantly more favorable than those of IP-CCRT.

[**Impact of prophylactic cranial irradiation and hippocampal sparing on 18 F-FDG brain metabolism in small cell lung cancer patients**](#) Radiother Oncol. 2021 Mar 3;158:200-206. doi: 10.1016/j.radonc.2021.02.016. Online ahead of print.Shaïma El Chammah 1 , Gilles Allenbach 2 , Raphaël Jumeau 1 , Sarah Boughdad 2 , John O Prior 2 , Marie Nicod Lalonde 2 , Niklaus Schaefer 3 , Marie Meyer 2

BACKGROUND AND PURPOSE: Prophylactic cranial irradiation (PCI) in small-cell lung cancer (SCLC) patients improves survival. However, it is also associated with cognitive impairment, although the underlying mechanisms remain poorly understood. Our study aims to evaluate the impact of PCI and potential benefit of hippocampal sparing (HS) on brain metabolism assessed by 18F-Fluoro-Deoxy-Glucose Positron Emission Tomography/Computed Tomography (18F-FDG PET/CT). **MATERIALS AND METHODS:** We retrospectively included 22 SCLC patients. 50% had hippocampal-sparing (HS) PCI. 18F-FDG PET/CT was performed 144.5 ± 73 days before and 383 ± 451 days after PCI. Brain 18F-FDG PET scans were automatically segmented in 12 regions using Combined-AAL Atlas from MI-Neurology Software (Syngo.Via, Siemens Healthineers). For all atlas regions, we computed SUV Ratio using brainstem as a reference region (SUVR = SUVmean/Brainstem SUVmean) and compared SUVR before and after PCI, using a Wilcoxon test, with a level of significance of p < 0.05. **RESULTS:** We found significant decreases in 18F-FDG brain metabolism after PCI in the basal ganglia (p = 0.004), central regions (p = 0.001), cingulate cortex (p < 0.001), corpus striata (p = 0.003), frontal cortex (p < 0.001), parietal cortex (p = 0.001), the occipital cortex (p = 0.002), precuneus (p = 0.001), lateral temporal cortex (p = 0.001) and cerebellum (p < 0.001). Conversely, there were no significant changes in the mesial temporal cortex (MTC) which includes the hippocampi (p = 0.089). The subgroup who received standard PCI showed a significant decrease in metabolism of the hippocampi (p = 0.033). Contrastingly, the subgroup of patients who underwent HS-PCI showed no significant variation in metabolism of the

hippocampi (p = 0.783). **CONCLUSION:** PCI induced a diffuse decrease in 18F-FDG brain metabolism. HS-PCI preserves metabolic activity of the hippocampi.

PALLIATIVE AND SUPPORTIVE CARE

Comparative Analysis of the Attitudes toward Palliative Care between Medical Oncologists and Pulmonologists Intern Med. 2021 Mar 29. doi: 10.2169/internalmedicine.6734-20. Online ahead of print. Tamio Okimoto 1 , Yukari Tsubata 1 , Mika Nakao 1 , Takamasa Hotta 1 , Megumi Hamaguchi 1 , Shunichi Hamaguchi 1 , Takeshi Isobe 1
OBJECTIVE: In Japan, both medical oncologists and pulmonologists treat lung cancer patients; however, the difference in their attitude toward palliative care referral is unknown. Thus, we retrospectively investigated the difference in attitudes toward palliative care referral between medical oncologists and pulmonologists in Japan. **METHODS:** We retrospectively reviewed the charts of patients with thoracic malignancy who died at Shimane University Hospital between June 2011 and October 2015. We compared the patients' demographics and medical history according to their doctor's specialty (i.e., medical oncologist or pulmonologist). **RESULTS:** We identified 182 patients, among whom 90 were treated by medical oncologists and 56 by pulmonologists at the outpatient clinic. Thirty-six patients did not undergo outpatient clinic treatment. Out of 59 patients, 22 (37.3%) referred by medical oncologists, and 7 out of 36 patients (19.4%) referred by pulmonologists, were referred to palliative care specialists in the outpatient setting (p=0.107, Fisher's exact test). The median survival time after admission to PCU was 21 (95% CI: 13-32) and 9 (95% CI: 5-15) days among the patients treated by medical oncologists and pulmonologists, respectively (p=0.128). **CONCLUSION:** Medical oncologists are more likely to refer their patients to palliative care in the outpatient setting, thus enabling patients to receive longer end of life care in the PCU. Bridging the research gap regarding differences between the physicians' attitudes toward palliative care referral may lead to patients receiving more quality palliative care.

Trends of concerns from diagnosis in patients with advanced lung cancer and their family caregivers: A 2-year longitudinal study Palliat Med. 2021 Mar 24;2692163211001721. doi: 10.1177/02692163211001721. Online ahead of print. Takashi Sato 1 2 3 , Daisuke Fujisawa 4 5 , Daisuke Arai 1 6 , et al.
BACKGROUND: Both advanced cancer patients and their family caregivers experience distress and have a range of concerns after cancer diagnosis. However, longitudinal studies on this topic have been lacking. **AIM:** To investigate concerns in both patients with advanced lung cancer and their family caregivers longitudinally from diagnosis. **DESIGN:** A multi-center prospective questionnaire-based study. **SETTING/PARTICIPANTS:** We recruited patients with newly diagnosed advanced lung cancer and their family caregivers at 16 hospitals in Japan. We prospectively assessed the prevalence of their concerns using the Concerns Checklist and investigated the associations between their concerns and mental status as well as quality of life until 24 months after diagnosis. **RESULTS**: A total of 248 patients and their 232 family caregivers were enrolled. The prevalence of serious concerns was highest at diagnosis (patients: 68.3%, family caregivers: 65.3%). The most common serious concern was concern about the future in both groups at diagnosis (38.2% and 40.5%, respectively) and this remained high in prevalence over time, while the high prevalence of concern about lack of information improved 3 months after diagnosis in both groups. Approximately one-third of patient-family caregiver dyads had discrepant reports of serious concerns. The presence of serious concerns was significantly associated with anxiety and depression continuously in both groups. **CONCLUSIONS:** The majority of advanced lung cancer patients and their family caregivers have serious concerns from diagnosis, which is associated with their psychological distress. The spectrum of concerns alters over the disease trajectory, warranting efficient tailored care and support for both groups immediately after diagnosis.

[Impact of Psychiatric Comorbidities on Surgical Outcomes for Non-Small Cell Lung Cancer](#) Ann Thorac Surg. 2021 Mar 24;S0003-4975(21)00557-9. doi: 10.1016/j.athoracsur.2021.03.034. Online ahead of print. Jacqueline K Olive 1 , Nicolas Zhou 2 , Kyle G Mitchell 2 , et al.

BACKGROUND: Psychiatric comorbidities (PC) have been associated with poor surgical outcomes in several malignancies. However, the impact of PC on surgical outcomes for non-small cell lung cancer (NSCLC) remains largely unknown. **METHODS:** NSCLC patients who underwent pulmonary resection at a single institution between 2006-2017 were included. Presence of preoperative PC was identified by documented diagnostic codes. Demographic, histopathologic, perioperative, and survival data were analyzed. Categorical variables were compared using chi-squared or Fisher's exact test. Overall and disease-free survival were analyzed using Kaplan-Meier method. Univariable and multivariable logistic regression analyses were performed for 30-day readmission. **RESULTS:** Among 2907 patients, PC were present preoperatively in 180 (6%), including 130 (72%) anxiety, 52 (29%) depression, 28 (16%) adjustment disorder, 16 (9%) alcohol abuse, 8 (4%) sleep disorder, and 3 (2%) schizophrenia. Patients with PC were younger, with fewer cardiovascular complications. There were no differences in length of stay. However, PC led to increased 30-day readmission (12% vs 6%, p=0.004). Reasons for readmission did not differ between groups (p=0.679). Upon multivariable analysis, PC independently predicted 30-day readmission (OR: 2.00, p=0.005). Importantly, there were no differences in 30- or 90-day mortality (p=0.495 and 0.748, respectively), overall survival (p=0.439), or disease-free survival (p=0.924). **CONCLUSIONS:** NSCLC patients with and without PC experienced similar perioperative and long-term outcomes, suggesting that individuals should not be denied surgical care on the basis of such comorbidities. However, further research should seek to identify reasons for increased risk of readmission for patients with PC and validate these findings in other settings.

COMPLEMENTARY & ALTERNATIVE THERAPY

[Aqueous extract of Taxus chinensis var. mairei regulates the Hippo-YAP pathway and promotes apoptosis of non-small cell lung cancer via ATF3 in vivo and in vitro](#) Biomed Pharmacother. 2021 Mar 16;138:111506. doi: 10.1016/j.biopha.2021.111506. Online ahead of print.
Gaochenxi Zhang 1 , Shuying Dai 1 , Yiyi Chen 1 , Haibin Wang 2 , Ting Chen 3 , Qijin Shu 4 , Shuyi Chen 5 , Liumei Shou 5 , Xiaolu Cai 1

Taxus chinensis var. mairei (TC) is a traditional Chinese ornamental and medicinal plant, the leaves and twigs of which are used in anti-tumor therapy in southern China. However, the mechanism and role of aqueous extract of TC (AETC) in promoting apoptosis in non-small cell lung cancer (NSCLC) cell lines has remained unclear. In this research, we observed that AETC inhibited the suppression of the proliferation of NSCLC cells and highly inhibited the proliferation of NCI-1975 cells. Furthermore, AETC exerted minimal inhibitory effects on normal human lung epithelial cells and induced apoptosis in NCI-1975 and A549 cells. The findings of RNA sequencing, qRT-PCR, western blotting, and immunofluorescence showed that upregulated ATF3 expression and ATF3 gene knockdown, respectively, increased and decreased the anti-tumor effects of AETC associated with Hippo pathway inhibition and decreased YAP degradation. Furthermore, AETC reduced the tumor volume and weight in nude mice; upregulated ATF3, p-MOB1, and p-YAP (Ser397); and actively regulated cleaved PARP and cleaved caspase-9/8/3. These findings suggest that AETC induced NSCLC cell apoptosis via the ATF3-Hippo-YAP pathway in vivo and in vitro. We also found that AETC is non-toxic to normal cells and nude mice. Thus, AETC might represent a promising adjuvant for anti-tumor therapy against NSCLC.

[TMT-Based Proteomics Analysis of the Effects of Qianjinweijing Tang on Lung Cancer](#) Biomed Chromatogr. 2021 Mar 16;e5116. doi: 10.1002/bmc.5116. Online ahead of print.

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BACKGROUND: Qianjinweijing Tang (QJWJ) is a classic traditional Chinese formula that is often used in the treatment of treat lung cancer (LC). However, the underlying cellular mechanisms of the anticancer effects of QJWJ remain unclear. **METHODS:** Cell viability was determined by MTS assay and levels of apoptosis measured by flow cytometry. Animal experiments were conducted to determine the effects of QJWJ on tumour growth in vivo. We used a proteomics approach to study the effects of QJWJ on LC cells and applied bioinformatics analysis to identify differentially expressed proteins that were validated by Western blotting. **RESULTS:** QJWJ inhibited the proliferation of LC cells and induced apoptosis. The tumour growth delay effects of QJWJ were confirmed in vivo. We identified 104 differentially expressed proteins following QJWJ treatments of which 45 proteins were upregulated and 59 proteins were downregulated. The levels of differentially expressed proteins were validated by Western blotting. **CONCLUSION:** Our study indicated that QJWJ has anticancer effects in vivo and in vitro and that these effects are mediated by modulating the expression of tumour-related proteins.

[Amentoflavone Induces Cell-cycle Arrest, Apoptosis, and Invasion Inhibition in Non-small Cell Lung Cancer Cells](#) Anticancer Res. 2021 Mar;41(3):1357-1364. doi: 10.21873/anticanres.14893. Wei-Ting Chen 1 , Cheng-Hsien Chen 2 , Hung-Tai Su 3 4 , Po-Fu Yueh 5 6 , Fei-Ting Hsu 6 , I-Tsang Chiang 7 8 9

BACKGROUND/AIM: Amentoflavone, an effective compound derived from medicinal plants, has been shown to boost therapeutic efficacy of chemotherapy in non-small cell lung cancer (NSCLC). However, anti-NSCLC effect of amentoflavone is ambiguous. The major purpose of the present study was to verify the inhibitory effects of amentoflavone in NSCLC cells. **MATERIALS AND METHODS:** The effects of amentoflavone on growth and invasion of NSCLC CL-1-5-F4 cells were evaluated by cell viability assay, flow cytometry, colony formation assay, nuclear factor-kappa B (NF-κB) reporter gene assay, immunofluorescence staining, transwell invasion, and western blot assay. **RESULTS:** Amentoflavone effectively induced cell growth inhibition, G1 cell-cycle arrest, apoptosis, and suppression of invasion. Furthermore, amentoflavone not only triggered expression of p27, cleaved caspase-3, -8 also reduced NF-κB signaling, protein levels of matrix metalloproteinase (MMP)-2, -9, Cyclin-D1, and vascular endothelial growth factor (VEGF). **CONCLUSION:** Cell-cycle arrest, apoptosis induction, NF-κB signaling inhibition are associated with amentoflavone-inhibited growth and invasion of NSCLC cells.

MISCELLANEOUS WORKS

[What cancer research makes the news? A quantitative analysis of online news stories that mention cancer studies](#) PLoS One. 2021 Mar 10;16(3):e0247553. doi: 10.1371/journal.pone.0247553. eCollection 2021. Laura Moorhead 1 , Melinda Krakow 2 , Lauren Maggio 3

Journalists' health and science reporting aid the public's direct access to research through the inclusion of hyperlinks leading to original studies in peer-reviewed journals. While this effort supports the US-government mandate that research be made widely available, little is known about what research journalists share with the public. This cross-sectional exploratory study characterises US-government-funded research on cancer that appeared most frequently in news coverage and how that coverage varied by cancer type, disease incidence and mortality rates. The subject of analysis was 11436 research articles (published in 2016) on cancer funded by the US government and 642 news stories mentioning at least one of these articles. Based on Altmetric data, researchers identified articles via PubMed and characterised each based on the news media attention received online. Only 1.88% (n = 213) of research articles mentioning US government-funded cancer research included at least one mention in an online news publication. This is in contrast to previous research that found 16.8% (n = 1925) of articles received

mention by online mass media publications. Of the 13 most common cancers in the US, 12 were the subject of at least one news mention; only urinary and bladder cancer received no mention. Traditional news sources included significantly more mentions of research on common cancers than digital native news sources. However, a general discrepancy exists between cancers prominent in news sources and those with the highest mortality rate. For instance, lung cancer accounted for the most deaths annually, while melanoma led to 56% less annual deaths; however, journalists cited research regarding these cancers nearly equally. Additionally, breast cancer received the greatest coverage per estimated annual death, while pancreatic cancer received the least coverage per death. Findings demonstrated a continued misalignment between prevalent cancers and cancers mentioned in online news media. Additionally, cancer control and prevention received less coverage from journalists than other cancer continuum stages, highlighting a continued underrepresentation of prevention-focused research. Results revealed a need for further scholarship regarding the role of journalists in research dissemination.

[Evolution of the Randomized Clinical Trial in the Era of Precision Oncology](#) JAMA Oncol. 2021 Mar 25. doi: 10.1001/jamaoncol.2021.0379. Online ahead of print. Joseph C Del Paggio 1 , John S Berry 2 , Wilma M Hopman 3   4 , Elizabeth A Eisenhauer 5 , Vinay Prasad 6 , Bishal Gyawali 2   4   5 , Christopher M Booth 2   4   5

IMPORTANCE: The randomized clinical trial (RCT) in oncology has evolved since its widespread adoption in the 1970s. In recent years, concerns have emerged regarding the use of putative surrogate end points, such as progression-free survival (PFS), and marginal effect sizes.
OBJECTIVE: To describe contemporary trends in oncology RCTs and compare these findings with earlier eras of RCT design and output. **DESIGN, SETTING, AND PARTICIPANTS:** Retrospective cohort study of systemic therapy RCTs in breast, colorectal, and non-small cell lung cancer published in 7 major journals between 2010 and 2020. This strategy replicates prior work and allows for comparison of trends with RCTs published between 1995 to 2004 and 2005 to 2009. **MAIN OUTCOMES AND MEASURES:** Data on RCT design, funding, results, and reporting were extracted from the published RCT report. Findings from the current period (2010-2020) were compared with data from RCTs published from 1995 to 2004 and 2005 to 2009. Descriptive and bivariate statistics were used to analyze temporal trends. **RESULTS:** The cohort included 298 RCTs (132 [44%] breast, 111 [37%] non-small cell lung cancer, 55 [19%] colorectal cancer). Experimental treatment included molecular inhibitor (171 of 298 [57%]), cytotoxic (83 of 298 [28%]), hormone (15 of 298 [5%]), and immune (24 of 298 [8%]) therapies. Sixty-nine percent (206 of 298) of RCTs were of palliative intent. The most common primary end point is now PFS; this has increased substantially over time (from 0% [0 of 167] to 18% [25 of 137] to 42% [125 of 298]; P < .001). Of 298 RCTs, 265 (89%) are now funded by industry (previously 95 of 167 [57%] and 107 of 137 [78%]; P < .001). Fifty-eight percent (173 of 298) of trials met their primary end point. Among positive trials, median improvement in overall survival and PFS was 3.4 and 2.9 months, respectively. More than one-third (117 of 298 [39%]) of reports used a professional medical writer; this increased substantially during the study period (from 3 of 27 [11%] in 2010 to 12 of 18 [67%] in 2020; P < .001). **CONCLUSIONS AND RELEVANCE:** This cohort study suggests that contemporary oncology RCTs now largely measure putative surrogate end points and are almost exclusively funded by the pharmaceutical industry. The increasing role of medical writers warrants attention. To demonstrate that new cancer treatments are high value, the oncology community needs to consider the extent to which study end points and target effect size provide meaningful benefit to patients.

[Improving Care for Patients With Stage III or IV NSCLC: Learnings for Multidisciplinary Teams From the ACCC National Quality Survey](#) JCO Oncol Pract. 2021 Mar 9;OP2000899. doi: 10.1200/OP.20.00899. Online ahead of print. Ravi Salgia 1 , Leigh M Boehmer 2 , Catherine Celestin 3   4 , Hong Yu 3 , David R Spigel 5

PURPOSE: Insufficient characterization of the optimal multidisciplinary team and lack of understanding of barriers to quality care are unmet needs in the management of stage III or IV non-small-cell lung cancer (NSCLC). A national survey was conducted to inform the design and execution of process improvement plans and address identified barriers. **METHODS:** A steering committee of multidisciplinary specialists and representation from patient advocacy collaborated for a comprehensive, double-blind, web-based survey (January-April 2019) to obtain insights on care delivery for patients with advanced NSCLC in a diverse set of US community cancer programs. **RESULTS:** Overall, 639 responses (160 unique cancer programs across 44 US states) were included; 41% (n = 261) of respondents indicated an absence of a thoracic multidisciplinary clinic in their cancer program. Engagement in shared decision making was significantly associated with the presence of navigation and radiation oncology disciplines (P ≤ .04); 19.2% and 33.3% of respondents belonged to cancer programs with no lung cancer screening and no protocol for biomarker testing, respectively. The frequency of tumor board meetings negatively correlated with time to complete disease staging (P = .03); the average time to first therapeutic intervention in newly diagnosed patients was 4 weeks. The most challenging barriers to quality care included insufficient quantity of biopsy material for biomarker testing, lack of primary care provider referrals, and diagnostic costs. **CONCLUSION:** Improving the quality of advanced NSCLC care, including optimization of a multidisciplinary team framework, may surmount barriers to care coordination, diagnosis and staging, and treatment planning, consequently improving adherence to evolving standards of care.