



Caring Ambassadors Lung Cancer Program Literature Review, November 2020

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BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Platelet Count is Associated with the Rate of Lymph Node Metastasis in Lung Adenocarcinoma](#)

Cancer Manag Res. 2020 Oct 7;12:9765-9774. doi: 10.2147/CMAR.S273328. eCollection 2020. Cheng-Hao Qu 1 2, Tong Li 1 2, Zhan-Peng Tang 1 2, Xi-Rui Zhu 1 2, Jing-Yi Han 1 2, Hui Tian 2

PURPOSE: Emerging studies have revealed that platelets are involved in tumor metastasis in lung adenocarcinoma (ADC). The solid pathological subtype of lung ADC is associated with metastasis, recurrence, and poor prognosis. However, there is no study exploring the relationship between platelets and different lung pathological subtypes. **PATIENTS AND METHODS:** The association between platelet counts and lymph node metastasis was analyzed in 852 patients with lung ADC who underwent surgery and lymph node dissection. Multivariate logistic analysis was conducted to identify the risk factors of lymph node metastasis. Then, lymph node metastasis and other factors were analyzed to determine their correlation with platelet count and histological subtype. **RESULTS:** We found that the platelet count was associated with lymph node metastasis ($P = 0.01$) in multivariable analysis, independent of tumor size, predominant subtype, visceral pleural invasion, and microvessel invasion. In patients with a platelet count $\geq 300 \times 10^9/L$, the rate of lymph node metastasis was 38.5%, almost twice as high as that in patients with a platelet count $< 300 \times 10^9/L$ (23.2%). Additionally, elevated platelet counts, even those within the normal range, were significantly associated with a higher rate of lymph node metastasis. The mean platelet count in patients with solid-predominant histology ($269.70 \pm 69.38 \times 10^9/L$) was significantly higher than that in patients with other histologies ($P < 0.001$).

CONCLUSION: Elevated platelet counts are significantly associated with a higher rate of lymph node metastasis, even if the platelet counts are within the reference range. Platelet counts were significantly higher in patients with solid-predominant histology than in patients with other histologies. In addition, VEGF-C may play an important role in lymphatic metastasis in patients with lung ADC. We hypothesize that antiplatelet therapy may reduce lymph node metastasis in lung ADC patients.

[Correlation Analysis Among the Level of IL-35, Microvessel Density, Lymphatic Vessel Density, and Prognosis in Non-Small Cell Lung Cancer](#) Clin Transl Sci. 2020 Oct 13. doi: 10.1111/cts.12891.

Online ahead of print. Tenglong Zhang¹, Jing Nie², Xiaojiang Liu³, Zenglei Han¹, Ning Ding¹, Kai Gai¹, Yang Liu¹, Ling Chen¹, Chengye Guo¹

The aim of this study was to determine the expression of IL-35 and the lymphatic vessel density (LVD) and microvessel density (MVD) in the pathological tissues from patients with non-small cell lung cancer (NSCLC) and to analyze their correlation with other common clinical prognostic factors, as well as patients' overall survival and progression-free survival. We analyzed the pathological characteristics of 130 patients with NSCLC and determined the IL-35 expression, MVD, and LVD changes in the pathological tissues by immunohistochemistry. The results showed that IL-35 expression was significantly correlated with tumor differentiation, lymph node metastasis, T staging, LVD, and MVD ($P < 0.05$) but was not associated with age, sex, smoking, and other factors. Univariate analysis of risk models showed that age, lymph node metastasis, T stage, and high IL-35 expression, LVD, and MVD were significantly associated with NSCLC prognosis ($P < 0.05$), whereas sex, smoking, and high differentiation were not correlated with prognosis. Multivariate analysis of the proportional risk model showed that the IL-35 expression, lymph node metastasis, high LVD, and high MVD were significantly correlated with NSCLC prognosis ($P < 0.05$). In conclusion, IL-35, MVD, and LVD may be independent prognostic markers. In addition, IL-35 might represent a promising clinical drug target for the treatment of NSCLC.

[NRF2 activation promotes aggressive lung cancer and associates with poor clinical outcomes](#)

Clin Cancer Res. 2020 Oct 19;clincanres.1985.2020. doi: 10.1158/1078-0432.CCR-20-1985. Online ahead of print. Anju Singh¹, Anneleen Daemen², Dorothee Nickles³, et al.

PURPOSE: Stabilization of the transcription factor NRF2 through genomic alterations in KEAP1 and NFE2L2 occurs in a quarter of lung adenocarcinoma (LUAD) and a third of lung squamous (LUSC) patients. In LUAD, KEAP1 loss often co-occurs with STK11 loss and KRAS activating alterations. Despite its prevalence, the impact of NRF activation on tumor progression and patient outcomes is not fully defined. **EXPERIMENTAL DESIGN:** We model NRF2 activation, STK11 loss and KRAS activation in vivo using novel genetically engineered mouse models. Further, we derive a NRF2 activation signature from human non-small cell lung tumors that we use to dissect how these genomic events impact outcomes and immune contexture of participants in the OAK and IMpower131 immunotherapy trials. **RESULTS:** Our in vivo data reveal roles for NRF2 activation in (i) promoting rapid-onset, multi-focal intra-bronchiolar carcinomas, leading to lethal pulmonary dysfunction, and (ii) decreasing elevated redox stress in KRAS-mutant, STK11-null tumors. In patients with non-squamous tumors, the NRF2 signature is negatively prognostic independently of STK11 loss. LUSC patients with low NRF2 signature survive longer when receiving anti-PD-L1 treatment. **CONCLUSIONS:** Our in vivo modeling establishes NRF2 activation as a critical oncogenic driver, cooperating with STK11 loss and KRAS activation to promote aggressive LUAD. In patients, oncogenic events alter the tumor immune contexture, possibly impacting treatment responses. Importantly, patients with NRF2 activated non-squamous or squamous tumors have poor prognosis and show limited response to anti-PD-L1 treatment.

[Allele-Specific Role of ERBB2 in the Oncogenic Function of EGFR L861Q in EGFR-Mutant Lung Cancers](#)

J Thorac Oncol. 2020 Oct 7;S1556-0864(20)30765-6. doi: 10.1016/j.jtho.2020.09.019. Online ahead of print. Hiroki Sato¹, Michael Offin², Daisuke Kubota¹, Helena A Yu², et al.

INTRODUCTION: Unlike common EGFR mutations, many less common EGFR mutations remain poorly characterized in terms of oncogenic function and drug sensitivity. Here, we characterize the subset of lung adenocarcinoma harboring EGFR L861Q through both preclinical and clinical investigations.

METHODS: We reviewed clinical and genomic data from patients with EGFR-mutant lung cancer. We established cells expressing EGFR mutations and performed functional analysis of L861Q in comparison with common EGFR mutations. **RESULTS:** Among the patients with lung cancer, 3.4% (47 of 1367)

possess an EGFR L861Q mutation. Of the patients with L861Q, 23.4% (11 of 47) had a concurrent exon 18 mutation (typically involving G719). In vitro studies revealed that the oncogenic activity of L861Q is dependent on asymmetric dimerization. Cells expressing L861Q were less sensitive to EGFR-specific inhibitors compared with cells expressing L858R but were similarly sensitive to pan-ERBB inhibitors. In cells expressing L861Q, ERBB2 phosphorylation was markedly higher compared with cells expressing L858R, and an enhanced interaction between EGFR and ERBB2 was observed in coimmunoprecipitation studies. In addition, treatment with osimertinib enhanced expression of the antiapoptotic protein MCL1, and knockdown of ERBB2 suppressed the expression of MCL1 in L861Q, raising the possibility of differential allele-specific cross-phosphorylation of ERBB2. Moreover, compared with EGFR-specific inhibitors, pan-ERBB inhibitors exerted superior growth inhibitory effects on cells expressing compound L861Q/G719X mutations. **CONCLUSIONS:** Our results suggest that ERBB2 plays a previously unrecognized role in EGFR L861Q-driven tumorigenesis, and pan-ERBB inhibitors are likely to be more effective than selective EGFR tyrosine kinase inhibitors in this setting.

[Lysosomal Acid Lipase Deficiency Controls Treg and Breg Homeostasis in the Lymph Nodes of Mice with Human Cancer Xenotransplants](#)

m J Pathol. 2020 Nov 4;S0002-9440(20)30488-0. doi: 10.1016/j.ajpath.2020.10.007. Online ahead of print. Xinchun Ding 1, Ting Zhao 1, Chih-Chun Lee 2, Cong Yan 3, Hong Du 4

Utilization of proper preclinical models accelerates development of immunotherapeutic and the study of the interplay between human malignant cells and immune cells. Lysosomal acid lipase (LAL) is a critical lipid hydrolase that generates free fatty acids and cholesterol. Ablation of LAL suppresses immune-rejection and allows growth of human lung cancer cells in *lal*^{-/-} mice. In the *lal*^{-/-} lymph nodes, the percentages of both T regulatory and B regulatory cells (Tregs and Bregs) are increased with elevated expression of PD-L1, IL-10, and decreased expression of IFN γ . In Tregs and Bregs of the *lal*^{-/-} lymph nodes, levels of enzymes in glucose and glutamine metabolic pathways are elevated. Pharmacologic inhibitor of pyruvate dehydrogenase (PDH), which controls the transition from glycolysis to the citric acid cycle, effectively reduces Treg and Breg elevation in the *lal*^{-/-} lymph nodes. Blocking the mammalian target of rapamycin (mTOR) or reactivating peroxisome proliferator-activated receptor gamma (PPAR γ), an LAL downstream effector, reduces *lal*^{-/-} Treg and Breg elevation, PD-L1 expression in *lal*^{-/-} Tregs and Bregs, and improves human cancer cell rejection. Treatment of PD-L1 antibody also reduces Treg and Breg elevation in the *lal*^{-/-} lymph nodes and improves human cancer cell rejection. These observations conclude that LAL-regulated lipid metabolism is essential to maintain anti-tumor immunity.

[Activation of Toll-Like Receptor 2 Promotes Proliferation of Human Lung Adenocarcinoma Cells](#)

Anticancer Res. 2020 Oct;40(10):5361-5369. doi: 10.21873/anticancerres.14544. Anna K Gergen 1, Patrick D Kohtz 2, Alison L Halpern 2, Anqi Li 2, Xianzhong Meng 2, T Brett Reece 2, David A Fullerton 2, Michael J Weyant 2

BACKGROUND/AIM: The aim of this study was to evaluate the role of toll-like receptor 2 (TLR2) in the proliferation of human lung cancer cells and identify the signaling pathway that mediates this effect. **MATERIALS AND METHODS:** Adenocarcinoma (A549 and H1650) and adenosquamous (H125) cells were treated with increasing doses of Pam3CSK4, a TLR2 agonist. Cell proliferation and NF- κ B activation were evaluated. NF- κ B was inhibited prior to treatment with Pam3CSK4 and proliferation was assessed. **RESULTS:** TLR2 expression was significantly higher in A549 and H1650 cells compared to H125 cells ($p < 0.001$). TLR2 stimulation induced proliferation in adenocarcinoma cells only and led to a corresponding increase in NF- κ B activity ($p < 0.05$). Inhibition of NF- κ B prior to treatment with Pam3CSK4 attenuated this proliferative response. **CONCLUSION:** TLR2 activation induced proliferation of lung adenocarcinoma cells through activation of NF- κ B. Thus, the TLR2 signaling pathway may be a potential therapeutic target in lung adenocarcinoma.

[Detection of EGFR Mutations Using Bronchial Washing-Derived Extracellular Vesicles in Patients with Non-Small-Cell Lung Carcinoma](#) Cancers (Basel). 2020 Sep 30;12(10):E2822. doi:

10.3390/cancers12102822. Juhee Park 1, Chaeun Lee 1 2, Jung Seop Eom 3, Mi-Hyun Kim 3, Yoon-Kyoung Cho 1 2

The detection of epidermal growth factor receptor (EGFR) mutation, based on tissue biopsy samples, provides a valuable guideline for the prognosis and precision medicine in patients with lung cancer. In this study, we aimed to examine minimally invasive bronchial washing (BW)-derived extracellular vesicles (EVs) for EGFR mutation analysis in patients with lung cancer. A lab-on-a-disc equipped with a filter with 20-nm pore diameter, Exo-Disc, was used to enrich EVs in BW samples. The overall detection sensitivity of EGFR mutations in 55 BW-derived samples was 89.7% and 31.0% for EV-derived DNA (EV-DNA) and EV-excluded cell free-DNA (EV-X-cfDNA), respectively, with 100% specificity. The detection rate of T790M in 13 matched samples was 61.5%, 10.0%, and 30.8% from BW-derived EV-DNA, plasma-derived cfDNA, and tissue samples, respectively. The acquisition of T790M resistance mutation was detected earlier in BW-derived EVs than plasma or tissue samples. The longitudinal analysis of BW-derived EVs showed excellent correlation with the disease progression measured by CT images. The EGFR mutations can be readily detected in BW-derived EVs, which demonstrates their clinical potential as a liquid-biopsy sample that may aid precise management, including assessment of the treatment response and drug resistance in patients with lung cancer.

[Factors Affecting Patient Adherence To Lung Cancer Screening](#) South Med J. 2020

Nov;113(11):564-567. doi: 10.14423/SMJ.0000000000001167. Christina Bellinger 1, Kristie Foley 1, Frank Genese 1, Aaron Lampkin 1, Stephen Kuperberg 1

OBJECTIVES: The National Lung Screening Trial (NLST) demonstrated a 20% reduction in mortality with low-dose computed tomography (CT) for lung cancer screening (LCS). The NLST found the greatest benefit to LCS for patients who underwent annual screening for a full 3-year follow-up period. The adherence to serial imaging in the NLST was 95%. **METHODS:** We conducted a prospective study of 268 patients who presented for LCS and who were not enrolled in a research study to determine the adherence to recommended follow-up imaging and biopsy at a single center. We evaluated the correlations among sociodemographic characteristics, Lung Imaging and Reporting Data System, and adherence. **RESULTS:** Only 48% of the patient population received recommended follow-up (either imaging or biopsy) after their referent LCS. Patients with abnormal LCS (Lung Imaging and Reporting Data System 3 or 4) were more likely to adhere to the recommended follow-up (additional imaging or biopsy) compared with those with negative screens. Sex, ethnicity, smoking status, and household income were not correlated with adherence to screening and biopsy. **CONCLUSIONS:** The benefits from LCS observed in the NLST may be undermined by low adherence to follow-up screening. Studies targeting LCS patients to bolster adherence to follow-up are needed.

[Association between serum level soluble programmed cell death ligand 1 and prognosis in patients with non-small cell lung cancer treated with anti-PD-1 antibody](#) Thorac Cancer. 2020 Oct 27. doi:

10.1111/1759-7714.13721. Online ahead of print.

BACKGROUND: Programmed cell death ligand 1 (PD-L1) is known to have soluble forms aside from its membrane-bound forms. The aim of this study was to evaluate the predictive and prognostic values of serum soluble PD-L1 (sPD-L1) in patients with non-small cell lung cancer (NSCLC) who were treated with anti-PD-1 antibody. **METHODS:** A total of 233 patients were enrolled in this study. We assessed the level of serum sPD-L1 before anti-PD-1 antibody treatment (pembrolizumab or nivolumab) and

evaluated the correlation with PD-L1 expression on tumor cells, the response to anti-PD-1 antibody treatment, and patient outcome. **RESULTS:** The median serum sPD-L1 concentration was 67.7 (range, 25 to 223) pg/mL. A weak correlation between serum sPD-L1 and tumor PD-L1 expression was observed. The disease control rate in the high sPD-L1 group (≥ 90 pg/mL) was significantly lower than that in the low sPD-L1 group (< 90 pg/mL) (37% vs. 57%, $P = 0.0158$). The progression-free survival (PFS) and overall survival (OS) in the high sPD-L1 group were significantly shorter than those in the low sPD-L1 group (median PFS, 57 days vs. 177 days, $P = 0.011$; median OS, 182 days vs. not reached, $P < 0.001$). The high level of serum sPD-L1 was independently associated with a shorter PFS (hazard ratio [HR], 1.910; $P = 0.061$) and OS (HR, 2.073; $P = 0.034$) in multivariate analysis. **CONCLUSIONS:** The serum sPD-L1 level, which was only weakly correlated with the tumor PD-L1 expression level, was an independent predictive and prognostic biomarker for NSCLC patients receiving anti-PD-1 antibody. **KEY POINTS: SIGNIFICANT FINDINGS OF THE STUDY:** The disease control rate in the high sPD-L1 group was significantly lower than that in the low sPD-L1 group. The progression-free survival (PFS) and overall survival (OS) in the high sPD-L1 group were significantly shorter than those in the low sPD-L1 group. The high level of serum sPD-L1 was independently associated with a shorter PFS and OS in multivariate analysis. **WHAT THIS STUDY ADDS:** This study demonstrated that serum sPD-L1 level was an independent predictive and prognostic biomarker for NSCLC patients receiving anti-PD-1 antibody.

Contribution of a blood-based protein biomarker panel to the classification of indeterminate pulmonary nodules

J Thorac Oncol. 2020 Oct 30;S1556-0864(20)30804-2. doi: 10.1016/j.jtho.2020.09.024. Online ahead of print. Edwin J Ostrin ¹, Leonidas E Bantis ², David O Wilson ³, et al.

RATIONALE: The workup and longitudinal monitoring for subjects presenting with pulmonary nodules is a pressing clinical problem. A blood-based biomarker panel potentially has utility for identifying subjects at higher risk for harboring a malignant nodule for whom additional work-up would be indicated or subjects at reduced risk for whom imaging based follow-up would be indicated. **OBJECTIVES:** To assess whether a previously described four-protein biomarker panel, previously reported to improve assessment of lung cancer risk compared to a smoking-based lung cancer risk model, can provide discrimination between benign and malignant indeterminate pulmonary nodules. **METHODS:** A previously validated multiplex enzyme linked immunoassay was performed on matched case and control samples from each cohort. **MEASUREMENTS:** The biomarker panel was tested in two case-control cohorts of patients presenting with indeterminate pulmonary nodules at the University of Pittsburgh Medical Center and The University of Texas Southwestern. **MAIN RESULTS:** In both cohorts, the biomarker panel resulted in improved prediction of lung cancer risk over a model based on nodule size alone. Of particular note, the addition of the marker panel to nodule size greatly improved sensitivity at a high specificity in both cohorts. **CONCLUSIONS:** A four-marker biomarker panel, previously validated to improve lung cancer risk prediction, also shows utility in distinguishing benign from malignant indeterminate pulmonary nodules. Its performance in improving sensitivity at a high specificity indicates potential utility of the marker panel in assessing likelihood of malignancy in otherwise indeterminate nodules.

Computer-Tailored Decision Support Tool for Lung Cancer Screening: Community-Based Pilot Randomized Controlled Trial

J Med Internet Res. 2020 Nov 3;22(11):e17050. doi: 10.2196/17050. Lisa Carter-Harris # ¹, Robert Skipworth Comer # ², James E Slaven II # ³, Patrick O Monahan # ³, Emilee Vode # ⁴, Nasser H Hanna # ³, DuyKhanh Pham Ceppa # ³, Susan M Rawl # ⁴

BACKGROUND: Lung cancer screening is a US Preventive Services Task Force Grade B recommendation that has been shown to decrease lung cancer-related mortality by approximately 20%.

However, making the decision to screen, or not, for lung cancer is a complex decision because there are potential risks (eg, false positive results, overdiagnosis). Shared decision making was incorporated into the lung cancer screening guideline and, for the first time, is a requirement for reimbursement of a cancer screening test from Medicare. Awareness of lung cancer screening remains low in both the general and screening-eligible populations. When a screening-eligible person visits their clinician never having heard about lung cancer screening, engaging in shared decision making to arrive at an informed decision can be a challenge. Methods to effectively prepare patients for these clinical encounters and support both patients and clinicians to engage in these important discussions are needed. **OBJECTIVE:** The aim of the study was to estimate the effects of a computer-tailored decision support tool that meets the certification criteria of the International Patient Decision Aid Standards that will prepare individuals and support shared decision making in lung cancer screening decisions. **METHODS:** A pilot randomized controlled trial with a community-based sample of 60 screening-eligible participants who have never been screened for lung cancer was conducted. Approximately half of the participants (n=31) were randomized to view LungTalk-a web-based tailored computer program-while the other half (n=29) viewed generic information about lung cancer screening from the American Cancer Society. The outcomes that were compared included lung cancer and screening knowledge, lung cancer screening health beliefs (perceived risk, perceived benefits, perceived barriers, and self-efficacy), and perception of being prepared to engage in a discussion about lung cancer screening with their clinician. **RESULTS:** Knowledge scores increased significantly for both groups with greater improvement noted in the group receiving LungTalk (2.33 vs 1.14 mean change). Perceived self-efficacy and perceived benefits improved in the theoretically expected directions. **CONCLUSIONS:** LungTalk goes beyond other decision tools by addressing lung health broadly, in the context of performing a low-dose computed tomography of the chest that has the potential to uncover other conditions of concern beyond lung cancer, to more comprehensively educate the individual, and extends the work of nontailored decision aids in the field by introducing tailoring algorithms and message framing based upon smoking status in order to determine what components of the intervention drive behavior change when an individual is informed and makes the decision whether to be screened or not to be screened for lung cancer.

[Distinguishing Non-Small Cell Lung Cancer Subtypes in Fine Needle Aspiration Biopsies by Desorption Electrospray Ionization Mass Spectrometry Imaging](#) Clin Chem. 2020 Nov

1;66(11):1424-1433. doi: 10.1093/clinchem/hvaa207. Alena V Bensussan 1 , John Lin 1 , Chunxiao Guo 2 , Ruth Katz 3 , Savitri Krishnamurthy 3 , Erik Cressman 2 , Livia S Eberlin 1

BACKGROUND: Distinguishing adenocarcinoma and squamous cell carcinoma subtypes of non-small cell lung cancers is critical to patient care. Preoperative minimally-invasive biopsy techniques, such as fine needle aspiration (FNA), are increasingly used for lung cancer diagnosis and subtyping. Yet, histologic distinction of lung cancer subtypes in FNA material can be challenging. Here, we evaluated the usefulness of desorption electrospray ionization mass spectrometry imaging (DESI-MSI) to diagnose and differentiate lung cancer subtypes in tissues and FNA samples. **METHODS:** DESI-MSI was used to analyze 22 normal, 26 adenocarcinoma, and 25 squamous cell carcinoma lung tissues. Mass spectra obtained from the tissue sections were used to generate and validate statistical classifiers for lung cancer diagnosis and subtyping. Classifiers were then tested on DESI-MSI data collected from 16 clinical FNA samples prospectively collected from 8 patients undergoing interventional radiology guided FNA.

RESULTS: Various metabolites and lipid species were detected in the mass spectra obtained from lung tissues. The classifiers generated from tissue sections yielded 100% accuracy, 100% sensitivity, and 100% specificity for lung cancer diagnosis, and 73.5% accuracy for lung cancer subtyping for the training set of tissues, per-patient. On the validation set of tissues, 100% accuracy for lung cancer diagnosis and 94.1% accuracy for lung cancer subtyping were achieved. When tested on the FNA samples, 100% diagnostic accuracy and 87.5% accuracy on subtyping were achieved per-slide. **CONCLUSIONS:** DESI-MSI can

be useful as an ancillary technique to conventional cytopathology for diagnosis and subtyping of non-small cell lung cancers.

Effectiveness of a Patient Education Class to Enhance Knowledge about Lung Cancer Screening: a Quality Improvement Evaluation J Cancer Educ. 2020 Oct;35(5):897-904. doi: 10.1007/s13187-019-01540-3. Lori C Sakoda ¹, Melanie A Meyer ², Neetu Chawla ^{3 4}, et al.

Best practices to facilitate high-quality shared decision-making for lung cancer screening (LCS) are not well established. In our LCS program, patients are first referred to attend a free group education class on LCS, taught by designated clinician specialists, before a personal shared decision-making visit is scheduled. We conducted an evaluation on the effectiveness of this class to enhance patient knowledge and shared decision-making about LCS. For quality improvement purposes, participants were asked to complete one-page surveys immediately before and after class to assess knowledge and decision-making capacity regarding LCS. To evaluate knowledge gained, we tabulated the distributions of correct, incorrect, unsure, and missing responses to eight true-false statements included on both pre- and post-class surveys and assessed pre-post differences in the number of correct responses. To evaluate decision-making capacity, we tabulated the distributions of post-class responses to items on decision uncertainty. From June 2017 to August 2018, 680 participants completed both pre- and post-class surveys. Participants had generally poor baseline knowledge about LCS. The proportion who responded correctly to each knowledge-related statement increased pre- to post-class, with a mean difference of 0.9 (paired t test, $p < 0.0001$) in the total number of correct responses between surveys. About 70% reported having all the information needed to make a screening decision. Our results suggest that a well-designed group education class is an effective system-level approach for initially educating and equipping patients with appropriate knowledge to make informed decisions about LCS.

Predictive and prognostic significance of M descriptors of the 8th TNM classification for advanced NSCLC patients treated with immune checkpoint inhibitors Transl Lung Cancer Res. 2020

Aug;9(4):1053-1066. doi: 10.21037/tlcr-19-396. Sangtian Liu ^{1 2}, Fei Zhou ¹, Zhiyu Liu ³, et al.

BACKGROUND: A strong association between M descriptors and prognosis of non-small cell lung cancer (NSCLC) has been demonstrated recently. However, its predictive and prognostic significance for advanced NSCLC patients treated with immune checkpoint inhibitors (ICIs) remain unclear. In this study, we aimed at investigating the impact of M descriptors on clinical outcomes in those patients.

METHODS: A retrospective analysis was conducted. Patients treated with more than two cycles of ICIs were included. Detailed characteristics and clinical response after immunotherapy were recorded. M descriptors were classified into M1a, M1b, and M1c according to the 8th TNM classification. **RESULTS:** A total of 103 patients were enrolled, including 42 with M1a disease, 16 with M1b disease and 45 with M1c disease. Patients with M1a disease demonstrated significant longer median progress-free survival (PFS) (11.9 vs. 4.1 and 3.2 months, respectively, $P=0.0002$) and overall survival (OS) (35 vs. 22.1 and 12 months, $P=0.02$) than those with M1b and M1c disease. Patients with M1a disease showed higher objective response rate (ORR) (28.6% vs. 14.8%, $P=0.08$) and disease control rate (DCR) (81% vs. 59%, $P=0.02$) compared with those with M1b and M1c disease. Multivariate analysis identified M1a stage as being independently associated with prolonged PFS and had better OS than those with M1c disease ($P=0.05$) but not M1b disease ($P=0.06$). **CONCLUSIONS:** The current study demonstrated a clear association between M descriptors and the therapeutic response to ICIs and confirmed its prognostic role in advanced patients treated with ICIs monotherapy. M descriptors may need to be stratified in future study design.

[Results of low-dose computed tomography as a regular health examination among Chinese hospital employees](#) J Thorac Cardiovasc Surg. 2020 Sep;160(3):824-831.e4. doi: 10.1016/j.jtcvs.2019.10.145. Epub 2019 Nov 14. Yang Zhang 1 , Sanghoon Jheon 2 , Huimin Li 3 , et al.

OBJECTIVE: Lung cancer is traditionally more prevalent in the elderly patients, men, and smokers. However, as low-dose computed tomography (LDCT) is increasingly popular, we hypothesized the disease spectrum might change. **METHODS:** LDCT was performed as a part of regular health examinations in 8392 of 15,686 employees from 6 hospitals in different regions of China in 2012 to 2018. Clinicopathologic characteristics, including age, sex, smoking status, radiologic features, tumor histology, and pathologic stage, were retrospectively analyzed. **RESULTS:** LDCT incidentally detected lung cancer (pathologically confirmed) in a total of 179 (2.1%) hospital employees. The lung cancer detection rate was significantly greater in female than male (2.5% vs 1.3%, $P = .001$) patients. There was also a greater detection rate among nonsmokers than smokers, although statistical significance was not reached (2.2% vs 1.4%, $P = .092$). The lung cancer detection rate was 1.0% in the "age ≤ 40 years" group, 2.6% in the "40 < age ≤ 55 years" group, and 2.9% in the "age > 55 years" group ($P < .001$). Among the hospital employees with lung cancer, 171 (95.5%) presented as ground-glass opacity, 177 (98.9%) were lung adenocarcinoma, 170 (95.0%) were early stage 0/IA, and 177 (98.9%) received curative surgical resection as the initial treatment. After a median follow-up of 38 months, no disease recurrence or death was observed among these patients. **CONCLUSIONS:** LDCT detected lung cancer in a significant proportion of young, female, and nonsmoking employees. The vast majority of these lung cancers were early stage, with extremely good prognosis.

[Potential Financial Impact of Incidental Cardiac Pathology Detected During Lung Cancer](#)

[Screening](#) Am Surg. 2020 Oct 28;3134820952379. doi: 10.1177/0003134820952379. Online ahead of print. Carsten Schroeder 1 2 , Peter Drevets 1 , Jane M Chung 1 , Melissa Shafer 1 , Richard Lee 1 , Adam E Berman 3 4

BACKGROUND: Lung cancer screening (LCS) is broadly accepted. Screening also identifies incidental cardiac findings (S findings) that need follow-up. We report the magnitude of the potential downstream revenue generated by appropriate S finding management after 4 years of our free LCS program. **MATERIALS AND METHODS:** A retrospective database and chart review of a single-center free LCS program in the underserved southeast were performed. All patients who were enrolled in the screening required a primary care physician (PCP) as part of the decision-making model. Referrals to cardiac specialists for S findings found on LCS were recorded. Cost analysis was performed to track potential downstream revenue generated for the institution based upon Medicare allowable or Diagnosis-related group calculations. **RESULTS:** One thousand one hundred thirty-two scans were reviewed with 262 (23%) yielding positive S findings for 1 or more organ systems. 181/262 (69%) patients had cardiac findings, only 64/181 (35%) of these patients were referred to cardiology specialists by the PCP. The total Medicare billable amount for all cardiac referrals/interventions was \$284 379, representing 35% of the potential billable amount of \$804 260. Percutaneous coronary intervention (PCI) was the highest billable amount at \$18 568. Eight percent of the patients undergoing appropriate cardiac evaluation required a PCI. If not for the screening and cardiac specialist referral, this patient group may not have received appropriate cardiovascular diagnosis and treatment. **DISCUSSION:** Lung cancer screening also identifies patients with significant cardiac disease, many of whom may not be appropriately referred. Identification and treatment of incidentally noted cardiovascular findings may both improve patient care and justify supporting free LCS programs.

[Promoting Clinical Conversations about Lung Cancer Screening: Exploring the Role of Perceived Online Social Support](#) J Health Commun. 2020 Oct 29;1-10. doi: 10.1080/10810730.2020.1836087.

Online ahead of print. Samantha R Paige 1 , Ramzi G Salloum 2 3 , Janice L Krieger 1 3 , Maribeth Williams 4 , Wei Xue 5 , Babette Brumback 5

The perceived availability of online social support may contribute to patient-provider conversations about lung cancer screening. This study examines how the perceived availability of instrumental and emotional online social support is associated with patient-provider communication about lung cancer screening among adults who meet U.S. Preventive Services Taskforce (USPSTF) eligibility criteria and live with a COPD diagnosis. In April 2018, 575 adults completed an online survey after being recruited from a large southeastern academic medical center's broad research registry and website listing. Nearly half of the participants were 55-to-80 years old (41%), a current or former smoker who had quit smoking within the past 15 years (42%), and reported a smoking prevalence of 30 pack years or more (PPY; 41%). Results demonstrate that having a COPD diagnosis, identifying as male, and being a current or former tobacco smoker resulted in greater odds of having a clinical conversation about lung cancer screening. Conversely, meeting the 30 PPY smoking and 55-to-80 age thresholds lowered the odds of having these conversations. A high degree of instrumental and emotional online social support was associated with a greater incidence of annual patient-provider conversations about screening. This combination of perceived online social support was especially useful for patients with COPD.

[Impact of a Hybrid Lung Cancer Screening Model on Patient Outcomes and Provider Behavior](#)

Clin Lung Cancer. 2020 Nov;21(6):e640-e646. doi: 10.1016/j.clcc.2020.05.018. Epub 2020 May 23.

Erin A Hirsch 1 , Melissa L New 2 , Stephanie L Brown 3 , Anna E Barón 1 , Peter B Sachs 4 , Stephen P Malkoski 5

BACKGROUND: Lung cancer screening (LCS) implementation is complicated by the Centers for Medicare and Medicaid Services reimbursement requirements of shared decision-making and tobacco cessation counseling. LCS programs can utilize different structures to meet these requirements, but the impact of programmatic structure on provider behavior and screening outcomes is poorly described.

PATIENTS AND METHODS: In a retrospective chart review of 624 patients in a hybrid structure, academic LCS program, we compared characteristics and outcomes of primary care provider (PCP)- and specialist-screened patients. We also assessed the impact of the availability of an LCS specialty clinic and best practice advisory (BPA) on PCP ordering patterns using electronic medical record generated reports.

RESULTS: During the study period of July 1, 2014 through June 30, 2018, 48% of patients were specialist-screened and 52% were PCP-screened; there were no clinically relevant differences in patient characteristics or screening outcomes between these populations. PCPs demonstrate distinct practice patterns when offered the choice of specialist-driven or PCP-driven screening. Increased exposure to a LCS BPA is associated with increased PCP screening orders. The addition of a nurse navigator into the LCS program increased documentation of shared decision-making and tobacco cessation counseling to > 95% and virtually eliminated screening of ineligible patients. **CONCLUSIONS:** Systematic interventions including a BPA and nurse navigator are associated with increased screening and improved program quality, as evidenced by reduced screening of ineligible patients, increased lung cancer risk of the screened population, and improved compliance with LCS guidelines. Individual PCPs demonstrate clear preferences regarding LCS that should be considered in program design.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[Prolonged Opioid Use Associated with Reduced Survival After Lung Cancer Resection](#) Ann Thorac Surg. 2020 Oct 27;S0003-4975(20)31756-2. doi: 10.1016/j.athoracsur.2020.09.015. Online ahead of print.

William Z Chancellor 1 , J Hunter Mehaffey 1 , Raj P Desai 2 , Jared Beller 1 , Rajesh Balkrishnan 2 , Dustin M Walters 1 , Linda W Martin 3

BACKGROUND: Lung cancer remains the leading cause of cancer death worldwide and the search for modifiable risk factors to improve survival is ongoing. There is a growing appreciation for a biological relationship between opioids and lung cancer progression. Our goal is to evaluate the association between perioperative opioid use and long-term survival after lung cancer resection. **METHODS:** Retrospective analysis of 2006-2012 SEER-Medicare datasets identified all patients undergoing pulmonary resection for non-small cell lung cancer (NSCLC) stages I-III. Patients were stratified by only filling opioid prescriptions 30 days pre or postoperatively (Standard Group), filling opioid prescriptions >30 days preoperatively (Chronic Group), or filling opioid prescriptions >90 days postoperatively but not preoperatively (Prolonged Group). Kaplan-Meier survival analysis compared each group and risk-adjusted survival analysis was performed using Cox Proportional Hazards model. **RESULTS:** A total of 3,273 patients were identified including 1,385 in the Standard Group (42.3%), 1,441 in the Chronic Group (44.0%), and 447 in the Prolonged Group (13.7%). Of previously opioid-naïve patients, 24.4% (447/1832) became new prolonged opioid users. Kaplan-Meier survival analysis illustrates lower overall and disease specific survival in Chronic and Prolonged opioid groups (both $p < 0.0001$). After risk-adjustment, Chronic (HR 1.27, 95% CI 1.09-1.47, $p < 0.01$) and Prolonged (HR 1.42, 95% CI 1.17-1.73, $p < 0.01$) opioid use were independently associated with reduced long-term survival. **CONCLUSIONS:** Chronic and prolonged opioid use were independently associated with reduced long-term, disease specific survival following lung cancer resection. These findings provide epidemiologic support for a biological relationship between opioid use and lung cancer progression.

[Feasibility of transbronchial brushing cytology specimens for next generation sequencing in peripheral lung cancer](#) Cancer Sci. 2020 Oct 30. doi: 10.1111/cas.14714. Online ahead of print.

Naoki Furuya 1 , Shingo Matsumoto 2 , Kazutaka Kakinuma 1 , et al.

Next generation sequencing (NGS) enables the diagnosis of large numbers of gene aberrations during one examination, and precision medicine has developed in patients with advanced non-small cell lung cancer (NSCLC). However, peripheral lung lesions account for the majority of advanced lung cancers, especially lung adenocarcinoma. In these cases, it is difficult to obtain tissue samples which contain sufficient tumor cells by transbronchial biopsy (TBB) with forceps. Even when the target lesions are quite small, bronchial brushing can obtain enough tumor cells by endobronchial ultrasonography using guide sheath (EBUS-GS). In this study, we investigate the feasibility of bronchial brushing cytology specimens obtained by EBUS-GS-TBB, to evaluate the correlation between the success rate of NGS and extracted DNA/RNA yields according to biopsy method. We prospectively collected 222 tumor samples obtained from patients with advanced lung cancer. All patients were enrolled in a prospective nationwide genomic screening project for lung cancer (LC-SCRUM-Japan/Asia). Genomic data were obtained from the clinico-genomic database of LC-SCRUM-Japan/Asia. Extraction yields of DNA/RNA from samples obtained by EBUS-GS-TBB were relatively lower than tissue samples. The success rate of DNA sequencing for EBUS-GS-TBB was 97.9%, and with no significant differences between biopsy method. The success rate of RNA sequencing for EBUS-GS-TBB was 80.4%, which was relatively lower than by surgical biopsy samples ($P = 0.069$). However, some rare oncogenic driver aberrations were detected from these specimens. This study demonstrated that cytology samples obtained by transbronchial brushing with EBUS-GS-TBB were feasible for NGS analysis.

[Prognostic impact and distinctive characteristics of surgically resected anaplastic lymphoma kinase-rearranged lung adenocarcinoma](#) J Thorac Cardiovasc Surg. 2020 Oct 8;S0022-5223(20)32726-4. doi: 10.1016/j.jtcvs.2020.09.120. Online ahead of print.

Yosuke Matsuura 1 , Hironori Ninomiya 2 , Junji Ichinose 3 , Masayuki Nakao 3 , Sakae Okumura 3 , Makoto Nishio 4 , Mingyon Mun 3

OBJECTIVE: Anaplastic lymphoma kinase (ALK) rearrangement is a representative lung cancer with driver mutation because of the efficacy of ALK-tyrosine kinase inhibitors. ALK-tyrosine kinase inhibitors are extensively used for ALK-rearranged lung cancer, whereas the therapeutic benefit of surgery remains unclear. Thus, we aimed to assess the clinical benefit of surgery in ALK-rearranged lung cancer and to elucidate the oncologic characteristics of ALK-rearranged lung cancer through surgically resected cases. **METHODS:** We retrospectively evaluated 1925 lung adenocarcinoma cases surgically resected between 1996 and 2017 at our institute. Moreover, 75 ALK-rearranged and 75 non-ALK-rearranged cases were extracted using propensity score matching. The survival rates, prognostic factors, and post-recurrence state were assessed. **RESULTS:** Multivariable analysis revealed that ALK rearrangement was an independent prognostic factor for improved cancer-specific survival (hazard ratio, 0.2; 95% confidence interval, 0.05-0.88; $P = .033$). In the matched cohort, the 5-year cancer-specific survival rates after surgery in the ALK-rearranged and non-ALK-rearranged groups were 97% and 77%, respectively. The ALK-rearranged group had a significantly better cancer-specific survival than did the non-ALK-rearranged group (log-rank test; $P = .003$). With respect to post-recurrence state, oligo-recurrence was highly frequent in the ALK-rearranged group, and post-recurrence survival was significantly improved by administration of either ALK-tyrosine kinase inhibitors (log-rank test; $P = .011$) or local ablative therapies (log-rank test; $P = .035$). **CONCLUSIONS:** Surgically resected ALK-rearranged lung adenocarcinoma has excellent long-term outcome. Not only ALK-tyrosine kinase inhibitors but also a combination of local and systemic therapies may be important treatment strategies for ALK-rearranged lung adenocarcinoma even in the post-recurrence state.

[Preoperative Lung Function is Associated with Patient Reported Outcomes After Lung Cancer Surgery](#) Ann Thorac Surg. 2020 Oct 29;S0003-4975(20)31814-2. doi: 10.1016/j.athoracsur.2020.09.016. Online ahead of print. Onkar Khullar 1 , Jane Wei 2 , Kaustabh Wagh 2 , Jose Binongo 2 , Allan Pickens 3 , Manu Sancheti 3 , Seth Force 3 , Theresa Gillespie 4 , Felix Fernandez 3

BACKGROUND: Patient quality of life (QOL) is a critical outcomes measure in lung cancer surgery. Patient reported outcomes (PRO) provide valuable insight into the patient experience and allow measurement of pre- and post-operative QOL. Our objective was to determine which clinical factors predict differences in QOL, as measured by patient-reported physical function and pain intensity among patients undergoing minimally-invasive lung cancer surgery. **METHODS:** PRO surveys assessing physical function and pain intensity were conducted using instruments from the NIH Patient Reported Outcome Measurement Information System (PROMIS). PRO surveys were administered to patients undergoing minimally-invasive lung cancer resections at preoperative, one and six month postoperative time points, in an academic institution. Linear mixed-effects regression models were constructed to assess the association between clinical variables on PRO scores over time. **RESULTS:** A total of 123 patients underwent a thoracoscopic lung resection for cancer. Mean age of the cohort was 67 ± 9.6 , 43% were male, and 80% were Caucasian. When comparing clinical variables with PRO scores after surgery, lower DLCO was associated with significantly worse physical function ($p < 0.01$) and greater pain intensity scores ($p < 0.01$) at 6 months, with no differences identified at 1 month. No other studied clinical factor was associated with significant differences in PRO scores. **CONCLUSIONS:** Low preoperative DLCO was associated with significant decreases in PRO following minimally-invasive lung cancer surgery. DLCO may be of utility in identifying patients who experience greater decline in QOL after surgery and for guiding surgical decision-making.

[Initial and Longitudinal Cost of Surgical Resection for Lung Cancer](#) Ann Thorac Surg. 2020 Oct 5;S0003-4975(20)31617-9. doi: 10.1016/j.athoracsur.2020.07.048. Online ahead of print. Patricia A Cowper 1 , Liqi Feng 2 , Andrzej S Kosinski 3 , et al.

BACKGROUND: The longitudinal cost of treating patients with non-small cell lung cancer (NSCLC) undergoing surgical resection has not been evaluated. We describe initial and 4-year resource use and cost for NSCLC patients ≥ 65 years of age treated surgically between 2008 and 2013. **METHODS:** Using clinical data for NSCLC resections from the Society of Thoracic Surgeons General Thoracic Surgery Database linked to Medicare claims, resource use and cost of preoperative staging, surgery and subsequent care through 4 years were examined (\$2017). Cost of hospital-based care was estimated using cost-to-charge ratios; professional services and care in other settings were valued using reimbursements. Inverse probability weighting was used to account for administrative censoring. Outcomes were stratified by pathologic stage, and by surgical approach for Stage I lobectomy patients. **RESULTS:** Resection hospitalizations averaged 6 days and cost \$31,900. In the first 90 days, costs increased with stage (\$12,430 Stage I to \$26,350 Stage IV). Costs then declined towards quarterly means more similar among stages. Cumulative costs ranged from \$131,032 (Stage I) to \$205,368 (Stage IV). In the Stage I lobectomy cohort, patients selected for minimally invasive procedures had lower 4-year costs than thoracotomy patients (\$120,346 versus \$136,250). **CONCLUSIONS:** The 4-year cost of surgical resection for NSCLC was substantial and increased with pathologic stage. Among Stage I lobectomy patients, those selected for minimally invasive surgery had lower costs, particularly through 90 days. Potential avenues for improving the value of surgical resection include judicious use of post-operative intensive care and earlier detection and treatment of disease.

[Stereotactic Body Radiotherapy Versus Delayed Surgery for Early-stage Non-small-cell Lung Cancer](#)

Ann Surg. 2020 Oct 14. doi: 10.1097/SLA.0000000000004363. Online ahead of print. Nicholas R Mayne 1 , Belle K Lin 2 , Alice J Darling 1 , Vignesh Raman 1 , Deven C Patel 3 , Douglas Z Liou 3 4 , Thomas A D'Amico 1 , Chi-Fu Jeffrey Yang 5

OBJECTIVE: To evaluate the overall survival of patients with operable stage IA non-small-cell lung cancer (NSCLC) who undergo "early" SBRT (within 0-30 days after diagnosis) versus "delayed" surgery (90-120 days after diagnosis). **SUMMARY OF BACKGROUND DATA:** During the COVID-19 pandemic, national guidelines have recommended patients with operable stage IA NSCLC to consider delaying surgery by at least 3 months or, alternatively, to undergo SBRT without delay. It is unknown which strategy is associated with better short- and long-term outcomes. **METHODS:** Multivariable Cox proportional hazards modeling and propensity score-matched analysis was used to compare the overall survival of patients with stage IA NSCLC in the National Cancer Data Base from 2004 to 2015 who underwent "early" SBRT (0-30 days after diagnosis) versus that of patients who underwent "delayed" wedge resection (90-120 days after diagnosis). **RESULTS:** During the study period, 570 (55%) patients underwent early SBRT and 475 (45%) underwent delayed wedge resection. In multivariable analysis, delayed resection was associated with improved survival [adjusted hazard ratio 0.61; 95% confidence interval (CI): 0.50-0.76]. Propensity-score matching was used to create 2 groups of 279 patients each who received early SBRT or delayed resection that were well-matched with regard to baseline characteristics. The 5-year survival associated with delayed resection was 53% (95% CI: 45%-61%) which was better than the 5-year survival associated with early SBRT (31% [95% CI: 24%-37%]). **CONCLUSION:** In this national analysis, for patients with stage IA NSCLC, extended delay of surgery was associated with improved survival when compared to early treatment with SBRT.

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

[Analysis of the clinical effect of osimertinib on 90 cases with advanced lung adenocarcinoma](#)

Transl Lung Cancer Res. 2020 Aug;9(4):1464-1471. doi: 10.21037/tlcr-20-685. Zhiqiang Gao 1 , Weimin Wang 1 , Aiqin Gu 1 , et al.

BACKGROUND: Primary or secondary drug resistance of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) is a new challenge in the treatment of advanced non-small cell lung cancer (NSCLC). Osimertinib is a third-generation EGFR-TKI, and its efficacy and safety in NSCLC patients with first-generation EGFR-TKI resistance, especially lung adenocarcinoma, are not yet clear. The purpose of this study was to observe the efficacy and adverse reactions of osimertinib in the treatment of patients with advanced lung adenocarcinoma. **METHODS:** From January 2017 to December 2018, 90 patients with advanced (stage IV) lung adenocarcinoma were diagnosed in Shanghai Chest Hospital. The disease of these patients (94.4%) progressed after first-line EGFR-TKI treatment, and 43.3% of patients received third-line or beyond third-line treatment. The efficacy and adverse reactions of osimertinib treatment were observed. **RESULTS:** Among 90 patients with advanced lung adenocarcinoma, 57 (63.3%) achieved partial response (PR), 27 (30.0%) had stable disease (SD), and 6 (6.7%) had progressive disease (PD). The objective response rate (ORR) was 63.3%, and the disease control rate (DCR) was 93.3%. The median progression-free time (mPFS) was 10.41 months (95% CI: 8.91-11.91 months), and the median overall survival (mOS) was 31.37 months (95% CI: 26.37-36.37 months). The incidence of adverse events of degree 3 and above was 7.78%. The main adverse events were diarrhea (28.9%) and rash (24.4%). After symptomatic treatment, the incidence of adverse events was significantly reduced. **CONCLUSIONS:** Osimertinib has a definite curative effect in the treatment of patients with advanced lung adenocarcinoma, and the incidence of adverse reactions is low.

[Soluble Immune Checkpoints, Gut Metabolites and Performance Status as Parameters of Response to Nivolumab Treatment in NSCLC Patients](#) J Pers Med. 2020 Nov 4;10(4):E208. doi:

10.3390/jpm10040208. Ilaria Grazia Zizzari ¹, Alessandra Di Filippo ¹, Fabio Scirocchi ¹, et al. Patients with non-small cell lung cancer (NSCLC) have been shown to benefit from the introduction of anti-PD1 treatment. However, not all patients experience tumor regression and durable response. The identification of a string of markers that are direct or indirect indicators of the immune system fitness is needed to choose optimal therapeutic schedules in the management of NSCLC patients. We analyzed 34 immuno-related molecules (14 soluble immune checkpoints, 17 cytokines/chemokines, 3 adhesion molecules) released in the serum of 22 NSCLC patients under Nivolumab treatment and the gut metabolomic profile at baseline. These parameters were correlated with performance status (PS) and/or response to treatment. Nivolumab affected the release of soluble immune checkpoints (sICs). Patients with a better clinical outcome and with an optimal PS (PS = 0) showed a decreased level of PD1 and maintained low levels of several sICs at first clinical evaluation. Low levels of PDL1, PDL2, Tim3, CD137 and BTLA4 were also correlated with a long response to treatment. Moreover, responding patients showed a high proportion of eubiosis-associated gut metabolites. In this exploratory study, we propose a combination of immunological and clinical parameters (sICs, PS and gut metabolites) for the identification of patients more suitable for Nivolumab treatment. This string of parameters validated in a network analysis on a larger cohort of patients could help oncologists to improve their decision-making in an NSCLC setting.

[Biomarker-driven therapies for previously treated squamous non-small-cell lung cancer \(Lung-MAP SWOG S1400\): a biomarker-driven master protocol](#) Lancet Oncol. 2020 Oct 27;S1470-

2045(20)30475-7. doi: 10.1016/S1470-2045(20)30475-7. Online ahead of print. Mary W Redman ¹, Vassiliki A Papadimitrakopoulou ², Katherine Minichiello ³, et al.

BACKGROUND: The Lung Cancer Master Protocol (Lung-MAP; S1400) is a completed biomarker-driven master protocol designed to address an unmet need for better therapies for squamous non-small-cell lung cancer. Lung-MAP (S1400) was created to establish an infrastructure for biomarker screening and rapid regulatory intent evaluation of targeted therapies and was the first biomarker-driven master protocol initiated with the US National Cancer Institute (NCI). **METHODS:** Lung-MAP (S1400) was

done within the National Clinical Trials Network of the NCI using a public-private partnership. Eligible patients were aged 18 years or older, had stage IV or recurrent squamous non-small-cell lung cancer, had previously been treated with platinum-based chemotherapy, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. The study included a screening component using the FoundationOne assay (Foundation Medicine, Cambridge, MA, USA) for next-generation sequencing, and a clinical trial component with biomarker-driven substudies and non-match substudies for patients who were ineligible for biomarker-driven substudies. Patients were pre-screened and received their substudy assignment upon progression, or they were screened at progression and received their substudy assignment upon completion of testing. Patients could enrol onto additional substudies after progression on a substudy. The study is registered with ClinicalTrials.gov, NCT02154490, and all research related to Lung-MAP (S1400) is completed. **FINDINGS:** Between June 16, 2014, and Jan 28, 2019, 1864 patients enrolled and 1841 (98.9%) submitted tissue. 1674 (90.9%) of 1841 patients had biomarker results, and 1404 (83.9%) of 1674 patients received a substudy assignment. Of the assigned patients, 655 (46.7%) registered to a substudy. The biomarker-driven substudies evaluated taselisib (targeting PIK3CA alterations), palbociclib (cell cycle gene alterations), AZD4547 (FGFR alteration), rilotumumab plus erlotinib (MET), talazoparib (homologous recombination repair deficiency), and telisotuzumab vedotin (MET). The non-match substudies evaluated durvalumab, and nivolumab plus ipilimumab for anti-PD-1 or anti-PD-L1-naïve disease, and durvalumab plus tremelimumab for anti-PD-1 or anti-PD-L1 relapsed disease. Combining data from the substudies, ten (7.0%) of 143 patients responded to targeted therapy, 53 (16.8%) of 315 patients responded to anti-PD-1 or anti-PD-L1 therapy for immunotherapy-naïve disease, and three (5.4%) of 56 responded to docetaxel in the second line of therapy. Median overall survival was 5.9 months (95% CI 4.8-7.8) for the targeted therapy groups, 7.7 months (6.7-9.2) for the docetaxel groups, and 10.8 months (9.4-12.3) for the anti-PD-1 or anti-PD-L1-containing groups. Median progression-free survival was 2.5 months (95% CI 1.7-2.8) for the targeted therapy groups, 2.7 months (1.9-2.9) for the docetaxel groups, and 3.0 months (2.7-3.9) for the anti-PD-1 or anti-PD-L1-containing groups. **INTERPRETATION:** Lung-MAP (S1400) met its goal to quickly address biomarker-driven therapy questions in squamous non-small-cell lung cancer. In early 2019, a new screening protocol was implemented expanding to all histological types of non-small-cell lung cancer and to add focus on immunotherapy combinations for anti-PD-1 and anti-PD-L1 therapy-relapsed disease. With these changes, Lung-MAP continues to meet its goal to focus on unmet needs in the treatment of advanced lung cancers. **FUNDING:** US National Institutes of Health, and AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Genentech, and Pfizer through the Foundation for the National Institutes of Health.

[Treatment of Patients With Non-small-cell Lung Cancer With Uncommon EGFR Mutations in Clinical Practice](#) Anticancer Res. 2020 Oct;40(10):5757-5764. doi: 10.21873/anticancer.14592.

Yutaka Yamada ¹, Tomohiro Tamura ², Yusuke Yamamoto ³, et al.

BACKGROUND/AIM: To describe real clinical outcomes in patients with non-small cell lung cancer who have uncommon epidermal growth factor receptor (EGFR) mutations. **MATERIALS AND METHODS:** We performed a retrospective chart review from 15 medical institutes that cover a population of three million people from April 2008 to March 2019. **RESULTS:** There were 102 patients with uncommon EGFR mutation. Progression-free survival (PFS) tended to be longer in patients receiving afatinib compared with first-generation EGFR tyrosine kinase inhibitors. PFS in patients treated with afatinib or osimertinib was significantly longer than in patients treated with gefitinib or erlotinib (p=0.030). Multivariate analysis also revealed the contribution of afatinib or osimertinib to increased survival. In patients with exon 20 insertions, chemotherapy was efficacious. **CONCLUSION:** In treating patients with uncommon EGFR mutations, our results indicate longer-term survival might be achieved with second-generation or later TKIs and cytotoxic chemotherapeutic drugs.

Mass balance, metabolic disposition, and pharmacokinetics of [¹⁴C]ensartinib, a novel potent anaplastic lymphoma kinase (ALK) inhibitor, in healthy subjects following oral administration

Cancer Chemother Pharmacol. 2020 Dec;86(6):719-730. doi: 10.1007/s00280-020-04159-0. Epub 2020 Oct 12. Sufeng Zhou 1, Wei Liu 2, Chen Zhou 1, et al.

PURPOSE: Ensartinib is a novel, potent and highly selective inhibitor of anaplastic lymphoma kinase (ALK) that has promising clinical activity and low toxicity in patients with ALK-positive non-small cell lung cancer. This study was conducted to investigate the pharmacokinetics, metabolism and excretion of ensartinib following a single 200 mg/100 μCi oral dose of radiolabeled ensartinib to healthy subjects.

METHODS: Six healthy male subjects were enrolled and administered an oral suspension in a fasted state. Blood, urine and feces were collected. Radioactivity concentrations were measured by liquid scintillation counting and plasma concentrations of ensartinib by liquid chromatography-tandem mass spectrometry. Both techniques were applied for metabolite profiling and characterization. **RESULTS:** The mean total recovery was 101.21% of the radiolabeled dose with 91.00% and 10.21% excreted in feces and urine, respectively. Unchanged ensartinib was the predominant drug-related component in urine and feces, representing 4.39% and 38.12% of the administered dose, respectively. Unchanged ensartinib and its metabolite M465 were the major circulating components, accounting for the same 27.45% of the plasma total radioactivity (AUC_{0-24h} pool), while other circulating metabolites were minor, accounting for less than 10%. Mean C_{max}, AUC_{0-∞}, T_{1/2} and T_{max} values for ensartinib in plasma were 185 ng/mL, 3827 h ng/mL, 18.3 h and 3.25 h, respectively. The total radioactivity in plasma was cleared with terminal half-life of 27.2 h. Treatment with ensartinib was well tolerated, and no serious adverse events were reported. **CONCLUSION:** It was well tolerated in the six healthy male subjects following a single oral administration of 200 mg/100 μCi dose of ensartinib. Besides unchanged ensartinib, metabolite of M465 was the predominant circulating drug-related component. The drug was primarily eliminated in feces.

Capmatinib in MET Exon 14-Mutated or MET-Amplified Non-Small-Cell Lung Cancer

N Engl J Med. 2020 Sep 3;383(10):944-957. doi: 10.1056/NEJMoa2002787. Jürgen Wolf 1, Takashi Seto 1, Ji-Youn Han 1, et al.

BACKGROUND: Among patients with non-small-cell lung cancer (NSCLC), MET exon 14 skipping mutations occur in 3 to 4% and MET amplifications occur in 1 to 6%. Capmatinib, a selective inhibitor of the MET receptor, has shown activity in cancer models with various types of MET activation.

METHODS: We conducted a multiple-cohort, phase 2 study evaluating capmatinib in patients with MET-dysregulated advanced NSCLC. Patients were assigned to cohorts on the basis of previous lines of therapy and MET status (MET exon 14 skipping mutation or MET amplification according to gene copy number in tumor tissue). Patients received capmatinib (400-mg tablet) twice daily. The primary end point was overall response (complete or partial response), and the key secondary end point was response duration; both end points were assessed by an independent review committee whose members were unaware of the cohort assignments. **RESULTS:** A total of 364 patients were assigned to the cohorts. Among patients with NSCLC with a MET exon 14 skipping mutation, overall response was observed in 41% (95% confidence interval [CI], 29 to 53) of 69 patients who had received one or two lines of therapy previously and in 68% (95% CI, 48 to 84) of 28 patients who had not received treatment previously; the median duration of response was 9.7 months (95% CI, 5.6 to 13.0) and 12.6 months (95% CI, 5.6 to could not be estimated), respectively. Limited efficacy was observed in previously treated patients with MET amplification who had a gene copy number of less than 10 (overall response in 7 to 12% of patients). Among patients with MET amplification and a gene copy number of 10 or higher, overall response was observed in 29% (95% CI, 19 to 41) of previously treated patients and in 40% (95% CI, 16 to 68) of those who had not received treatment previously. The most frequently reported adverse events were peripheral edema (in 51%) and nausea (in 45%); these events were mostly of grade 1 or 2. **CONCLUSIONS:**

Capmatinib showed substantial antitumor activity in patients with advanced NSCLC with a MET exon 14 skipping mutation, particularly in those not treated previously. The efficacy in MET-amplified advanced NSCLC was higher in tumors with a high gene copy number than in those with a low gene copy number. Low-grade peripheral edema and nausea were the main toxic effects. (Funded by Novartis Pharmaceuticals; GEOMETRY mono-1 ClinicalTrials.gov number, NCT02414139.).

[Neoadjuvant and Adjuvant Immunotherapy: Opening New Horizons for Patients With Early-Stage Non-small Cell Lung Cancer](#) Front Oncol. 2020 Oct 9;10:575472. doi: 10.3389/fonc.2020.575472.

Rilan Bai 1 , Lingyu Li 1 , Xiao Chen 1 , Naifei Chen 1 , Wei Song 1 , Jiuwei Cui 1

Lung cancer is the most common malignant tumor with the highest mortality, and about 84% are non-small cell lung cancer (NSCLC). However, only a small proportion of patients with newly diagnosed lung tumors can receive curative surgery and have a high risk of postoperative recurrence. At present, there are many perioperative treatment methods being continuously explored, such as chemotherapy and targeted therapy, continuously enriching the content of neoadjuvant and adjuvant therapy in early-stage NSCLC. But disappointingly, for patients with driver gene mutation, the significant disease-free survival (DFS) benefit of targeted drugs failed to translate into overall survival (OS) benefit, and for negative patients, chemotherapy has reached a plateau in improving efficacy and survival. Immunotherapy represented by immune checkpoint inhibitors (ICIs) has been researched in more and more clinical trials in patients with early-stage operable disease, gradually enriching the existing treatments. This review focuses on the research progress of clinical trials of neoadjuvant and adjuvant therapy with ICIs in early-stage NSCLC, the exploration of response evaluation and predictive biomarkers, and the urgent problems to be solved in the future.

[Phase III study of selpercatinib vs chemotherapy +/- pembrolizumab in untreated RET positive non-small-cell lung cancer](#) Future Oncol. 2020 Nov 5. doi: 10.2217/fon-2020-0935. Online ahead of print.

Benjamin J Solomon 1 , Cai Cun Zhou 2 , Alexander Drilon 3 , et al.

Selpercatinib, a novel, highly selective and potent, inhibitor of RET, demonstrated clinically meaningful antitumor activity with manageable toxicity in heavily pretreated and treatment-naïve RET fusion-positive non-small-cell lung cancer patients in a Phase I/II clinical trial. LIBRETTO-431 (NCT04194944) is a randomized, global, multicenter, open-label, Phase III trial, evaluating selpercatinib versus carboplatin or cisplatin and pemetrexed chemotherapy with or without pembrolizumab in treatment-naïve patients with locally advanced/metastatic RET fusion-positive nonsquamous non-small-cell lung cancer. The primary end point is progression-free survival by independent review. Key secondary end points include overall survival, response rate, duration of response and progression-free survival.

[Phase 1 Expansion Cohort of Ramucirumab Plus Pembrolizumab in Advanced Treatment-Naïve Non-Small Cell Lung Cancer](#) J Thorac Oncol. 2020 Oct 14;S1556-0864(20)30809-1. doi:

10.1016/j.jtho.2020.10.004. Online ahead of print. Roy S Herbst 1 , Hendrik Tobias Arkenau 2 , Johanna Bendell 3 , et al.

INTRODUCTION: Data of first-line ramucirumab plus pembrolizumab treatment of programmed death ligand 1 (PD-L1)-positive, non-small cell lung cancer (NSCLC; Cohort E) are reported (NCT02443324).

METHODS: In this multicenter, open-label phase 1a/b trial, patients received ramucirumab 10 mg/kg and pembrolizumab 200 mg every 21 days for up to 35 cycles. PD-L1 positivity was defined as tumor proportion score (TPS) $\geq 1\%$. Exploratory NanoString biomarker analyses included three T-cell signatures (T-cell-inflamed, Gajewski, and effector T-cells) and CD274 gene expression. **RESULTS:** Cohort E included 26 patients. Treatment-related adverse events (TRAEs) of any grade occurred in 22 (84.6%) patients. TRAEs of grade ≥ 3 were reported in 11 (42.3%) patients; the most frequent was hypertension (n=4, 15.4%). Objective response rate was 42.3% in the treated population, and 56.3% and 22.2% for

patients with high (TPS $\geq 50\%$), and lower levels (TPS 1%-49%) of PD-L1 expression. Median PFS in the treated population was 9.3 months and 12-month and 18-month PFS rates were each 45%. Median PFS was not reached in patients with PD-L1 TPS $\geq 50\%$ and was 4.2 months in patients with PD-L1 TPS 1%-49%. Median OS was not reached in the treated population, and 12-month and 18-month OS rates were 73% and 64%. Biomarker data suggested a positive association among clinical response, three T-cell signatures, CD274 gene expression, and PD-L1 immunohistochemistry. **CONCLUSIONS:** First-line therapy with ramucirumab plus pembrolizumab has a manageable safety profile in patients with NSCLC, and the efficacy signal appears to be strongest in tumors with high PD-L1 expression.

Adjuvant Chemotherapy Improves Survival in pN+ cIIIA NSCLC After Neoadjuvant Therapy and Resection Ann Thorac Surg. 2020 Oct 26;S0003-4975(20)31744-6. doi:

10.1016/j.athoracsur.2020.08.047. Online ahead of print. Scott M Atay 1, Maziar Amini 2, Li Ding 3, Elizabeth A David 3, P Michael Mcfadden 3, Sean C Wightman 3, Anthony W Kim 3

BACKGROUND: The utility of adjuvant chemotherapy (AC) following neoadjuvant therapy and curative intent surgery for clinical IIIA non-small cell lung cancer (NSCLC) is not defined. We sought to evaluate the contribution of AC to overall survival (OS) in patients with cIIIA NSCLC who underwent neoadjuvant therapy followed by curative intent surgical resection. **METHODS:** The National Cancer Database (NCDB) was queried from 2010 to 2016 for patients with cIIIA NSCLC who underwent curative intent surgical resection following neoadjuvant therapy. Patients were grouped by receipt of AC and OS was calculated using the Kaplan-Meier (KM) method. The association between mortality and AC was evaluated using Cox regression. 90-day landmark and propensity score matched (PSM) analyses were performed to address bias associated with early post-operative morbidity/mortality. **RESULTS:** 3847 patients met inclusion criteria, 780 received AC (20.2%). In the unadjusted cohort there was no difference in 5-year OS between the AC and no AC groups (42.8% vs. 43.9%, $p=0.105$). Cox regression demonstrated a decreased risk of mortality in $pN>0$ patients receiving AC (HR 0.79 CI 0.68-0.92, $p < 0.003$), while no difference was seen in node negative patients (HR 0.95 CI 0.78-1.17 $p=0.64$). In the propensity score matched groups OS was significantly increased in $pN>0$ patients who received AC (5-yr OS 42.4% vs. 37%, $p<0.01$), while no survival benefit was seen in those who were $pN0$.

CONCLUSIONS: For patients with completely resected cIIIA NSCLC following neoadjuvant therapy, AC is associated with an increase in overall survival for patients with residual pathologic lymph node involvement.

Chemotherapy in non-small cell lung cancer patients after prior immunotherapy: The multicenter retrospective CLARITY study Lung Cancer. 2020 Oct 22;150:123-131. doi:

10.1016/j.lungcan.2020.10.008. Online ahead of print. Melissa Bersanelli 1, Sebastiano Buti 2, Diana Giannarelli 3, et al.

OBJECTIVES: In the most of cases, for non-small cell lung cancer (NSCLC) patients who progressed to previous immune checkpoint inhibitors (CKI) administered as first- or as second-line therapy, chemotherapy (CT) remains the only viable options in the absence of "druggable" mutations. We aimed to explore the efficacy of salvage chemotherapy after immunotherapy (SCAI) in advanced NSCLC patients.

MATERIALS AND METHODS: We designed a retrospective, multicenter study, involving 20 Italian centers, with the primary objective of describing the clinical outcome of advanced NSCLC patients treated with SCAI at the participating institutions from November 2013 to July 2019. The primary endpoint of the study was represented by overall survival (OS), defined as the time from CT initiation to death. Secondary outcome endpoints of the SCAI (progression free survival, PFS, objective response rate, ORR and toxicity) and explorative biomarkers (lactate dehydrogenase, LDH, and neutrophil-to-lymphocyte ratio, NLR during immunotherapy) were also analyzed. **RESULTS:** In our study population of 342 NSCLC patients, SCAI obtained a median OS of 6.8 months (95 % confidence interval, CI 5.5-

8.1), median PFS of 4.1 months (95 % CI 3.4-4.8) and ORR of 22.8 %. A "Post-CKI score" was constructed by combining significant predictors of OS at the multivariate analyses (sex, ECOG PS, disease control with prior immunotherapy), Harrell'C was 0.65, (95 % CI:0.59-0.71). **CONCLUSIONS:** Despite the late-line settings, our findings support the hypothesis that previous immunotherapy might increase the sensitivity of the tumor to the subsequent chemotherapy. The "Post-CKI score" was clinically effective in successfully discriminating three distinct prognostic subgroups of patients after the failure of CKI, representing a possibly useful tool for the tailored decision-making process of advanced treatment-line settings in NSCLC.

Randomized Trial of Afatinib Plus Cetuximab Versus Afatinib Alone for First-Line Treatment of EGFR-Mutant Non-Small-Cell Lung Cancer: Final Results From SWOG S1403 J Clin Oncol. 2020

Oct 6;JCO2001149. doi: 10.1200/JCO.20.01149. Online ahead of print. Sarah B Goldberg 1 , Mary W Redman 2 , Rogerio Lilenbaum 1 , et al.

PURPOSE: The irreversible ErbB family tyrosine kinase inhibitor (TKI) afatinib plus the EGFR monoclonal antibody cetuximab was previously shown to overcome resistance to EGFR TKIs. We studied whether the combination of afatinib plus cetuximab compared with afatinib alone would improve progression-free survival (PFS) in patients with treatment-naïve EGFR-mutant non-small-cell lung cancer (NSCLC) by preventing or delaying resistance. **METHODS:** Patients with EGFR-mutant NSCLC without prior treatment of advanced disease were enrolled in this phase II, multicenter trial and randomly assigned to receive afatinib 40 mg orally daily plus cetuximab 500 mg/m² intravenously every 2 weeks or afatinib alone. The primary end point was PFS. **RESULTS:** Between March 25, 2015 and April 23, 2018, 174 patients were randomly assigned, and 168 (83 on afatinib + cetuximab and 85 on afatinib) were eligible. There was no improvement in PFS in patients receiving afatinib plus cetuximab compared with afatinib alone (hazard ratio [HR], 1.01; 95% CI, 0.72 to 1.43; P = .94; median, 11.9 months v 13.4 months). Similarly, there was no difference in response rate (67% v 74%; P = .38) or overall survival (HR, 0.82; 95% CI, 0.50 to 1.36; P = .44). Toxicity was greater with the combination: grade ≥ 3 adverse events related to treatment occurred in 72% of patients receiving afatinib plus cetuximab compared with 40% of those receiving afatinib alone, most commonly rash and diarrhea. Dose reductions were more common in patients receiving the combination, and 30% of patients in this arm discontinued cetuximab due to toxicity. At interim analysis, there was insufficient evidence to support continued accrual, and the trial was closed. **CONCLUSIONS:** The addition of cetuximab to afatinib did not improve outcomes in previously untreated EGFR-mutant NSCLC, despite recognized activity in the acquired resistance setting.

NSCLC - RADIOTHERAPY

The Combined Use of SBRT and Immunotherapy-a Literature Review Curr Oncol Rep. 2020 Sep 15;22(12):117. doi: 10.1007/s11912-020-00986-9. Maryanne J Lubas 1 , Sameera S Kumar 2

PURPOSE OF REVIEW: The purpose of this paper is to review all recent and relevant data regarding the combined use of immunotherapy (particularly immune checkpoint inhibitors) and radiotherapy.

RECENT FINDINGS: The use of radiotherapy, specifically stereotactic body radiation therapy (SBRT), and immunotherapy may be synergistic in the treatment of non-small cell lung cancer (NSCLC). There have been many preclinical and clinical studies that have shown that the combination of SBRT and immunotherapy is both safe and effective. In many cases, the benefits are greater than either SBRT or immunotherapy alone. Several ongoing trials are testing the combination of SBRT and immunotherapy for the treatment of all stages of NSCLC. **CONCLUSION:** The combined use of SBRT and +immunotherapy is a promising new development. The techniques may synergistically work better than either alone.

Oligometastasis: Past, Present, Future Int J Radiat Oncol Biol Phys. 2020 Nov 1;108(3):530-538. doi: 10.1016/j.ijrobp.2020.02.019. Stanley I Gutiontov 1 , Sean P Pitroda 1 , Ralph R Weichselbaum 2
In this review, we discuss the oligometastatic state, with a focus on its current and future relevance within the field of radiation therapy. We first outline the scope of the problem and the evolving understanding of metastatic disease existing along a spectrum. We then transition to a discussion of the clinical data that led to the formulation of the oligometastatic hypothesis, delving in some detail into the clinical factors associated with improved outcomes in the setting of local therapy-whether surgical or radiotherapeutic. In particular, we highlight the marked limitations of using clinical criteria alone to determine the absence or presence of true extracranial oligometastatic disease. After this, we briefly discuss the radiation therapy literature that has recently demonstrated benefits in cancer-specific outcomes with ablative treatment of oligometastatic disease. We emphasize data in the setting of non-small cell lung cancer and prostate cancer and briefly discuss the importance of our enhanced ability to detect occult metastatic disease with improved imaging technologies. After noting that resulted and ongoing prospective trials of ablative radiation therapy use the most rudimentary of oligometastatic classifiers-number of metastases-as their inclusion criteria, we transition to our core argument: a growing body of preclinical and translational work aims to refine the definition of oligometastatic disease using molecular features. We address genomic, epigenetic, and immunologic features that have, across histology, demonstrated an improved ability to prognosticate when combined with classic clinical correlates of oligometastatic disease. We also discuss studies that suggest particular molecular targets which, when manipulated for therapeutic purposes, have the potential to revert the polymetastatic phenotype to the oligometastatic one. We conclude with what we believe are the repercussions of this work for radiation therapy trials and clinical practice, and the importance of enriching and supporting these inquiries for the future of our field.

Predictive value of vascular calcification identified in 4D planning CT of lung cancer patients treated with stereotactic body radiation therapy Phys Med. 2020 Oct;78:173-178. doi: 10.1016/j.ejmp.2020.09.010. Epub 2020 Oct 7. Azadeh Abravan 1 , Marcel van Herk 2 , Frank Brewster 3 , Corinne Faivre-Finn 2 , Alan McWilliam 2 , Eliana M Vasquez Osorio 2

PURPOSE: The aim was to identify vascular calcification in 4DCT scan of lung cancer patients and establish the association between overall survival (OS) and vascular calcification, as surrogate for vascular health.

METHODS: Vascular calcification within the thoracic cavity were segmented in 334 lung cancer patients treated with stereotactic body radiation therapy (SBRT). This has been done automatically on 4D planning CT and average reconstruction scans. Correlation between cardiac comorbidity and calcification volumes was evaluated for patients with recorded Adult Co-Morbidity Evaluation (n = 303). Associations between the identified calcifications and OS were further investigated. **RESULTS:** The volume of calcification from the average scan was significantly lower than from each phase ($p < 0.001$). The highest level of correlations between cardiac comorbidity and volume of the calcifications were found for one phase representing inhale and two phases representing exhale with the least motion blurring due to respiration ($p < 0.005$). The volume of the calcifications was subsequently averaged over these three phases. The average of calcification volumes over the three phases (denoted by inhale-exhale) showed the highest likelihood in univariate analysis and was chosen as vascular calcification measure. Cox-model suggested that tumor volume (Hazard Ratio [HR] = 1.46, $p < 0.01$) and inhale-exhale volume (HR = 1.05, $p < 0.05$) are independent factors predicting OS after adjusting for age, sex, and performance status. **CONCLUSION:** It was feasible to use. It 4DCT scan for identifying thoracic calcifications in lung cancer patients treated with SBRT. Calcification volumes from inhale-exhale phases had the highest correlation with overall cardiac comorbidity and the average of the calcification volume obtained from these phases was an independent predictive factor for OS.

[Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: a randomized phase I/II trial](#) J Immunother Cancer. 2020 Oct;8(2):e001001. doi: 10.1136/jitc-2020-001001. James Welsh # 1 , Hari Menon # 2 , Dawei Chen # 3 , et al.

BACKGROUND: In this phase I/II trial, we evaluated the safety and effectiveness of pembrolizumab, with or without concurrent radiotherapy (RT), for lung and liver lesions from metastatic non-small cell lung cancer (mNSCLC). **METHODS:** Patients with lung or liver lesions amenable to RT plus at least one additional non-contiguous lesion were included regardless of programmed death-ligand 1 (PD-L1) status. Pembrolizumab was given at 200 mg every 3 weeks for up to 32 cycles with or without concurrent RT. Metastatic lesions were treated with stereotactic body RT (SBRT; 50 Gy in 4 fractions) if clinically feasible or with traditionally fractionated RT (45 Gy in 15 fractions) if not. The primary end point was the best out-of-field lesion response, and a key secondary end point was progression-free survival (PFS).

RESULTS: The median follow-up time was 20.4 months. One hundred patients (20 phase I, 80 phase II) were evaluable for toxicity, and 72 phase II patients were evaluable for treatment response. No patients in the phase I group experienced grade 4-5 events; in the phase II group, two had grade 4 events and nine had grade 3 events. The ORR in the combined-modality cohort (irrespective of RT schema) was 22%, vs 25% in the pembrolizumab group (irrespective of receipt of salvage RT) ($p=0.99$). In the concurrent pembrolizumab+RT groups, the out-of-field ORRs were 38% in the pembrolizumab+SBRT group and 10% in the pembrolizumab+traditional RT group. When examining the pembrolizumab-alone patients, the out-of-field ORRs were 33% in those designated to receive salvage SBRT (if required) and 17% for salvage traditional RT. In all patients, the median PFS for pembrolizumab alone was 5.1 months (95% CI 3.4 to 12.7 months), and pembrolizumab/RT (regardless of schema) was 9.1 months (95% CI 3.6 to 18.4 months) ($p=0.52$). An exploratory analysis revealed that for patients with low PD-L1 expression, the median PFS was 4.6 vs 20.8 months for pembrolizumab with and without RT, respectively ($p=0.004$).

CONCLUSIONS: Concurrent immunoradiotherapy for mNSCLC is safe, although larger trials are required to address which patients benefit most from RT.

[Evaluation of the prognostic value of derived neutrophil/lymphocyte ratio in early stage non-small cell lung cancer patients treated with stereotactic ablative radiotherapy](#) Medicine (Baltimore). 2020 Oct 16;99(42):e22603. doi: 10.1097/MD.00000000000022603. Xin Wang 1 , Zhi Lou, Lei Zhang, Zhenghong Liu, Jie Zhang, Jia Gao, Yajun Ji

The derived neutrophil-lymphocyte ration (dNLR) is a systemic inflammatory marker. The present study focusing on the prognostic value of pre-treatment dNLR in patients of early stage non-small cell lung cancer (NSCLC). From 2012 to 2016, patients with newly diagnosed early stage NSCLC were investigated. Only these who treated with stereotactic ablative radiotherapy (SABR) were enrolled in this study. dNLR was calculated from complete blood count prior to SABR. The optimal cut-off value of dNLR was determined by receiver operating curve. Kaplan-Meier curves and Cox proportional models were used to analyze the impact of pre-treatment dNLR on disease free survival (DFS) and overall survival (OS). There were 69 patients eligible for analysis, the median follow-up period was 30.9 months. Calculated by receiver operating characteristic curves, the optimal cut off value of dNLR was 1.99. Kaplan-Meier curves demonstrated that a decreased dNLR was correlated with favorable DFS and OS. In univariate analysis, high dNLR was associated with decreased survival; moreover, multivariate analysis revealed that a decreased dNLR was an independent significant favorable prognostic factor for both DFS and OS. An elevated pre-treatment dNLR may be an independent prognostic biomarker for DFS and OS in patients with early stage NSCLC that are eligible for SABR. dNLR is a reliable, inexpensive, simple, and readily available tool for risk-stratification and should be considered in daily clinical practice.

[Radiomic Analysis of CT Predicts Tumor Response in Human Lung Cancer with Radiotherapy](#)

J Digit Imaging. 2020 Oct 6. doi: 10.1007/s10278-020-00385-3. Online ahead of print. Mengmeng Yan 1 2 , Weidong Wang 3 4

PURPOSE: Radiomics features can be positioned to monitor changes throughout treatment. In this study, we evaluated machine learning for predicting tumor response by analyzing CT images of lung cancer patients treated with radiotherapy. **EXPERIMENTAL DESIGN:** For this retrospective study, screening or standard diagnostic CT images were collected for 100 patients (mean age, 67 years; range, 55-82 years; 64 men [mean age, 68 years; range, 55-82 years] and 36 women [mean age, 65 years; range, 60-72 years]) from two institutions between 2013 and 2017. Radiomics analysis was available for each patient. Features were pruned to train machine learning classifiers with 50 patients, then trained in the test dataset.

RESULT: A support vector machine classifier with 2 radiomic features (flatness and coefficient of variation) achieved an area under the receiver operating characteristic curve (AUC) of 0.91 on the test set.

CONCLUSION: The 2 radiomic features, flatness, and coefficient of variation, from the volume of interest of lung tumor, can be the biomarkers for predicting tumor response at CT.

[Technical Note: Comparison of the internal target volume \(ITV\) contours and dose calculations on 4DCT, average CBCT, and 4DCBCT imaging for lung stereotactic body radiation therapy \(SBRT\)](#)

J Appl Clin Med Phys. 2020 Oct 12. doi: 10.1002/acm2.13041. Online ahead of print. Michael Dumas 1, Eric Laugeman 2 , Parag Sevak 3 , Karen C Snyder 1 , Weihua Mao 1 , Indrin J Chetty 1 , Munther Ajlouni 1 , Ning Wen 1

PURPOSE: To investigate the differences between internal target volumes (ITVs) contoured on the simulation 4DCT and daily 4DCBCT images for lung cancer patients treated with stereotactic body radiotherapy (SBRT) and determine the dose delivered on 4D planning technique.

METHODS: For nine patients, 4DCBCTs were acquired before each fraction to assess tumor motion. An ITV was contoured on each phase of the 4DCBCT and a union of the 10 ITVs was used to create a composite ITV. Another ITV was drawn on the average 3DCBCT (avgCBCT) to compare with current clinical practice. The Dice coefficient, Hausdorff distance, and center of mass (COM) were averaged over four fractions to compare the ITVs contoured on the 4DCT, avgCBCT, and 4DCBCT for each patient. Planning was done on the average CT, and using the online registration, plans were calculated on each phase of the 4DCBCT and on the avgCBCT. Plan dose calculations were tested by measuring ion chamber dose in the CIRS lung phantom. **RESULTS:** The Dice coefficients were similar for all three comparisons: avgCBCT-to-4DCBCT (0.7 ± 0.1), 4DCT-to-avgCBCT (0.7 ± 0.1), and 4DCT-to-4DCBCT (0.7 ± 0.1); while the mean COM differences were also comparable (2.6 ± 2.2 mm, 2.3 ± 1.4 mm, and 3.1 ± 1.1 mm, respectively). The Hausdorff distances for the comparisons with 4DCBCT (8.2 ± 2.9 mm and 8.1 ± 3.2 mm) were larger than the comparison without (6.5 ± 2.5 mm). The differences in ITV D95% between the treatment plan and avgCBCT calculations were $4.3 \pm 3.0\%$ and $-0.5 \pm 4.6\%$, between treatment plan and 4DCBCT plans, respectively, while the ITV V100% coverages were $99.0 \pm 1.9\%$ and $93.1 \pm 8.0\%$ for avgCBCT and 4DCBCT, respectively. **CONCLUSION:** There is great potential for 4DCBCT to evaluate the extent of tumor motion before treatment, but image quality challenges the clinician to consistently delineate lung target volumes.

[Deep learning-based real-time volumetric imaging for lung stereotactic body radiation therapy: a proof of concept study](#)

Phys Med Biol. 2020 Oct 20. doi: 10.1088/1361-6560/abc303. Online ahead of print. Yang Lei 1 , Zhen Tian 2 , Tonghe Wang 1 , Kristin Higgins 3 , Jeffrey D Bradley 4 , Walter J Curran 3 , Tian Liu 1 , Xiaofeng Yang 1

Due to the inter- and intra- variation of respiratory motion, it is highly desired to provide real-time volumetric images during the treatment delivery of lung stereotactic body radiation therapy (SBRT) for accurate and active motion management. In this proof-of-concept study, we propose a novel generative

adversarial network integrated with perceptual supervision to derive instantaneous volumetric images from a single 2D projection. Our proposed network, named TransNet, consists of three modules, i.e., encoding, transformation and decoding modules. Rather than only using image distance loss between the generated 3D images and the ground truth 3D CT images to supervise the network, perceptual loss in feature space is integrated into loss function to force the TransNet to yield accurate lung boundary. Adversarial supervision is also used to improve the realism of generated 3D images. We conducted a simulation study on 20 patient cases, who had received lung SBRT treatments in our institution and undergone 4D-CT simulation, and evaluated the efficacy and consistency of our method for four different projection angles, i.e., 0°, 30°, 60° and 90°. For each 3D CT image set of a breathing phase, we simulated its 2D projections at these angles. For each projection angle, a patient's 3D CT images of 9 phases and the corresponding 2D projection data were used to train our network for that specific patient, with the remaining phase used for testing. The MAE of the 3D images obtained by our method are 99.3 ± 14.1 HU. The PSNR and structural similarity index metric (SSIM) within the tumor region of interest (ROI) are 15.4 ± 2.5 dB and 0.839 ± 0.090 , respectively. These results demonstrate the feasibility and efficacy of our 2D-to-3D method for lung cancer patients, which provides a potential solution for in-treatment real-time on-board volumetric imaging for accurate dose delivery to ensure the effectiveness of lung SBRT treatment.

SMALL CELL LUNG CANCER - SCLC

[Identification of RUNX1T1 as a potential epigenetic modifier in small cell lung cancer](#) Mol Oncol. 2020 Oct 20. doi: 10.1002/1878-0261.12829. Online ahead of print. Tian He 1 , Gary Wildey 2 , Karen McColl 2 , et al.

Small cell lung cancer (SCLC) can be sub-grouped into common 'pure' and rare 'combined' SCLC (c-SCLC). c-SCLC features a mixed tumor histology of both SCLC and non-small cell lung cancer (NSCLC). We performed targeted exon sequencing on 90 SCLC patients, including two with c-SCLC, and discovered RUNX1T1 amplification specific to small cell tumors of both c-SCLC patients, but in only 2 of 88 'pure' SCLC patients. RUNX1T1 was first identified in the fusion transcript AML1/ETO, which occurs in 12%-15% of acute myelogenous leukemia (AML). We further show higher expression of RUNX1T1 in the SCLC component of another c-SCLC tumor by in situ hybridization. RUNX1T1 expression was enriched in SCLC compared to all other cancers, including NSCLC, in both cell lines and tumor specimens, as shown by mRNA level and western blotting. Transcriptomic analysis of hallmark genes decreased by stable RUNX1T1 overexpression revealed a significant change in E2F targets. Validation experiments in multiple lung cancer cell lines showed that RUNX1T1 overexpression consistently decreased CDKN1A (p21) expression and increased E2F transcriptional activity, which is commonly altered in SCLC. Chromatin immunoprecipitation (ChIP) in these overexpressing cells demonstrated that RUNX1T1 interacts with the CDKN1A (p21) promoter region, which displayed parallel reductions in histone 3 acetylation. Furthermore, reduced p21 expression could be dramatically restored by HDAC inhibition using Trichostatin A. Reanalysis of ChIP-seq data in Kasumi-1 AML cells showed that knockdown of the RUNX1T1 fusion protein was associated with increased global acetylation, including the CDKN1A (p21) promoter. Thus, our study identifies RUNX1T1 as a biomarker and potential epigenetic regulator of SCLC.

[Camrelizumab Plus Apatinib in Extensive-Stage Small-Cell Lung Cancer \(PASSION\): A Multicenter, Two-Stage, Phase 2 Trial](#) J Thorac Oncol. 2020 Nov 6;S1556-0864(20)30806-6. doi: 10.1016/j.jtho.2020.10.002. Online ahead of print. Yun Fan 1 , Jun Zhao 2 , Qiming Wang 3 , et al. **INTRODUCTION:** Treatment options in second-line extensive-stage small-cell lung cancer (ED-SCLC) setting are limited. PASSION (ClinicalTrials.gov identifier: NCT03417895) was a phase 2 study of

camrelizumab plus apatinib in ED-SCLC after platinum-based chemotherapy. **METHODS:** In Stage 1, patients were randomized (1:1:1) to receive camrelizumab 200 mg every 2 weeks plus apatinib 375 mg once daily (QD), 5 days on/2 days off, or 7 days on/7 days off (six patients each cohort). Based on the tolerability during the first 28-day cycle and efficacy data in Stage 1, one cohort was chosen to expand to 45 patients in Stage 2. The primary endpoint was objective response rate (ORR). **RESULTS:** From Apr 20, 2018 to Mar 12, 2019, 59 patients were enrolled, with 47 patients in the QD cohort. In the QD cohort, confirmed ORR reached 34.0% (95% CI 20.9–49.3), the median progression-free survival (PFS) was 3.6 months, and the median overall survival (OS) was 8.4 months. Chemotherapy-sensitive and chemotherapy-resistant patients (defined as patients with disease relapsed ≥ 90 and < 90 days after platinum-based chemotherapy, respectively) had comparable confirmed ORR (37.5% versus 32.3%), median PFS (3.6 versus 2.7 months), and median OS (9.6 versus 8.0 months). Treatment-related adverse events (TRAEs) of grade ≥ 3 were reported in 43 (72.9%) of 59 patients. Five (8.5%) patients discontinued due to TRAEs. **CONCLUSION:** Camrelizumab plus apatinib showed potential antitumor activity in both chemotherapy-sensitive and chemotherapy-resistant ED-SCLC patients who had failed platinum-based chemotherapy with acceptable toxicity profile. This phase 2 data warrant further clinical studies of camrelizumab plus apatinib in SCLC.

[The combination of pretreatment prognostic nutritional index and neuron-specific enolase enhances prognosis predicting value of small cell lung cancer](#) Clin Respir J. 2020 Oct 15. doi:

10.1111/crj.13291. Online ahead of print. Chunyan Wang 1, Shi Jin 2, Shanqi Xu 3, Shoubo Cao 1
INTRODUCTION: Tumor and immune-inflammatory biomarkers have been demonstrated to be closely associated with cancer prognosis. **OBJECTIVE:** The present study aims to assess the prognostic value of pretreatment prognostic nutritional index (PNI), carcinoembryonic antigen (CEA), and neuron-specific enolase (NSE) in small cell lung cancer (SCLC). **METHODS:** A retrospective analysis of 301 SCLC patients treated with platinum-based chemotherapy was performed. Overall survival (OS) was assessed by Kaplan-Meier and multivariate Cox hazard analyses. **RESULTS:** The median OS for total cases was 15.0 months. On univariate analysis, tumor stage ($P < 0.001$), pretreatment PNI ($P < 0.001$), CEA ($P = 0.039$), NSE ($P = 0.010$), distant metastasis numbers ($P < 0.001$), and thoracic radiotherapy ($P < 0.001$) were found to be the predictors of OS. Multivariate analysis showed limited stage, high PNI, NSE $< 15 \mu\text{g/L}$, and chemoradiotherapy were positive independent prognostic factors ($P < 0.05$). Low PNI and NSE $\geq 15 \mu\text{g/L}$ were closely correlated with a high tumor burden status. Three cohorts of SCLC with significant different survival outcomes were divided based on variable PNI and NSE levels. Patients with high PNI and NSE $< 15 \mu\text{g/L}$ showed the best OS of 24.5 months, while patients with low PNI and NSE $\geq 15 \mu\text{g/L}$ had the worst survival outcome of 10.0 months. Patients with low PNI and NSE $< 15 \mu\text{g/L}$ or high PNI and NSE $\geq 15 \mu\text{g/L}$ had the similar outcome of 16.5 and 17.0 months, respectively. **CONCLUSIONS:** Pretreatment PNI and NSE were independent prognostic factors of SCLC. The combination of PNI and NSE enhanced the OS predicting ability, and patients with high PNI and NSE $< 15 \mu\text{g/L}$ had the best survival outcome.

[Pilot Study: Texture analysis of PET imaging demonstrates changes in 18 F-FDG uptake of the brain after prophylactic cranial irradiation](#) J Nucl Med Technol. 2020 Oct 5; jnmt.120.248393. doi:

10.2967/jnmt.120.248393. Online ahead of print. David M Sawyer 1, Travis W Sawyer 2, Naghmehossadat Eshghi 1, Charles Hsu 3, Russell J Hamilton 3, Linda L Garland 4, Phillip H Kuo 5
RATIONALE: Prophylactic cranial irradiation (PCI) is used to decrease the probability of developing brain metastases in patients with small cell lung cancer and has been linked to deleterious cognitive effects. While no well-established imaging markers for these effects exist, previous studies have shown that structural and metabolic changes of the brain can be detected with magnetic resonance imaging and positron emission tomography (PET). This study utilized an image processing technique called texture

analysis to explore whether global changes in brain glucose metabolism could be characterized in PET images. **METHODS:** 18F-FDG PET images of the brain from patients with small cell lung cancer, obtained before and after the administration of PCI, were processed using texture analysis. Texture features were compared between the pre- and post-PCI images. **RESULTS:** Multiple texture features demonstrated statistically significant differences before and after PCI, when texture analysis was applied to the brain parenchyma as a whole. Regional differences were also seen but were not statistically significant. **CONCLUSION:** Global changes in brain glucose metabolism occur after PCI and are detectable using advanced image processing techniques. These changes may reflect radiation-induced damage and thus may provide a novel method for studying radiation-induced cognitive impairment.

[American Radium Society™ Appropriate Use Criteria: Radiation Therapy for Limited-stage Small Cell Lung Cancer](#) 2020 J Thorac Oncol. 2020 Nov 6;S1556-0864(20)30846-7. doi:

10.1016/j.jtho.2020.10.020. Online ahead of print. Stephen G Chun¹, Charles B Simone 2nd², Arya Amini³, et al.

INTRODUCTION: Combined modality therapy with concurrent chemotherapy and radiation has long been the standard of care for limited-stage small cell lung cancer (LS-SCLC). However, there is controversy over best combined modality practices for LS-SCLC. To address these controversies, the American Radium Society (ARS) Thoracic Appropriate Use Criteria® Committee have developed updated consensus guidelines for the treatment of LS-SCLC. **MATERIALS/METHODS:** The ARS Appropriateness Criteria® (AUC) are evidence-based guidelines for specific clinical conditions that are reviewed by a multidisciplinary expert panel. The guidelines include a review and analysis of current evidence with application of consensus methodology (modified Delphi) to rate the appropriateness of treatments recommended by the panel for LS-SCLC. Agreement/consensus was defined as ≤ 3 rating points from the panel median. The consensus ratings and recommendations were then vetted by the ARS Executive Committee and subject to public comment prior to finalization. **RESULTS:** The ARS Thoracic AUC committee developed multiple consensus recommendations for LS-SCLC. There was strong consensus that patients with unresectable LS-SCLC should receive concurrent chemotherapy with radiation delivered either once or twice daily. For medically-inoperable T1-T2N0 LS-SCLC, either concurrent chemoradiation or stereotactic body radiation (SBRT) followed by adjuvant chemotherapy are reasonable treatment options. The panel continues to recommend whole brain prophylactic cranial irradiation (PCI) after response to chemoradiation for LS-SCLC. There was panel agreement that PCI with hippocampal avoidance and PD-1/PD-L1 directed immune therapy should not be routinely administered outside the context of clinical trials at this time. **CONCLUSIONS:** The ARS Thoracic AUC Committee provide consensus recommendations for LS-SCLC that aim to provide a groundwork for multidisciplinary care and clinical trials.

[Galectin-9-based immune risk score model helps to predict relapse in stage I-III small cell lung cancer](#) J Immunother Cancer. 2020 Oct;8(2):e001391. doi: 10.1136/jitc-2020-001391. Peixin Chen^{1,2},

Liping Zhang³, Wei Zhang³, Chenglong Sun^{1,2}, Chunyan Wu³, Yayi He⁴, Caicun Zhou⁴

BACKGROUND: For small cell lung cancer (SCLC) therapy, immunotherapy might have unique advantages to some extent. Galectin-9 (Gal-9) plays an important role in antitumor immunity, while little is known of its function in SCLC. **MATERIALS AND METHODS:** By mean of immunohistochemistry (IHC), we tested the expression level of Gal-9 and other immune markers on both tumor cells and tumor-infiltrating lymphocytes (TILs) in 102 surgical-resected early stage SCLC clinical samples. On the basis of statistical analysis and machine learning results, the Gal-9-based immune risk score model was constructed and its predictive performance was evaluated. Then, we thoroughly explored the effects of Gal-9 and immune risk score on SCLC immune microenvironment and immune infiltration in different cohorts and platforms. **RESULTS:** In the SCLC cohort for IHC, the expression level of Gal-9 on TILs

was statistically correlated with the levels of program death-1 ($p=0.001$), program death-ligand 1 (PD-L1) ($p<0.001$), CD3 ($p<0.001$), CD4 ($p<0.001$), CD8 ($p<0.001$), and FOXP3 ($p=0.047$). High Gal-9 protein expression on TILs indicated better recurrence-free survival (30.4 months, 95% CI: 23.7-37.1 vs 39.4 months, 95% CI: 31.6-47.3, $p=0.009$). The immune risk score model which consisted of Gal-9 on TILs, CD4, and PD-L1 on TILs was established and validated so as to differentiate high-risk or low-risk patients with SCLC. The prognostic predictive performance of immune risk score model was better than single immune biomarker (area under the curve 0.671 vs 0.621-0.644). High Gal-9-related enrichment pathways in SCLC were enriched in immune system diseases and rheumatic disease. Furthermore, we found that patients with SCLC with low immune risk score presented higher fractions of activated memory CD4 T cells than patients with high immune risk score ($p=0.048$). **CONCLUSIONS:** Gal-9 is markedly related to tumor-immune microenvironment and immune infiltration in SCLC. This study emphasized the predictive value and promising clinical applications of Gal-9 in stage I-III SCLC

PALLIATIVE AND SUPPORTIVE CARE

[Incidence and Risk of Colitis With Programmed Death 1 Versus Programmed Death Ligand 1 Inhibitors for the Treatment of Cancer](#) J Immunother. Nov/Dec 2020;43(9):291-298. doi:

10.1097/CJI.0000000000000339. Hirota Miyashita 1 , Takahisa Mikami 1 , Sera Sato 2 , Christina Cruz 1 , Matthew D Galsky 3

Colitis is a major immune-related adverse event associated with programmed death 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors, but the risk of colitis with PD-1 versus PD-L1 inhibitors is not well characterized. We performed a meta-analysis for the incidence of all grade and grade 3-4 colitis with PD-1 inhibitor (nivolumab, pembrolizumab, and cemiplimab) or PD-L1 inhibitor (atezolizumab, avelumab, and durvalumab) monotherapy using a fixed effects model. We also conducted subgroup meta-analyses of non-small cell lung cancer (NSCLC) or urothelial carcinoma (UC) trials, and a network meta-analysis of randomized trials comparing PD-1 or PD-L1 inhibitors with docetaxel for NSCLC. We also analyzed the Food and Drug Administration Adverse Event Reporting System database to estimate the reporting odds ratio of each medication. PD-1 inhibitors were associated with a higher incidence of all grade and grade 3-4 colitis compared with PD-L1 inhibitors in the analysis of all cancer types [1.49% vs. 0.83%, relative risk; 1.80, 95% confidence interval (CI); 1.22-2.67 for all grade colitis, and 0.85% vs. 0.34%, relative risk; 2.52, 95% CI; 1.46-4.37 for grade 3-4 colitis]. The meta-analyses of NSCLC and UC trials, and the network meta-analysis of NSCLC trials were also suggestive of a higher risk of colitis with PD-1 versus PD-L1 inhibitors. The reporting odds ratio of colitis with PD-1 versus PD-L1 inhibitors was 1.80 (95% CI; 1.53-2.14). In this meta-analysis of clinical trials exploring PD-1 and PD-L1 inhibitors in solid tumors, PD-1 inhibitors were associated with a higher risk of colitis.

[Symptom burden in patients with common cancers near end-of-life and its associations with clinical characteristics: a real-world study](#) Support Care Cancer. 2020 Oct 26. doi: 10.1007/s00520-020-05827-

w. Online ahead of print. Atul Batra 1 2 , Lin Yang 3 , Devon J Boyne 4 , Andrew Harper 3 , Colleen A Cuthbert 2 5 3 , Winson Y Cheung 6 7

BACKGROUND: Patients dying with cancer can experience various physical and psychological symptoms. We aimed to determine the type and severity of symptoms within the last 6 months of life in a large real-world cohort of patients with cancer. **METHODS:** We examined prospectively collected patient-reported outcomes of patients with lung, colorectal, breast, prostate or pancreatic cancer using the revised Edmonton Symptom Assessment System (ESASr) questionnaire from a large province in Canada from 2016 to 2017. The ESASr was categorized into physical and psychological symptom subscores and total symptom score, and each was classified as none to mild (0-3) or moderate to severe (4-10) based on intensity. Multivariable logistic regression analyses were performed to evaluate the relationship between

clinical characteristics and symptom scores. **RESULTS:** We identified 1159 patients eligible for analysis, of whom 52.2% were men and median age was 68 years. There were 613, 192, 149, 111 and 94 patients with lung, colorectal, breast, prostate and pancreatic cancer, respectively. While approximately half of patients reported moderate to severe physical symptom subscores and total symptom scores, only one-third reported moderate to severe psychological subscores. On multivariable logistic regression analyses, women were more likely to report moderate to severe physical (odds ratio [OR], 1.52; 95% confidence interval [CI], 1.08-2.12; P = 0.016), psychological (OR, 1.60; 95% CI, 1.14-2.26; P = 0.006) and total symptom scores (OR, 1.80; 95% CI, 1.28-2.51; P = 0.001). Patients with lung cancer were also more likely to report moderate to severe physical and psychological subscores (OR, 1.95; 95% CI, 1.28-2.96; P = 0.002 and OR, 1.78; 95% CI, 1.13-2.81; P = 0.013) and total symptom scores (OR, 1.83; 95% CI, 1.20-2.81; P = 0.005). Finally, those closer to death were more likely to report moderate to severe physical symptom subscores (OR, 2.07; 95% CI, 1.33-3.23; P = 0.001) and total symptom scores (OR, 2.29; 95% CI, 1.46-3.60; P < 0.001), but not psychological symptom scores (OR, 1.34; 95% CI, 0.84-2.14; P = 0.210). **CONCLUSIONS:** There is significant symptom burden in patients with cancer near the end-of-life. Further, physical symptoms appear to be more intense than psychological symptoms. Symptom-directed care is still needed to improve the quality of end-of-life.

Timing, Costs, and Survival Outcome of Specialty Palliative Care in Medicare Beneficiaries With Metastatic Non-Small-Cell Lung Cancer JCO Oncol Pract. 2020 Oct 2;OP2000298. doi:

10.1200/OP.20.00298. Online ahead of print. Jinhai Huo 1 , Young-Rock Hong 1 , Kea Turner 2 3 , Vakaramoko Diaby 4 , Cheng Chen 4 , Jiang Bian 5 , Reetu Grewal 6 , Diana J Wilkie 7

PURPOSE: ASCO recommends early integration of palliative care in treating patients diagnosed with metastatic lung cancer. Our study sought to examine utilization of timely specialty palliative care (SPC) and its association with survival and cost outcomes in patients diagnosed with metastatic non-small-cell lung cancer (NSCLC). **METHODS:** The 2001-2015 SEER-Medicare data were used to determine the baseline characteristics and outcomes of 79,253 patients with metastatic NSCLC. The predictors of early SPC use were examined using logistic regression. Mean and adjusted total and SPC-related costs were calculated using generalized linear regression. We used Cox regression model to determine the survival outcomes by SPC service settings. All statistical tests were two sided. **RESULTS:** The time from cancer diagnosis to the first SPC use has reduced significantly, from 13.7 weeks in 2001 to 8.3 weeks in 2015 (P < .001). SPC use was associated with lower health care costs compared with those who had no SPC, from -\$3,180 in 2011 (P < .001) to -\$1,285 in 2015 (P = .059). Outpatient SPC use was associated with improved survival compared with patients who received SPC in other settings (hazard ratio, 0.83; 95% CI, 0.79 to 0.88; P < .001). **CONCLUSION:** Patients diagnosed with metastatic NSCLC now have more timely SPC service utilization, which was demonstrated to be a cost-saving treatment. Strategies to improve outpatient palliative care use might be associated with longer survival in patients with metastatic NSCLC.

The Value of Hope: Patients' and Physicians' Preferences for Survival in Advanced Non-Small Cell Lung Cancer Patient Prefer Adherence. 2020 Oct 30;14:2093-2104. doi: 10.2147/PPA.S248295.

eCollection 2020. Brett Hauber 1 , John R Penrod 2 , David Gebben 1 , Lina Musallam 2

PURPOSE: Immuno-oncology treatments offer patients with advanced non-small cell lung cancer (NSCLC) treatment options with greater probability of durable survival and a different toxicity profile compared with traditional chemotherapy. The objective of this study was to explore the importance of increases in the probability of long-term survival versus changes in expected (median) survival and treatment toxicities among patients with advanced NSCLC and physicians. **PATIENTS AND METHODS:** In a discrete-choice experiment, oncologists and patients diagnosed with NSCLC chose between profiles of treatments for advanced NSCLC offering different combinations of benefits

(expected, best-case, and worst-case survival) and risks. We analyzed preference data from each sample using a random-parameters logit model that controls for preference heterogeneity and the panel nature of the data. **RESULTS:** Both patients and physicians expressed a strong preference for improving the probability of best-case survival; however, patients viewed increases in the probability of long-term survival as more important than increases in expected survival, while the opposite was true for physicians. Both patients and physicians weighted survival to be more important than toxicities. **CONCLUSION:** This study identified a potentially important divergence between physician and patient perspectives on survival statistics. Physicians placed more importance on increases in expected survival than did patients with NSCLC. The importance patients placed on long-term survival reinforce previous research identifying the primacy of hope as a value among seriously ill patients. The findings underscore the importance of considering patients' priorities and in shared decision-making when choosing treatment.

CANcer BEhavioural nutrition and exercise feasibility trial (CanBenefit); phase I qualitative interview findings J Geriatr Oncol. 2020 Oct 12;S1879-4068(20)30453-7. doi:

10.1016/j.jgo.2020.09.026. Online ahead of print. Flavia Swan 1 , Hong Chen 2 , Cynthia C Forbes 3 , Miriam J Johnson 3 , Michael Lind 4

BACKGROUND: Older people with lung cancer are often frail and unfit due to their cancer and comorbidities and may tolerate cancer treatments poorly. Physical activity (PA) and a healthy diet offer quality of life benefit to people with cancer before, during, and post treatment. However, older adults are poorly represented in the clinical trials on which recommendations were made. **OBJECTIVE:** To assess the acceptability, usefulness, and practicality of delivering a tailored wellbeing (PA and nutrition) intervention for older adults with lung cancer before, during, and after cancer treatments (chemotherapy and/or immunotherapy). **METHODS:** Semi-structured interviews conducted with nine patients with lung cancer and three patients with mesothelioma, ≥ 70 years and ten informal carers, and nine Multidisciplinary Team (MDT) members. A topic guide covered the acceptability, usefulness, and practicality of a wellbeing intervention as well as specific feedback on individual components. Data were subjected to thematic analysis. **FINDINGS:** Four themes were generated: current lack of wellbeing care in clinical work; preferred "can have" dietary and "can do" PA advice; peer support as facilitating factor; and barriers to compliance including patients' psychological and physical issues as well as current cancer pathway and staffing issues. **CONCLUSION:** Older adults with lung cancer would welcome a proactive, clear and instructive, wellbeing intervention. Many barriers to compliance exist, particularly before and during cancer treatments due to the psycho-social impact of diagnosis, and the effects of cancer treatment. The intervention must be tailored to individual need and address physical limitations, psychological and social welfare in addition to PA and nutritional advice.

Dimensions of Distress in Lung Cancer Oncol Nurs Forum. 2020 Nov 1;47(6):732-738. doi:

10.1188/20.ONF.732-738. Lee Ann Johnson 1 , Ann M Schreier 1 , Melvin Swanson 1, Sheila Ridner 2

OBJECTIVES: to (a) compare the domains of distress between patients who were distressed and patients who were not distressed and (b) examine the relationship between the National Comprehensive Cancer Network Distress Thermometer and Problem List for Patients (DT-PL) and the Hospital Anxiety and Depression Scale (HADS) in individuals with advanced lung cancer. **SAMPLE & SETTING:** Individuals with advanced lung cancer receiving chemotherapy were recruited from a comprehensive cancer center in the southeastern United States. **METHODS & variables:** A cross-sectional, descriptive, exploratory design was used. Individuals with lung cancer completed the DT-PL and the HADS. Data were analyzed using descriptive statistics, t tests, and chi-square analysis. **RESULTS:** Significant differences were found between the nondistressed group and the clinically distressed group in three domains of distress. **IMPLICATIONS FOR NURSING:** Distress in individuals with advanced lung cancer goes beyond psychological stressors and includes family problems and physical problems.

[Associations between Spirituality, Mindfulness, and Psychological Symptoms among Advanced Lung Cancer Patients and Their Spousal Caregivers](#) J Pain Symptom Manage. 2020 Oct 8;S0885-

3924(20)30796-X. doi: 10.1016/j.jpainsymman.2020.10.001. Online ahead of print. Dalnim Cho 1 , Seokhun Kim 1 , Sania Durrani 1 , Zhongxing Liao 1 , Kathrin Milbury 1

CONTEXT: Metastatic lung cancer (LC) patients and their spousal caregivers are at high risk of psychological symptoms. Mindfulness may improve psychological symptoms via spiritual well-being (SW); yet, this mediation model has not been examined in a dyadic context. **OBJECTIVES:** We examined the mediating role of two dimensions of SW (meaning/peace, faith) in the mindfulness-symptoms link in stage IV LC patients and their spousal caregivers. **METHODS:** We examined the actor-partner interdependence model of mediation (APIMeM) using multivariate multilevel modeling with 78 couples. Four APIMeM analyses were conducted to examine: 1 predictor (mindfulness) × 2 mediators (meaning/peace, faith) × 2 psychological symptoms (depressive symptoms, cancer distress). We also tested four alternative models in which mindfulness mediates the associations between SW and psychological symptoms. **RESULTS:** The alternative model (SW→ Mindfulness→ Psychological symptoms) was preferred than the original model (Mindfulness→ SW→ Psychological Symptoms). For patients, meaning/peace was directly associated with their own psychological symptoms, while faith was only indirectly associated with their own psychological symptoms via mindfulness. For spouses, meaning/peace was both directly and indirectly associated with their own psychological symptoms, while faith was only directly associated with their own depressive symptoms (but not cancer distress). Moreover, spouses' faith was indirectly associated with patients' psychological symptoms through patients' mindfulness. **CONCLUSIONS:** SW are associated with patients and spouses' psychological symptoms both directly and indirectly through mindfulness. Thus, interventions that target SW, particularly meaning and peace, along with mindfulness may be beneficial to the psychological management of patients facing a terminal disease and their spousal caregivers.

[Effects of Lung Rehabilitation Therapy in Improving Respiratory Motor Ability and Alleviating Dyspnea in Patients with Lung Cancer After Lobectomy: A Clinical Study](#) Altern Ther Health Med. 2020 Oct 31;AT6400. Online ahead of print. Xi Cheng

PURPOSE: The primary aim of our study was to identify the effect of lung rehabilitation therapy on improving respiratory motor ability and alleviating dyspnea in patients with lung cancer after lobectomy. **METHODS:** The prospective study included a total of 58 patients with lung cancer who underwent lobectomy in our hospital from February 2017 to 2018. The patients were randomly divided into observation group (n = 29) and control group (n = 29). Patients in the control group were treated with routine nursing after operation, and patients in the observation group received lung rehabilitation therapy in combination with routine nursing. The pulmonary function, respiratory function and exercise ability of the patients in the two groups were compared, and fasting venous blood was taken before and after the beginning of the study. Moreover, the related serum factors were detected by enzyme-linked immunosorbent assay (Elisa). **RESULTS:** After treatment, the percentage of FEV1 and FEV1/FVC in the predicted value in the observation group was significantly different compared to that before treatment. The CAT score and exercise endurance score in the observation group showed significant difference compared to those in the control group. Compared with patients in the control group, the average hospitalization time of patients in the observation group was reduced by 2 days, and the probability of pulmonary complications decreased from 13.8% to 3.4%, with an average decrease of 10.4%. Additionally, the patients with pulmonary complications were reduced by 3 cases, and the retention time of chest tube was also remarkably reduced. CRP, IL-6 and TNF- α in serum of the observation group were significantly improved, with statistical difference. **CONCLUSION:** Lung rehabilitation therapy is an effective approach for the recovery of motor ability and respiratory function of postoperative patients. A

simple lung rehabilitation exercise training program can significantly improve the exercise tolerance of respiration for patients, alleviate dyspnea, hence improve their quality of life. In addition, routine nursing in the combination of lung rehabilitation therapy exerted greater beneficial effect in terms of reducing the inflammation and achieving improved life quality of patients.

COMPLEMENTARY & ALTERNATIVE THERAPY

[The investigation of the healing effect of active ingredients in traditional medicinal plants on lung cancer](#)

Med Oncol. 2020 Oct 15;37(11):102. doi: 10.1007/s12032-020-01428-z. Faik Gökalp 1
The healing effect of herbal active compounds on lung cancer has been recently investigated. Lung cancer is one of the leading types of cancer. The causes and prevention of lung cancer diagnosis have an important role as the inhibition of proteins in the initial treatment of the disease. The docking score was used to investigate the effect of some active compounds in traditional medicinal plants. The use of widespread medicinal plants and determination of active substances reveal the importance of docking studies in choosing the right active substance in a short time. The inhibition of essentially active compounds on lung cancer has been an important condition as the traditional medicinal plants that are rich in active substance and direct the experimental studies. In this study, the effects of the active ingredients in traditional food supplements used in many countries on the lung cancer were calculated based on the drugs used as standard. It will be hope that these active substances with high healing effects will be tested in the clinical field and turned into drugs.

[The effects of traditional Chinese medicine combined with chemotherapy on immune function and quality of life in patients with non-small cell lung cancer: A protocol for systematic review and meta-analysis](#)

Medicine (Baltimore). 2020 Nov 6;99(45):e22859. doi: 10.1097/MD.00000000000022859.
Li-Na Zhao 1 , Yin-Qing Yang 2 , Wen-Wen Wang 1 , Qian Li 1 , Hua Xiao 1
BACKGROUND: This article will evaluate the effects of traditional Chinese medicine (TCM) combined with chemotherapy on the immune function and quality of life of patients with non-small cell lung cancer (NSCLC), and evaluate the published side effects. **METHODS:** The systematic review and meta-analysis will be conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. The databases we will search include: PubMed, EMBASE, Cochrane Library, Web of Science, China National Knowledge Infrastructure, China Biomedicine, Wan fang Data, and Technology Periodical Database. The search date is from inception to June 30, 2020. There are no restrictions on the document language. The literatures included in this study are randomized controlled trials. The main results include ratio of CD3, CD4, CD8, CD4/CD8, NK cells, the level of IgA, IgG, IgM, and Karnofsky performance status score. The secondary result is to evaluate various side effects during treatment. We will use the Cochrane Collaboration tool to evaluate each study and use Review Manager software (RevMan, version 5.3) to merge and analyze the data. The 2 researchers will independently cross-screen the literature, extract data, and evaluate the quality. If there are differences, we will resolve them through discussion or consultation with a third reviewer. **RESULTS:** The results of this study will provide high-quality evidence for the effect of TCM combined with chemotherapy on the immune function and quality of life of patients with NSCLC. **CONCLUSION:** This article will comprehensively evaluate the effects of TCM combined with chemotherapy on the immune function and quality of life of patients with NSCLC, and provide evidence-based evidence for clinical practice.

[Synthesis and evaluation of new compounds bearing 3-\(4-aminopiperidin-1-yl\)methyl magnolol scaffold as anticancer agents for the treatment of non-small cell lung cancer via targeting](#)

[autophagy](#) Eur J Med Chem. 2020 Oct 10;112922. doi: 10.1016/j.ejmech.2020.112922. Online ahead of print. Min Zhao 1 , Yun-Hua Zheng 1 , Qi-Yuan Zhao 1 , et al.

Magnolol and honokiol are the two major active ingredients with similar structure and anticancer activity from traditional Chinese medicine *Magnolia officinalis*, and honokiol is now in a phase I clinical trial (CTR20170822) for advanced non-small cell lung cancer (NSCLC). In search of potent lead compounds with better activity, our previous study has demonstrated that magnolol derivative C2, 3-(4-aminopiperidin-1-yl)methyl magnolol, has better activity than honokiol. Here, based on the core of 3-(4-aminopiperidin-1-yl)methyl magnolol, we synthesized fifty-one magnolol derivatives. Among them, compound 30 exhibited the most potent antiproliferative activities on H460, HCC827, H1975 cell lines with the IC₅₀ values of 0.63-0.93 μM, which were approximately 10- and 100-fold more potent than those of C2 and magnolol, respectively. Besides, oral administration of 30 and C2 on an H460 xenograft model also demonstrated that 30 has better activity than C2. Mechanism study revealed that 30 induced G₀/G₁ phase cell cycle arrest, apoptosis and autophagy in cancer cells. Moreover, blocking autophagy by the autophagic inhibitor enhanced the anticancer activity of 30 *in vitro* and *in vivo*, suggesting autophagy played a cytoprotective role on 30-induced cancer cell death. Taken together, our study implied that compound 30 combined with autophagic inhibitor could be another choice for NSCLC treatment in further investigation.

[Rose \(*Rosa gallica*\) Petal Extract Suppress Proliferation, Migration, and Invasion of Human Lung Adenocarcinoma A549 Cells through via the EGFR Signaling Pathway](#) *Molecules*. 2020 Nov 4;25(21):E5119. doi: 10.3390/molecules25215119. Won-Chul Lim ¹, Hyo-Kyung Choi ¹, Kyung-Tack Kim ¹, Tae-Gyu Lim ^{1 2}

We sought to investigate the effect of rose petal extract (RPE) on the proliferation, migration, and invasion of cancer cells. RPE significantly inhibited the growth of lung and colorectal cancer cell lines, with rapid suppression of A549 lung cancer cells at low concentrations. These effects occurred concomitantly with downregulation of the cell proliferation mediators PCNA, cyclin D1, and c-myc. In addition, RPE suppressed the migration and invasion of A549 cells by inhibiting the expression and activity of matrix metalloproteinase-2 and matrix metalloproteinase-9 (MMP-2 and -9). We hypothesize that the suppressive activity of RPE against lung cancer cell proliferation and early metastasis occurs via the EGFR-MAPK and mTOR-Akt signaling pathways. These early results highlight the significant potency of RPE, particularly for lung cancer cells, and warrant further investigation.

MISCELLANEOUS WORKS

[Associations of aspirin, statins, and metformin with lung cancer risk and related mortality: time-dependent analysis of population-based nationally representative data](#) *J Thorac Oncol*. 2020 Sep 12;S1556-0864(20)30712-7. doi: 10.1016/j.jtho.2020.08.021. Online ahead of print. Jihun Kang ¹, Su-Min Jeong ², Dong Wook Shin ³, Mihee Cho ⁴, Jong Ho Cho ⁵, Jehun Kim ⁶

Affiliations

OBJECTIVES: The aim of this study was to investigate the associations of aspirin, metformin, and statins with lung cancer risk and mortality using population-based nationwide cohort data. **METHODS:** This study included a total of 732,199 participants who had undergone a national health check-up in 2002-2003. Lung cancer incidence and mortality were identified using a registered lung cancer diagnosis code (ICD-10 code C34) and the Korean National Death Registry. The study participants were followed from January 1, 2004 to 31 December 2013. Medication exposure was defined by cumulative duration of use and cumulative defined daily dose (cDDD) per 2-year interval. To avoid immortal time bias, drug exposure was inserted as a time-dependent variable in Cox analysis, which evaluated the associations of these medications with lung cancer. **RESULTS:** Metformin use had protective association with lung cancer incidence (P's-for-trend = 0.008) and mortality (P's-for-trend <0.001) in a dose-response fashion, and these associations were prominent among participants with cDDD of metformin ≥ 547.5, compared

with non-diabetic patients. Lung cancer mortality was dose-dependently reduced with the use of aspirin ([P's-for-trends 0.046] and statin [P's-for-trends <0.001]). Combined use of aspirin, statins and metformin showed more prominent protective associations with lung cancer risk and mortality. **CONCLUSION:** Use of aspirin, metformin, and statins had independent protective associations with lung cancer mortality, and metformin had inverse association with lung cancer risk. Further studies are necessary to develop clinically applicable anticancer strategies of these drugs for the reduction of lung cancer and related mortality.

[Comprehensive review of implications of COVID-19 on clinical outcomes of cancer patients and management of solid tumors during the pandemic](#) Cancer Med. 2020 Oct 20. doi: 10.1002/cam4.3534.

Online ahead of print. Ankit Madan ¹, Joshua Siglin ², Alem Khan ³

Coronavirus disease-2019 (COVID-19) has emerged as a novel infection which has spread rapidly across the globe and currently presents a grave threat to the health of vulnerable patient populations like those with malignancy, elderly, and immunocompromised. Healthcare systems across the world are grappling with the detrimental impact of this pandemic while learning about this novel disease and concurrently developing vaccines, strategies to mitigate its spread, and treat those infected. Cancer patients today face with a unique situation. They are susceptible to severe clinically adverse events and higher mortality from COVID-19 infection as well as morbidity and mortality from their underlying malignancy. Conclusion: Our review suggests increased risk of mortality and serious clinical events from COVID-19 infection in cancer patients. However, risk of adverse events does not seem to be increased by cancer therapies. True impact of COVID-19 on cancer patients will unravel over the next few months. We have also reviewed clinical features of COVID-19, recent recommendations from various medical, surgical, and radiation oncology societies for major solid tumor types like lung, breast, colorectal, and prostate cancer during the duration of this pandemic.

[Active Treatment Improves Overall Survival in Extremely Older Non-Small Cell Lung Cancer Patients: A Multicenter Retrospective Cohort Study](#) Cancer Res Treat. 2020 Oct 5. doi:

10.4143/crt.2020.894. Online ahead of print. Su Yeon Lee ¹, Yoon-Ki Hong ², Wonjun Ji ¹, Jae Cheol Lee ³, Chang Min Choi ^{1,3}, KALC; KCCR

PURPOSE: As the aging of society progresses, the proportion of extremely older lung cancer patients has also increased; However, studies of these patients with non-small cell lung cancer are limited. Therefore, we investigated the initial treatment modalities and survival outcomes for patients aged 80 years or over. **MATERIAL AND METHODS:** We included a multicenter retrospective cohort from the Korean Association for Lung Cancer Registry, which surveys 10% of the newly diagnosed lung cancer patients across 52 hospitals in Korea. We analyzed and compared the 2014-2016 data of the non-small cell lung cancer patients aged ≥ 80 years and those aged < 80 years. **RESULTS:** Of the 6,576 patients reviewed, 780 patients were aged ≥ 80 years, and 5,796 patients were aged < 80 years. In the patients aged ≥ 80 years, surgery and radiation therapy resulted in longer patient survival among those with a resectable tumor (stage I-II) than the best supportive care (median survival, not reached [surgery] vs. 32.2 months [radiation therapy] vs. 11.43 months [best supportive care]). The duration of survival in patients with advanced-stage (IV) lung cancers was higher after chemotherapy than after the best supportive care (median survival, 8.63 months vs. 2.5 months). Patients with stage IV adenocarcinoma who received targeted therapy had better survival than those who did not (median survival, 9.0 months vs. 4.3 months). **CONCLUSION:** Even in extremely older patients, active treatments, such as surgery, radiation therapy, and chemotherapy, can result in better survival outcomes than the best supportive care.

[Fears and Perception of the Impact of COVID-19 on Patients With Lung Cancer: A Mono-Institutional Survey](#) Front Oncol. 2020 Oct 14;10:584612. doi: 10.3389/fonc.2020.584612. eCollection

2020. Chiara Catania¹, Gianluca Spitaleri¹, Ester Del Signore¹, Ilaria Attili¹, Davide Radice², Valeria Stati¹, Letizia Gianoncelli¹, Stefania Morganti^{3,4}, Filippo de Marinis¹

In February 2020, Italy became one of the first countries to be plagued by the SARS-CoV-2 pandemic, COVID-19. In March 2020, the Italian government decreed a lockdown for the whole country, which overturned communication systems, hospital organization, and access to patients and their relatives and carers. This issue had a particular regard for cancer patients. Our Thoracic Oncology Division therefore reorganized patient access in order to reduce the risk of contagion and, at the same time, encourage the continuation of treatment. Our staff contacted all patients to inform them of any changes in treatment planning, check that they were taking safety measures, and ascertain their feelings and whether they had any COVID-19 symptoms. To better understand patients' fears and expectations of during the pandemic period, we created a nine-question interview, administered from April to May 2020 to 156 patients with lung cancer. Patients were classified by age, sex, comorbidity, disease stage, prior treatment, and treatment type. The survey showed that during the pandemic period some patients experienced fear of COVID-19, in particular: women (55% vs. 33%), patients with comorbidities (24% vs. 9%), and patients who had already received prior insult (radiotherapy or surgery) on the lung (30% vs. 11%). In addition, the patients who received oral treatment at home or for whom intravenous treatment was delayed, experienced a sense of relief (90% and 72% respectively). However, only 21% of the patients were more afraid of COVID-19 than of their cancer, in particular patients with long-term (> 12 months) vs. short-term cancer diagnosis (28% vs. 12.5%, respectively). Furthermore, the quarantine period or even just the lockdown period alone, worsened the quality of life of some patients (40%), especially those in oral treatment (47%). Our data demonstrate how lung cancer patients are more afraid of their disease than of a world pandemic. Also this interview indirectly highlights the clinician's major guiding principle in correctly and appropriately managing not just the patient's expectations of their illness and its treatment, but also and especially of the patient's fears.

[Genetic Determinants of Lung Cancer Prognosis in Never Smokers: A Pooled Analysis in the International Lung Cancer Consortium](#) Cancer Epidemiol Biomarkers Prev. 2020 Oct;29(10):1983-1992. doi: 10.1158/1055-9965.EPI-20-0248. Epub 2020 Jul 22. Yonathan Brhane¹, Ping Yang², David C Christiani³, et al.

BACKGROUND: Lung cancer remains the leading cause of cancer death worldwide, with 15% to 20% occurring in never smokers. To assess genetic determinants for prognosis among never smokers, we conducted a genome-wide investigation in the International Lung Cancer Consortium (ILCCO).

METHODS: Genomic and clinical data from 1,569 never-smoking patients with lung cancer of European ancestry from 10 ILCCO studies were included. HRs and 95% confidence intervals of overall survival were estimated. We assessed whether the associations were mediated through mRNA expression-based 1,553 normal lung tissues from the lung expression quantitative trait loci (eQTL) dataset and Genotype-Tissue Expression (GTEx). For cross-ethnicity generalization, we assessed the associations in a Japanese study (N = 887). **RESULTS:** One locus at 13q22.2 was associated with lung adenocarcinoma survival at genome-wide level, with carriers of rs12875562-T allele exhibiting poor prognosis [HR = 1.71 (1.41-2.07), P = 3.60 × 10⁻⁸], and altered mRNA expression of LMO7DN in lung tissue (GTEx, P = 9.40 × 10⁻⁷; Lung eQTL dataset, P = 0.003). Furthermore, 2 of 11 independent loci that reached the suggestive significance level (P < 10⁻⁶) were significant eQTL affecting mRNA expression of nearby genes in lung tissues, including CAPZB at 1p36.13 and UBAC1 at 9q34.3. One locus encoding NWD2/KIAA1239 at 4p14 showed associations in both European [HR = 0.50 (0.38-0.66), P = 6.92 × 10⁻⁷] and Japanese populations [HR = 0.79 (0.67-0.94), P = 0.007]. **CONCLUSIONS:** Based on the largest genomic investigation on the lung cancer prognosis of never smokers to date, we observed that lung cancer prognosis is affected by inherited genetic variants. **IMPACT:** We identified one locus near LMO7DN at

genome-wide level and several potential prognostic genes with cis-effect on mRNA expression. Further functional genomics work is required to understand their role in tumor progression.

Do Patients Regret Having Received Systemic Treatment for Advanced Non-Small Cell Lung

Cancer: A Prospective Evaluation Oncologist. 2020 Oct 23. doi: 10.1002/onco.13571. Online ahead of print. Patricia J Hollen¹, Richard J Gralla², Ryan D Gentzler¹, et al.

BACKGROUND: Thousands of patients annually receive treatment for advanced NSCLC, but little is known about their views on the decision to receive that treatment, or regret. This trial prospectively evaluated the incidence of regret and whether baseline characteristics, patient decision-making parameters, or clinical progress early in the treatment course predicts regret. **MATERIALS AND METHODS:** Patients receiving systemic treatment for advanced NSCLC completed every 3-week PRO assessment using the electronic LCSS, including the 3-Item Global Index ("3-IGI," assessing overall distress, activities, and QL). A prespecified secondary aim was to determine the frequency of regret evaluated at three months after starting treatment. Patients were randomized to usual care, or enhanced care (which included use of the DecisionKEYS decision aid). **RESULTS:** Of 164 patients entered, 160 received treatment and 142 were evaluable for regret. In total, 11.5% of patients, and 9% of their supporters expressed regret. Baseline characteristics did not predict regret; regret was rarely expressed by those who had a less than 20% decline or improvement in the 3-IGI PRO score after two treatment cycles. In contrast, when asked if they would make the same decision again, only 1% not having a 20% 3-IGI decline expressed regret, versus 14% with a 3-IGI decline ($p=0.01$). **CONCLUSION:** The majority of patients having regret were identified early using the PRO 3-IGI of the eLCSS-QL measure. Identifying patients at risk for regret allows for interventions, including frank discussions of progress and goals early in the treatment course, which could address regret in patients and their supporters. **IMPLICATIONS FOR PRACTICE:** This report documents prospectively for the first time the incidence of treatment-related regret in patients with advanced lung cancer, and outlines that risk of regret is associated with patient-determined worsening health status early in the course of treatment. Identifying patients at risk for regret early in treatment (before the 3rd cycle of treatment) appears to be crucial. Counseling at that time should include a discussion of consideration of treatment change and the reason for this change.

Modeling the Impact of Delaying the Diagnosis of Non-Small Cell Lung Cancer during COVID-19

Ann Thorac Surg. 2020 Oct 19;S0003-4975(20)31698-2. doi: 10.1016/j.athoracsur.2020.08.025. Online Maren E Shipe¹, Diane N Haddad¹, Stephen A Deppen², Benjamin D Kozower³, Eric L Grogan⁴

BACKGROUND: The novel coronavirus (COVID-19) pandemic has led surgical societies to recommend delaying diagnosis and treatment of suspected lung cancer in lesions <2 cm. Delaying diagnosis can lead to disease progression, but the impact of this delay on mortality is unknown. The COVID-19 infection rate at which immediate operative risk exceeds benefit is unknown. We sought to model immediate versus delayed surgical resection in a suspicious lung nodule <2 cm. **METHODS:** A decision analysis model was developed, and sensitivity analyses performed. The base case was a 65-year-old male smoker with COPD presenting for surgical biopsy of 1.5-2.0 cm lung nodule highly suspicious for cancer during the COVID-19 pandemic. We compared immediate surgical resection to delayed resection after three months. The likelihood of key outcomes was derived from the literature where available. The outcome was 5-year overall survival. **RESULTS:** Immediate surgical resection resulted in a similar but slightly higher 5-year overall survival when compared to delayed resection (0.77 versus 0.74), due to the risk of disease progression. However, if the probability of acquired COVID-19 infection is greater than 13%, delayed resection is favorable (0.74 vs 0.73). **CONCLUSIONS:** Immediate surgical biopsy of lung nodules suspicious for cancer in hospitals with low COVID-19 prevalence likely results in improved 5-year survival. However, as the risk of perioperative COVID-19 infection increases above

13%, a delayed approach has similar or improved survival. This balance should be frequently re-examined at each healthcare facility throughout the curve of the pandemic.

Smoking-Related Social Interactions as Experienced by Persons Who Smoked Long-term Clin

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PURPOSE/AIMS: Smoking-related stigma is manifested in the everyday social interactions of persons who smoke and can result in low self-esteem, diminished self-efficacy, and resistance to smoking cessation. The purpose of this study was to describe smoking-related social interactions as experienced by persons with a history of long-term smoking. **DESIGN:** This study used a qualitative descriptive approach. **METHODS:** This study is part of a larger study designed to identify factors that influence lung cancer screening participation. Data were drawn from 39 qualitative interviews with persons from the parent study. All descriptions about smoking-related social interactions found in the narratives were extracted, coded, categorized, and summarized with content analytic techniques. **RESULTS:** Seven different types of social interactions were identified: (a) being looked down on for smoking, (b) being humiliated for smoking in public, (c) being banished while smoking, (d) being blamed for one's health problems, (e) not "really" being blamed for smoking, (f) being told "just quit," and (g) being worried about hurting others. **CONCLUSIONS:** Clinical nurse specialists should promote antismoking campaigns that are not stigmatizing, discuss health risks of smoking in a respectful manner, provide evidence-