



Caring Ambassadors Lung Cancer Program Literature Review, July 2020

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES	1-2
SCREENING, DIAGNOSIS AND STAGING	2-6
CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES	
NSCLC SURGERY	6-8
NSCLC CHEMOTHERAPY	8-13
NSCLC RADIOTHERAPY	13-16
SMALL CELL LUNG CANCER (SCLC)	16-17
PALLIATIVE AND SUPPORTIVE CARE	17-21
COMPLEMENTARY AND ALTERNATIVE THERAPY	
MISCELLANEOUS WORKS	21-26

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Sirtuin 7 promotes non-small cell lung cancer progression by facilitating G1/S phase and epithelial-mesenchymal transition and activating AKT and ERK1/2 signaling](#) Oncol Rep. 2020 Sep;44(3):959-972. doi: 10.3892/or.2020.7672. Epub 2020 Jul 7. Yingying Zhao 1 , Xia Ye 1 , et al. Increasing evidence has indicated the roles of sirtuin 7 (SIRT7) in numerous human cancers. However, the effects and the clinical significance of SIRT7 in human lung cancer is largely unknown. The present research demonstrated that SIRT7 was increased in human lung cancer tumor tissues. SIRT7 upregulation was associated with clinicopathological characteristics of lung cancer malignancy including positive lymph node metastasis, high pathologic stage and large tumor size. SIRT7 was also upregulated in human non-small cell lung cancer (NSCLC) cell lines. Furthermore SIRT7-overexpressed A549 (A549-SIRT7) and SIRT7-knocked down H292 (H292-shSIRT7) human NSCLC cell lines were established. Using these NSCLC cells and xenograft mouse models, it was revealed that SIRT7 overexpression markedly promoted growth and G1 to S cell cycle phase transition as well as migration, invasion and distant lung metastasis in A549 NSCLC cells, whereas SIRT7 knockdown suppressed these processes in H292 NSCLC cells. Mechanistically, in A549 NSCLC cells, SIRT7 overexpression significantly activated not only protein kinase B (AKT) signaling but also extracellular signal-regulated kinase 1/2 (ERK1/2) signaling. SIRT7 overexpression also significantly downregulated cyclin-dependent kinase (CDK) inhibitors including p21 and p27 as well as upregulated cyclins including cyclin D1 and cyclin E1, and CDKs including CDK2 and CDK4. Notably, the epithelial-mesenchymal transition (EMT) process of A549 NSCLC cells was facilitated by SIRT7 overexpression, as evidenced by E-cadherin epithelial marker downregulation and mesenchymal markers (N-cadherin, vimentin, Snail and Slug) upregulation. In addition, SIRT7 knockdown in H292 NSCLC cells exhibited the opposite regulatory effects. Moreover, inhibition of AKT signaling abated the promoting effects of SIRT7 in NSCLC cell proliferation and EMT progression. The present data indicated that SIRT7 accelerated human NSCLC cell growth and metastasis possibly by promotion of G1 to S-phase transition and EMT through modulation of the expression of G1-phase checkpoint molecules and EMT markers as well as activation of AKT and ERK1/2 signaling. SIRT7 could be an innovative potential target for human NSCLC therapy.

[Surgical Management of Non-Small Cell Lung Cancer Invading the Fissure: Less Is More?](#) Ann Thorac Surg. 2020 Jul 9;S0003-4975(20)31114-0. doi: 10.1016/j.athoracsur.2020.05.082. Online ahead of print. Shane P Smith 1 , Adam J Bograd 2 , Gal Levy 2 , Shu-Ching Chang 3 , Alex S Farivar 2 , Ralph W Aye 2 , Brian E Louie 2 , Eric Vallières 2

BACKGROUND: When encountering a resectable lung cancer that invades across the fissure into an adjacent lobe, options include a bilobectomy on the right or a pneumonectomy on the left versus a parenchymal sparing resection combined with a lobectomy. Though parenchymal sparing combinations are technically possible, the available literature reporting on the related oncological outcomes is limited. We sought to examine the influence of resection extent on overall survival and recurrence patterns in this scenario. **METHODS:** A single center retrospective chart review from 2006-2018 was performed on all preoperative computed tomography and operative reports of resections greater than a lobectomy. Patients were grouped into maximal resection: bilobectomy or pneumonectomy, and parenchymal sparing resection: lobectomy with en bloc segment or non-anatomical wedge. Overall survival and cumulative incidence of recurrence were calculated. **RESULTS:** The size of our cohort was 54 patients; 19 maximal and 35 parenchymal sparing resections. All resections were reported as complete (R0). The parenchymal sparing group had lower odds of immediate surgical morbidity [OR=0.13; 95% CI= (0.02, 0.74); p=0.02]. Parenchymal sparing was not associated with an increased cumulative incidence of recurrence (p = 0.98). Post-resection estimated overall survival between the two cohorts was not significantly different (p = 0.30). **CONCLUSIONS:** When technically feasible, a parenchymal sparing resection is a good option for the resection of tumors that invade across the fissure. R0 parenchymal sparing resections do not appear to compromise the oncologic outcomes of either overall survival or cumulative incidence of recurrence and also seem to carry be less morbidity.

SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

[Evaluating Knowledge, Attitudes, and Beliefs About Lung Cancer Screening Using Crowdsourcing](#)

Chest. 2020 Jul;158(1):386-392. doi: 10.1016/j.chest.2019.12.048. Epub 2020 Feb 7.

John Monu 1 , Matthew Triplette 2 , Douglas E Wood 1 , Erika M Wolff 1 , Danielle C Lavalley 1 , David R Flum 1 , Farhood Farjah 3

BACKGROUND: Lung cancer screening, despite its proven mortality benefit, remains vastly underutilized. Previous studies examined knowledge, attitudes, and beliefs to better understand the reasons underlying the low screening rates. These investigations may have limited generalizability because of traditional participant recruitment strategies and examining only subpopulations eligible for screening. The current study used crowdsourcing to recruit a broader population to assess these factors in a potentially more general population. **METHODS:** A 31-item survey was developed to assess knowledge, attitudes, and beliefs regarding screening among individuals considered high risk for lung cancer by the United States Preventive Services Task Force. Amazon's crowdsourcing platform (Mechanical Turk) was used to recruit subjects. **RESULTS:** Among the 240 respondents who qualified for the study, 106 (44%) reported knowledge of a screening test for lung cancer. However, only 36 (35%) correctly identified low-dose CT scanning as the appropriate test. A total of 222 respondents (93%) reported believing that early detection of lung cancer has the potential to save lives, and 165 (69%) were willing to undergo lung cancer screening if it was recommended by their physician. Multivariable regression analysis found that knowledge of lung cancer screening, smoking status, chronic pulmonary disease, and belief in the efficacy of early detection of lung cancer were associated with willingness to screen. **CONCLUSIONS:** Although a minority of individuals at high risk for lung cancer are aware of screening, the majority believe that early detection saves lives and would pursue screening if recommended by their primary care physician. Health

systems may increase screening rates by improving patient and physician awareness of lung cancer screening.

[Impact of invasive nodal staging on regional and distant recurrence rates after SBRT for inoperable stage I NSCLC](#) Radiother Oncol. 2020 Jul 3;150:206-210. doi:

10.1016/j.radonc.2020.06.043. Online ahead of print. William R Kennedy 1, Pamela P Samson 1, Prashant Gabani 1, John Nikitas 1, Jeffrey D Bradley 2, Michael C Roach 3, Clifford G Robinson 4
PURPOSE/OBJECTIVES: Before definitive stereotactic body radiation therapy (SBRT) for presumably node-negative, early-stage NSCLC, many patients are staged with PET/CT alone. In patients undergoing PET/CT prior to SBRT, the role of invasive nodal staging (INS) with endobronchial ultrasound (EBUS) or mediastinoscopy is uncertain. We sought to characterize the impact of nodal staging modality on outcomes. **MATERIALS/METHODS:** Patients receiving definitive SBRT for T1-2N0 NSCLC deemed node-negative by either PET/CT plus INS (EBUS or mediastinoscopy) or PET/CT alone were identified. Patients with initially equivocal or positive nodes on PET/CT were excluded from this analysis. All patients received 3-5 fraction SBRT according to institutional guidelines. Control was assessed by at least one follow-up CT in all patients. Multivariable logistic regression (MVA) was performed to identify variables independently associated with use of INS. **RESULTS:** We identified 651 eligible patients at our institution from 2005-2016. INS was performed in 15.2% of patients (n = 99) with EBUS (n = 78) or mediastinoscopy (n = 21). Median follow-up was 19.4 months (0.2-135.1). Median survival was 28.5 months (0.6-140). Factors predictive of increased likelihood of INS after negative PET/CT on MVA were age (OR for decreasing age 1.033; 95% CI 1.058-1.010), Caucasian race (OR vs. non-white 1.852; 1.044-3.289), male sex (1.629; 1.031-2.575), central location (1.978; 1.218-3.211) and squamous histology (2.564; 1.243-5.287). Nodal and/or distant control at 2 years was similar between PET/CT alone (78%, 95% CI 74-82%) and INS + PET/CT (75%, 95% CI 65-85%) (p = 0.877) as well as on MVA. Overall survival did not differ based on staging modality. **CONCLUSIONS:** In patients with early-stage NSCLC deemed node-negative by PET/CT, addition of INS did not appreciably alter patterns of failure or survival after definitive SBRT. This study does not question the established value of INS for equivocal or suspicious nodes.

[Private Payer and Medicare Coverage for Circulating Tumor DNA Testing: A Historical Analysis of Coverage Policies From 2015 to 2019](#)

J Natl Compr Canc Netw. 2020 Jul;18(7):866-872. doi: 10.6004/jnccn.2020.7542. Michael P Douglas 1, Stacy W Gray 2 3, Kathryn A Phillips 1 4 5

BACKGROUND: Clinical adoption of the sequencing of circulating tumor DNA (ctDNA) for cancer has rapidly increased in recent years. This sequencing is used to select targeted therapy and monitor nonresponding or progressive tumors to identify mechanisms of therapeutic resistance. Our study objective was to review available coverage policies for cancer ctDNA-based testing panels to examine trends from 2015 to 2019. **METHODS:** We analyzed publicly available private payer policies and Medicare national coverage determinations and local coverage determinations (LCDs) for ctDNA-based panel tests for cancer. We coded variables for each year representing policy existence, covered clinical scenario, and specific ctDNA test covered. Descriptive analyses were performed. **RESULTS:** We found that 38% of private payer coverage policies provided coverage of ctDNA-based panel testing as of July 2019. Most private payer policy coverage was highly specific: 87% for non-small cell lung cancer, 47% for EGFR gene testing, and 79% for specific brand-name tests. There were 8 final, 2 draft, and 2 future effective final LCDs (February 3 and March 15, 2020) that covered non-FDA-approved ctDNA-based tests. The draft and future effective LCDs were the first policies to cover pan-cancer use.

CONCLUSIONS: Coverage of ctDNA-based panel testing for cancer indications increased from 2015 to 2019. The trend in private payer and Medicare coverage is an increasing number of coverage policies,

number of positive policies, and scope of coverage. We found that Medicare coverage policies are evolving to pan-cancer uses, signifying a significant shift in coverage frameworks. Given that genomic medicine is rapidly changing, payers and policymakers (eg, guideline developers) will need to continue to evolve policies to keep pace with emerging science and standards in clinical care.

[Atypical skin manifestations during immune checkpoint blockage in COVID19-infected lung cancer patients](#) J Thorac Oncol. 2020 Jul 9;S1556-0864(20)30543-8. doi: 10.1016/j.jtho.2020.06.019. Online ahead of print.

A new coronavirus, named SARS-CoV-2 by the World Health Organization (WHO), has rapidly spread around the world since its first reported case in late December of 2019 from Wuhan, China. As of mid-April 2020, this virus has affected more than 180 countries and territories, infecting more than 1,650,000 individuals and causing over 100,000 deaths. With ≈ 20 million new cases per year globally, cancer affects a significant portion of the population. Individuals affected by cancer are more susceptible to infections due to coexisting chronic diseases (cardiovascular, pulmonary and diabetes), overall poor health status, and systemic immunosuppressive states caused by both cancer and anticancer treatments. As a consequence, patients with malignancies, and especially with lung cancer who develop COVID19 experience more difficult outcomes. A recent multicenter study developed by the Hubei Anti-Cancer Association also documented that lung cancer patients had an increased risk of death, ICU requirement, risk of presenting severe or critical symptoms, and use of invasive mechanical ventilation. Here we present two representative cases of patients with lung cancer and COVID19 without respiratory compromise and with atypical and severe skin manifestations, findings that could be influenced by the chronic use of anti-PD1 antibodies.

[Management of Lung Nodules and Lung Cancer Screening During the COVID-19 Pandemic: CHEST Expert Panel Report](#) J Am Coll Radiol. 2020 Jul;17(7):845-854. doi:

10.1016/j.jacr.2020.04.024. Epub 2020 Apr 23. Peter J Mazzone ¹, Michael K Gould ², Douglas A Arenberg ³, et al.

BACKGROUND: The risks from potential exposure to coronavirus disease 2019 (COVID-19), and resource reallocation that has occurred to combat the pandemic, have altered the balance of benefits and harms that informed current (pre-COVID-19) guideline recommendations for lung cancer screening and lung nodule evaluation. Consensus statements were developed to guide clinicians managing lung cancer screening programs and patients with lung nodules during the COVID-19 pandemic. **METHODS:** An expert panel of 24 members, including pulmonologists (n = 17), thoracic radiologists (n = 5), and thoracic surgeons (n = 2), was formed. The panel was provided with an overview of current evidence, summarized by recent guidelines related to lung cancer screening and lung nodule evaluation. The panel was convened by video teleconference to discuss and then vote on statements related to 12 common clinical scenarios. A predefined threshold of 70% of panel members voting agree or strongly agree was used to determine if there was a consensus for each statement. Items that may influence decisions were listed as notes to be considered for each scenario. **RESULTS:** Twelve statements related to baseline and annual lung cancer screening (n = 2), surveillance of a previously detected lung nodule (n = 5), evaluation of intermediate and high-risk lung nodules (n = 4), and management of clinical stage I non-small-cell lung cancer (n = 1) were developed and modified. All 12 statements were confirmed as consensus statements according to the voting results. The consensus statements provide guidance about situations in which it was believed to be appropriate to delay screening, defer surveillance imaging of lung nodules, and minimize nonurgent interventions during the evaluation of lung nodules and stage I non-small-cell lung cancer.

CONCLUSIONS: There was consensus that during the COVID-19 pandemic, it is appropriate to defer enrollment in lung cancer screening and modify the evaluation of lung nodules due to the added risks

from potential exposure and the need for resource reallocation. There are multiple local, regional, and patient-related factors that should be considered when applying these statements to individual patient care.

[Quantitative analysis of endobronchial ultrasound elastography in computed tomography-negative mediastinal and hilar lymph nodes](#) Thorac Cancer. 2020 Jul 21. doi: 10.1111/1759-7714.13579. Online ahead of print. Keigo Uchimura 1 , Kei Yamasaki 1 , et al.

BACKGROUND: Endobronchial ultrasound (EBUS) elastography assists in the differentiation of benign and malignant lymph nodes (LNs) during transbronchial needle aspiration (TBNA). However, previous studies have not compared B-mode sonographic images (BSIs) and EBUS elastography images (EEl) with final pathological diagnoses in radiologically normal-sized (computed tomography [CT]-negative) LNs. **METHODS:** Consecutive patients with CT-negative LNs, who received EBUS-TBNA, were retrospectively reviewed. Images of BSIs and EEl of each LN were stored and independently evaluated. EEl were assessed by calculating the stiffness area ratio (SAR, blue/overall areas). The receiver operating characteristic curve was used to calculate the cutoff value for the SAR. Diagnostic test parameters were evaluated for each EBUS finding. **RESULTS:** A total of 132 patients (149 LNs) were enrolled, and the median SAR of malignant LNs was significantly higher than that of benign LNs (0.58 vs. 0.32, $P < 0.001$). At the SAR cutoff of 0.41, the sensitivity, specificity, positive predictive value, negative predictive value (NPV), and diagnostic accuracy rate (DAR) of elastography were 88.2%, 80.2%, 78.9%, 89.0%, and 83.9%, respectively. The logistic regression analysis showed that elastography was the strongest predictor of malignancy (odds ratio, 18.5; 95% confidence interval [CI]: 6.48-52.6; $P < 0.001$). The highest NPV (96.6%) was achieved with a combination of BSIs and EEl. **CONCLUSIONS:** EBUS elastography predicted malignant LNs with a high DAR and NPV in CT-negative LNs. The NPV was highest when EEl were combined with BSIs. Therefore, the combined evaluation of CT-negative LNs using EEl and BSIs may help bronchoscopists perform EBUS-TBNA more efficiently. **KEY POINTS: SIGNIFICANT FINDINGS OF THE STUDY:** Endobronchial ultrasound elastography accurately predicted malignancy with a high diagnostic accuracy rate and negative predictive value in radiologically normal-sized lymph nodes. The additional use of B-mode sonographic features resulted in a higher negative predictive value. **WHAT THIS STUDY ADDS:** Endobronchial ultrasound elastography can guide the accurate collection of specimens with transbronchial needle aspiration, even in radiologically normal-sized lymph nodes. It can also readily distinguish benign and malignant lymph nodes, thus avoiding unnecessary punctures.

[Conventional Computed Tomographic Calcium Scoring vs full chest CTCS for lung cancer screening: a cost-effectiveness analysis](#) BMC Pulm Med. 2020 Jul 6;20(1):187. doi: 10.1186/s12890-020-01221-8. Boxiang Jiang 1 , Philip A Linden 1 , et al.

Amit Gupta 2 , Craig Jarrett 1 , Stephanie G Worrell 1 , Vanessa P Ho 3 , Yaron Perry 1 , Christopher **BACKGROUND:** Conventional CTCS images the mid/lower chest for coronary artery disease (CAD). Because many CAD patients are also at risk for lung malignancy, CTCS often discovers incidental pulmonary nodules (IPN). CTCS excludes the upper chest, where malignancy is common. Full-chest CTCS (FCT) may be a cost-effective screening tool for IPN. **METHODS:** A decision tree was created to compare a FCT to CTCS in a hypothetical patient cohort with suspected CAD. (Figure) The design compares the effects of missed cancers on CTCS with the cost of working up non-malignant nodules on FCT. The model was informed by results of the National Lung Screening Trial and literature review, including the rate of malignancy among patients receiving CTCS and the rate of malignancy in upper vs lower portions of the lung. The analysis outcomes are Quality-Adjusted Life Year (QALY) and incremental cost-effectiveness ratio (ICER), which is generally considered beneficial when $< \$50,000/\text{QALY}$. **RESULTS:** Literature review suggests that rate of IPNs in the upper portion of the lung varied from 47 to 76%. Our model assumed that IPNs occur in upper and lower portions of the lung

with equal frequency. The model also assumes an equal malignancy potential in upper lung IPNs despite data that malignancy occurs 61-66% in upper lung fields. In the base case analysis, a FCT will lead to an increase of 0.03 QALYs comparing to conventional CTCS (14.54 vs 14.51 QALY, respectively), which translates into an QALY increase of 16 days. The associated incremental cost for FCT is \$278 (\$1027 vs \$748, FCT vs CTCS respectively). The incremental cost-effectiveness ratio (ICER) is \$10,289/QALY, suggesting significant benefit. Sensitivity analysis shows this benefit increases proportional to the rate of malignancy in upper lung fields. **CONCLUSION:** Conventional CTCS may be a missed opportunity to screen for upper lung field cancers in high risk patients. The ICER of FCT is better than screening for breast cancer screening (mammograms \$80 k/QALY) and colon cancer (colonoscopy \$6 k/QALY). Prospective studies are appropriate to define protocols for FCT.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[Health-Related Quality of Life after Lobectomy for Lung Cancer: Conceptual Framework and Measurement](#) Ann Thorac Surg. 2020 Jul 21;S0003-4975(20)31112-7. doi:

10.1016/j.athoracsur.2020.05.080. Online ahead of print. Lisa M Brown 1 , Melissa M Gosdin 2 , David T Cooke 3 , Ester Carolina Apeso-Varano 4 , Anna L Kratz 5

BACKGROUND: Lung cancer surgery has a significant impact on health-related quality of life (HRQOL). In prior studies of HRQOL after lung cancer surgery, HRQOL domains of interest were selected by the researchers. To increase the patient-centeredness of these studies, we conducted a qualitative study to ascertain which aspects of HRQOL are most relevant to them postoperatively, and to identify Patient-Reported Outcome Measurement Information System (PROMIS) measures most germane to patients undergoing lobectomy for lung cancer. **METHODS:** We conducted in-depth semi-structured interviews with 25 patients after lobectomy for lung cancer to solicit input regarding the physical, social and emotional HRQOL domains relevant after surgery. Interviews were transcribed verbatim and a thematic content analysis to identify HRQOL themes was performed; themes were integrated to create a conceptual framework to guide outcome measurement selection. **RESULTS:** Qualitative analysis indicated that within the physical health domain, patients were most concerned about general physical function (100% of participants), pain (96%), fatigue (96%) and dyspnea (76%). Neuropathic pain was reported by 28% of participants. Instrumental (100%) and emotional social support (88%) and positive emotions/relief/hope (96%) were also important. Two cross-cutting themes were the desire to maintain independence (32%) and preparing for surgery/expectations (92%). **CONCLUSIONS:** Our results indicate that a number of physical, social and emotional HRQOL domains are relevant after lobectomy for lung cancer. These domains are currently represented by PROMIS measures and can be readily assessed for clinical or research purposes.

[The Effect of Tumor Size and Histology on Outcomes Following Segmentectomy vs. Lobectomy for Clinically Node-negative Non-small Cell Lung Cancer](#)

Chest. 2020 Jul 8;S0012-3692(20)31868-7. doi: 10.1016/j.chest.2020.06.066. Online ahead of print.

Vignesh Raman 1 , Oliver K Jawitz 2 , Soraya L Voigt 2 , Kristen E Rhodin 2 , Thomas A D'Amico 2 , David H Harpole 2 , Chi-Fu Jeffrey Yang 3 , Betty C Tong 2

BACKGROUND: The interaction between tumor size and the comparative prognosis of lobar and sublobar resection has been poorly defined. **RESEARCH QUESTION:** The purpose of this study was to characterize the relationship between tumor size and the receipt of segmentectomy or lobectomy in association with overall survival in patients with clinically node-negative non-small cell lung cancer (NSCLC). **STUDY DESIGN: AND METHODS:** The 2004-2015 National Cancer Database (NCDB)

was queried for patients with cT1-3N0M0 NSCLC who underwent segmentectomy or lobectomy without neoadjuvant therapy or missing survival data. The primary outcome was overall survival (OS), which was evaluated using multivariable Cox proportional hazards including an interaction term between tumor size and type of surgery. **RESULTS:** A total of 143,040 patients were included: 135,446 (95%) underwent lobectomy and 7594 (5%) segmentectomy. In multivariable Cox regression, a significant three-way interaction was found between tumor size, histology, and type of surgery ($p < 0.001$). When patients were stratified by histology, lobectomy was associated with significantly improved survival compared to segmentectomy beyond a tumor size of approximately 10 mm for adenocarcinoma and 15 mm for squamous cell carcinoma, which was recapitulated in subgroup analyses. No interaction between tumor size and type of surgery was found for patients with neuroendocrine tumors. **INTERPRETATION:** In this NCDB study of patients with node-negative NSCLC, we found different tumor size thresholds, based on histology, that identified populations of patients who least and most benefit from lobectomy compared to segmentectomy.

Combined sleeve lobectomy for centrally located primary lung cancer and lung cancer with hilar lymph node metastasis Jpn J Clin Oncol. 2020 Jul 9;50(7):794-799. doi: 10.1093/jjco/hyaa037.

Takuma Tsukioka 1 , Nobuhiro Izumi 1 , Hiroaki Komatsu 1 , Hidetoshi Inoue 1 , Hikaru Miyamoto 1 , Ryuichi Ito 1 , Takuya Kimura 1 , Noritoshi Nishiyama 1

BACKGROUND: Centrally located lung cancer or metastatic hilar lymph nodes can invade the airway and other hilar structures, and they must be removed to achieve complete resection. **METHODS:** We retrospectively assessed the clinical course of 47 patients with centrally located lung cancer or metastatic hilar lymph nodes who underwent sleeve lobectomy from January 2010 to December 2017.

RESULTS: The invaded structure other than the airway was the pulmonary artery in 21 patients, chest wall in 3, esophageal muscular wall in 2, vagus nerve in 2, pericardium in 2, left atrium in 1, phrenic nerve in 1 and superior vena cava in 1. Twenty-four patients were treated with sleeve lobectomy alone (simple sleeve lobectomy), and 23 patients were treated with sleeve lobectomy with additional methods (combined sleeve lobectomy). Adverse events occurred in 10 patients (48%) in the simple sleeve lobectomy group and 7 patients (30%) in the combined sleeve lobectomy group. During the follow-up period, 15 patients developed recurrent disease and 12 patients died. Patients in the combined sleeve lobectomy group had significantly shorter overall survival ($P = 0.004$) and disease-free survival periods ($P = 0.013$). Combined sleeve lobectomy was a significantly poor prognostic factor in the univariate and multivariate analyses. Patients who underwent sleeve lobectomy with an additional method other than angioplasty had a significantly poorer prognosis. However, no patient developed recurrent disease in the hilar area. **CONCLUSIONS:** Combined sleeve lobectomy has acceptable adverse events and good local controllability. However, combined sleeve lobectomy is associated with a significantly poorer prognosis than simple sleeve lobectomy in terms of overall survival and disease-free survival.

Comparison of the Short- and Long-term Outcomes of Video-assisted Thoracoscopic Surgery versus Open Thoracotomy Bronchial Sleeve Lobectomy for Central Lung Cancer: A Retrospective Propensity Score Matched Cohort Study Ann Surg Oncol. 2020 Jul 8. doi: 10.1245/s10434-020-08805-y. Online ahead of print. Yanbo Yang 1 2 , Jiandong Mei 1 2 , Feng Lin 1 2 , et al.

PURPOSE: The purpose of this study was to evaluate the short- and long-term outcomes of video-assisted thoracoscopic surgery (VATS) versus open thoracotomy bronchial sleeve lobectomy (BSL) for patients with central lung cancer. **METHODS:** This is a retrospective cohort study. Perioperative outcomes and long-term survival of patients who underwent VATS versus open thoracotomy BSL for central lung cancer from June 2010 and June 2018 in the Western China Lung Cancer Database were compared using propensity score matching (PSM) between the two surgical approaches. **RESULTS:** The retrospective study included 187 patients who divided into VATS group ($n = 44$) and open group ($n =$

143) according to surgical approach, and PSM resulted in 43 patients in each group, which were well matched by 11 potential prognostic factors. The VATS group was associated with lower overall incidence of postoperative complications (20.3% vs. 30.2%, $P = 0.029$), less postoperative drainage (875 ml [250-3960] vs. 1280 ml [100-4890], $P = 0.039$). The 5-year overall survival (OS) and disease-free survival (DFS) were comparable between the VATS and open groups (55.9% vs. 65.2% $P = 0.836$ and 54.1% vs. 60.2% $P = 0.391$, respectively) after matching. Multivariable adjusted analysis demonstrated that the surgical approach was not an independent favorable prognostic factor for OS (hazard ratio [HR] = 0.922; 95% confidence interval [CI], 0.427-1.993; $P = 0.836$) but just the pTNM stage (HR = 2.003; 95% CI 1.187-3.382; $P = 0.009$). **CONCLUSIONS:** VATS BSL may achieve equivalent long-term outcomes for central lung cancer patients when comparing with open thoracotomy. Although slightly longer duration of surgery, VATS approach may be a feasible option for lung cancer patients requiring BSL.

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

[PD-L1 promotes tumor growth and progression by activating WIP and \$\beta\$ -catenin signaling pathways and predicts poor prognosis in lung cancer](#)

Cell Death Dis. 2020 Jul 6;11(7):506. doi: 10.1038/s41419-020-2701-z. Wendan Yu ¹, Yijun Hua ², Huijuan Qiu ², et al.

PD-L1 is overexpressed in tumor cells and contributes to cancer immunoevasion. However, the role of the tumor cell-intrinsic PD-L1 in cancers remains unknown. Here we show that PD-L1 regulates lung cancer growth and progression by targeting the WIP and β -catenin signaling. Overexpression of PD-L1 promotes tumor cell growth, migration and invasion in lung cancer cells, whereas PD-L1 knockdown has the opposite effects. We have also identified WIP as a new downstream target of PD-L1 in lung cancer. PD-L1 positively modulates the expression of WIP. Knockdown of WIP also inhibits cell viability and colony formation, whereas PD-L1 overexpression can reverse this inhibition effects. In addition, PD-L1 can upregulate β -catenin by inhibiting its degradation through PI3K/Akt signaling pathway. Moreover, we show that in lung cancer cells β -catenin can bind to the WIP promoter and activate its transcription, which can be promoted by PD-L1 overexpression. The in vivo experiments in a human lung cancer mouse model have also confirmed the PD-L1-mediated promotion of tumor growth and progression through activating the WIP and β -catenin pathways. Furthermore, we demonstrate that PD-L1 expression is positively correlated with WIP in tumor tissues of human adenocarcinoma patients and the high expression of PD-L1 and WIP predicts poor prognosis. Collectively, our results provide new insights into understanding the pro-tumorigenic role of PD-L1 and its regulatory mechanism on WIP in lung cancer, and suggest that the PD-L1/Akt/ β -catenin/WIP signaling axis may be a potential therapeutic target for lung cancers.

[Value of Precision Medicine in Advanced Non-Small Cell Lung Cancer: Real-World Outcomes Associated With the Use of Companion Diagnostics](#)

Oncologist. 2020 Jul 6. doi: 10.1634/theoncologist.2019-0864. Online ahead of print.

Ani John ¹, Roma A Shah ¹, William B Wong ², Charles E Schneider ³, Marliese Alexander ⁴ ⁵

BACKGROUND: Companion diagnostic (CDx) testing for patients with advanced non-small cell lung cancer (aNSCLC) identifies patients more likely to benefit from biomarker-driven treatments.

PATIENTS AND METHODS: Patients with non-squamous cell (non-Sq) aNSCLC from the Flatiron Health database (diagnosed January 1, 2011-May 31, 2018) who had CDx testing were compared with those who had no reported evidence of testing. The association between CDx testing and overall survival was evaluated by unadjusted and adjusted Cox proportional hazards regression models. Logistic regression analysis identified characteristics associated with CDx testing. The revised modified Lung Cancer Prognostic Index and other factors identified a priori were included in the adjusted models.

RESULTS: A total of 17,555 patients with non-Sq aNSCLC (CDx, n = 14,732; no CDx, n = 2,823) with mean (SD) age of 67.2 (10.0) years were included. Most were insured (91.7%) and white (67.1%). Asian patients and those who were never-smokers were more likely to undergo CDx testing. Those with CDx testing lived longer than those without (median [95% CI] survival, 13.04 [12.62-13.40] versus 6.01 [5.72-6.24] months) and had a decreased mortality risk (adjusted hazard ratio [95% CI], 0.72 [0.69-0.76]). A survival advantage was also seen for patients with CDx testing who received biomarker-driven first-line therapy. **CONCLUSION:** Patients with non-Sq aNSCLC who had CDx testing had a greater survival benefit than those without, supporting broader use of CDx testing in routine clinical practice to identify patients more likely to benefit from precision medicine. **IMPLICATIONS FOR PRACTICE:** Companion diagnostic (CDx) testing coupled with biomarker-driven treatment offers a greater survival benefit for patients with advanced non-small cell lung cancer (aNSCLC). In this study, patients with non-squamous aNSCLC from Flatiron Health—a large, real-world oncology database—with CDx testing had a reduced mortality risk and lived longer than patients without reported evidence of CDx testing; those who received biomarker-driven therapy as their first line of treatment were likely to survive three times longer than those who did not. These results demonstrate the clinical utility of CDx testing as the first step in treating non-squamous aNSCLC in real-world clinical practice.

[Osimertinib improves overall survival in EGFR-mutated non-small cell lung cancer patients with leptomeningeal metastases regardless of T790M mutational status](#)

J Thorac Oncol. 2020 Jul 8;S1556-0864(20)30505-0. doi: 10.1016/j.jtho.2020.06.018. Online ahead of print. Jiyoung Lee 1, Yoon La Choi 2, Joungho Han 2, Sehhoon Park 1, Hyun Ae Jung 1, Jong-Mu Sun 1, Se-Hoon Lee 1, Jin Seok Ahn 1, Keunchil Park 1, Myung-Ju Ahn 3

INTRODUCTION: Osimertinib, a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), efficiently penetrates the blood-brain barrier. Current study explored whether treatment with osimertinib leads to improved overall survival (OS) for EGFR-mutated NSCLC patients with leptomeningeal metastases (LM) compared with those not treated with osimertinib. **METHODS:** From October 2008 to October 2019, patients with EGFR-mutated NSCLC and cytologically confirmed LM were retrospectively analyzed for OS according to osimertinib treatment and T790M mutational status. OS was defined as the time from diagnosis of LM to death. **RESULTS:** For the 351 LM patients included in analysis, the median OS (mOS) was 8.1 months (95% confidence interval [CI] 7.2-9.0). T790M mutation was detected in 88 of 197 patients tested, and a total of 110 patients were treated with osimertinib after LM. No significant difference in mOS was demonstrated according to T790M mutational status (10.1 months [95% CI 4.31-15.82] vs. 9.0 [6.81-11.21], P= 0.936). However, patients treated with osimertinib showed a superior OS of 17.0 months (95% CI, 15.13-18.94) compared with those not treated with osimertinib who showed a mOS 5.5 months (95% CI 4.34-6.63) regardless of T790M mutational status (HR 0.36; 95% CI 0.28-0.47, P <0.001). This was considerably longer even compared to those who were never treated with osimertinib but with first-/second-generation EGFR TKIs showing a mOS of 8.7 months (95% CI 7.01-10.39). **CONCLUSIONS:** Osimertinib is a promising treatment option for EGFR-mutated NSCLC with LM regardless of T790M mutational status.

[Immunotherapy in Advanced Lung Cancer](#) Oncology (Williston Park). 2020 Jul 15;34(7):272-279.

Joy Huang 1, Karen L Reckamp 2

Historically, platinum-based chemotherapy was the standard of care for metastatic lung cancer. However, since the success of immune checkpoint inhibitors (ICIs) in melanoma, PD-1/PD-L1 and CTLA-4 immune checkpoint pathways have been established as effective therapies to manage advanced non-small cell lung cancer (NSCLC) and extensive-stage (ES) small cell lung cancer (SCLC). Multiple large-scale randomized clinical trials have analyzed the effects of ICIs in NSCLC, and results of these trials have since translated to the approval of single-agent PD-1/PD-L1 inhibitors, and the combination of PD-1

inhibitors with platinum-based chemotherapy has become the new standard of care for patients with advanced NSCLC. Furthermore, in ES SCLC, in which chemotherapy or chemoradiation has been the standard of care for decades, 2 anti-PD-1/PD-L1 agents have been approved for use in the frontline setting for ES SCLC, in combination with chemotherapy. Despite progressive integration of immunotherapy into treatment regimens, there remains a need for reliable biomarkers to precisely determine therapy candidates.

[LK-Brain Prognostic Index-Preliminary Study of a Prognostic Tool for Patients with ALK-Rearranged, Non-small Cell Lung Cancer and Brain Metastases](#) Cancers (Basel). 2020 Jul

6;12(7):E1804. doi: 10.3390/cancers12071804. Georgios Tsakonas 1 2 , Caroline Kamali 1 2 , Luigi De Petris 1 2 , Signe Friesland 1 2 , Rolf Lewensohn 1 2 , Simon Ekman 1 2

BACKGROUND: Disease-specific Graded Prognostic Assessment (DS-GPA) is the most validated prognostic tool for patients with brain metastasized lung cancer. The Lung-molGPA scoring system was recently introduced for oncogenic-driven brain metastasized lung cancer, but has not yet been validated in cohorts including only ALK-translocated tumors. **METHODS:** We designed a retrospective cohort study consisting of 44 patients with brain metastasized ALK-positive, non-small cell lung cancer (NSCLC) who were treated between January 2009 and November 2019 at Karolinska University Hospital in Stockholm, Sweden. Information about demographics and clinicopathological parameters were collected. Predictors of overall survival (OS) were identified by Cox regression analyses. A bootstrap validation with 1000 samples was performed in order to compare the different prognostic scores. **RESULTS:** The variables found to independently influence OS in the multivariate analysis, i.e., PS, sex and brain metastases at diagnosis, were used as prognostic variables in our new prognostic index (ALK-BPI). Patients were divided into two prognostic groups. The median OS was 65.7 months for the good prognostic group and 22.7 months for the poor prognostic group ($p = 0.0068$). In the univariate analysis of the different prognostic scores, ALK-BPI performed better than the others (HR = 3.6; 95% CI: 1.3-9.9). The mean C-statistics of the different prognostic scores were compared to each other, and no significant difference was observed. **CONCLUSION:** We propose the ALK-BPI score as a new prognostic tool that can easily be applied for ALK-positive lung cancer patients with brain metastases in daily clinical practice, as it has at least the same prognostic value as Lung-molGPA.

[New therapeutic approaches to overcoming resistant EGFR exon 20 alterations](#) Crit Rev Oncol

Hematol. 2020 Jul;151:102990. doi: 10.1016/j.critrevonc.2020.102990. Epub 2020 May 20.

Alex M Li 1 , Amélie Boichard 2 , Enriqueta Felip 3 , Razelle Kurzrock 4

EGFR exon 20 alterations are rare events seen mainly in non-small cell lung cancer (NSCLC). They include EGFR T790 and C797S mutations (associated with secondary resistance to classic EGFR tyrosine kinase inhibitors (TKIs)), and EGFR exon 20 in-frame insertions (associated with resistance to first- and second-generation EGFR TKIs). In silico modeling of structural changes in aberrant proteins has informed selection of compounds with potential clinical activity: poziotinib (whose smaller size permits access to the restricted kinase pocket created by EGFR and ERBB2 exon 20 insertions); cetuximab (an antibody that attenuates dimerization caused by EGFR exon 20 insertions), and TAK-788 (another EGFR/ERBB2 TKI). Other alterations, such as EGFR T790 M, are responsive to osimertinib, while the EGFR C797S alteration seen in osimertinib resistance demonstrates preclinical sensitivity to combined brigatinib and cetuximab. These observations indicate that clinical resistance can be overcome by utilizing advanced genomic interrogation coupled with computer modeling.

[Capmatinib: First Approval](#) Drugs. 2020 Jul;80(11):1125-1131. doi: 10.1007/s40265-020-01347-3.

Sohita Dhillon 1

Capmatinib (Tabrecta™) is an oral, small molecule mesenchymal-epithelial transition (MET) inhibitor being developed by Novartis Oncology, under a license from Incyte Corporation, for the treatment of lung cancer. Capmatinib targets and selectively binds to MET, including the mutant variant produced by exon 14 skipping, and inhibits cancer cell growth driven by the mutant MET variant. In May 2020, oral capmatinib received its first global approval in the USA for the treatment of adults with metastatic non-small cell lung cancer (NSCLC) whose tumours have a mutation that leads to MET exon 14 skipping, as detected by an FDA-approved test. Clinical development for the treatment of glioblastoma, liver cancer, malignant melanoma, breast cancer, colorectal cancer, head and neck cancer and solid tumours is ongoing in several countries. This article summarizes the milestones in the development of capmatinib leading to its first approval.

[Immunotherapy in older patients with non-small cell lung cancer: Young International Society of Geriatric Oncology position paper](#) Br J Cancer. 2020 Jul 22. doi: 10.1038/s41416-020-0986-4. Online ahead of print.

Fabio Gomes 1 , Melisa Wong 2 , Nicolò Matteo Luca Battisti 3 , Tiana Kordbacheh 4 , Mandy Kiderlen 5 , Alastair Greystoke 6 , Andrea Luciani 7

Immunotherapy with checkpoint inhibitors against programmed cell death receptor (PD-1) and programmed cell death ligand (PD-L1) has been implemented in the treatment pathway of patients with non-small cell lung cancer (NSCLC) from locally advanced disease to the metastatic setting. This approach has resulted in improved survival and a more favourable toxicity profile when compared with chemotherapy. Following the successful introduction of single-agent immunotherapy, current clinical trials are focusing on combination treatments with chemotherapy or radiotherapy or even other immunotherapeutic agents. However, most of the data available from these trials are derived from, and therefore might be more applicable to younger and fitter patients rather than older and often frail lung cancer real-world patients. This article provides a detailed review of these immunotherapy agents with a focus on the data available regarding older NSCLC patients and makes recommendations to fill evidence gaps in this patient population.

[Mechanisms of osimertinib resistance and emerging treatment options](#) Lung Cancer. 2020 Jul 18;147:123-129. doi: 10.1016/j.lungcan.2020.07.014. Online ahead of print. Sabine Schmid 1 , Janice J N Li 2 , Natasha B Leighl 3

Osimertinib is an irreversible EGFR-tyrosine kinase inhibitor initially approved for treatment of EGFR-positive patients exhibiting a T790 M resistance mutation in the second line setting and now emerging as the new standard of care for all EGFR positive patients as first-line treatment. Despite its efficacy, resistance to osimertinib inevitably develops and mechanisms of resistance can be grouped broadly in two categories: on-target EGFR-dependent and off-target EGFR-independent mechanisms. EGFR-dependent resistance typically is associated with additional EGFR-mutations disrupting the osimertinib binding through changes in the binding site by allosteric/ conformational transitions; EGFR-independent mechanisms are related mostly to alternate pathway activation or aberrant downstream signalling but also to lineage plasticity leading to small cell transformation. MET amplification is the most frequent off-target mechanisms of resistance to osimertinib treatment and recently published early trials show promising results for combination of MET-inhibitors with osimertinib upon development of resistance. This review will summarize mechanisms of resistance overall and in different treatment settings and will focus on potential new treatment options targeting specific acquired alterations after osimertinib failure.

[Neoadjuvant treatment is associated with superior outcomes in T4 lung cancers with local extension](#)

Ann Thorac Surg. 2020 Jul 11;S0003-4975(20)31118-8. doi: 10.1016/j.athoracsur.2020.05.084. Online ahead of print. Christopher W Towe 1 , Stephanie G Worrell 2 , Katelynn Bachman 2 , Anuja L Sarode 2 , Yaron Perry 2 , Philip A Linden 2

BACKGROUND: Neoadjuvant chemoradiation is associated with improved survival of superior sulcus cancers, but little data exists regarding clinical T4 lung cancers with mediastinal invasion. We hypothesized neoadjuvant treatment would be associated with improved survival in T4 lung cancer patients with mediastinal invasion. **METHODS:** Clinical T4-N0/1-M0 non-small cell lung cancers were identified in the National Cancer Database (NCDB) from 2006-2015. Patients with T4 extension to mediastinal structures undergoing lobectomy, bilobectomy or pneumonectomy were included. Neoadjuvant treatment was defined as preoperative chemotherapy and/or radiation. Patients receiving surgery >120 days after radiation were excluded. Study endpoints were pathologic margin status and overall survival. To adjust for heterogeneity, a 1:1 propensity match analysis was performed. **RESULTS:** 1,101 patients with cT4N0/1M0 cancers were analyzed. 595(54.0%) received primary surgery and 506(46.0%) received neoadjuvant treatment. Neoadjuvant therapy was associated with fewer positive surgical margins (46/506(9.3%) vs 186/595(33.1%), $p<0.001$). Multivariate analysis showed an association of neoadjuvant therapy with a lower rate of positive margin (OR 0.220, $p<0.001$). Overall survival was longer among patients receiving neoadjuvant treatment (65.9 vs 27.5 months, $p<0.001$). Propensity matching identified 331 matched pairs of patients. Among them, positive margins were less likely after receiving neoadjuvant treatment (10.5% vs 31.3%, $p<0.001$). Overall survival among the matched pairs was improved in those receiving neoadjuvant treatment (57.0 vs 27.5 months, $p<0.001$). **CONCLUSIONS:** In the NCDB, T4N0/1 mediastinal invasion patients who receive neoadjuvant treatment have decreased rates of positive surgical margins and improved overall survival. The use of neoadjuvant treatment should be considered in these patients.

[Occurrence and number of immune-related adverse events are independently associated with survival in advanced non-small-cell lung cancer treated by nivolumab](#)

Bull Cancer. 2020 Jul 6;S0007-4551(20)30263-0. doi: 10.1016/j.bulcan.2020.04.019. Online ahead of print. Linda Bouhlel 1 , Jérôme Doyen 2 , Emmanuel Chamorey 3 , et al.

It has been found that occurrence of immune-related adverse events (irAEs) is associated with outcome in the treatment of advanced non-small-cell lung cancer (NSCLC) with anti-programmed cell death (PD)-1 or anti-PDL1 agents. Independent correlation with survival was not consistently demonstrated and correlation with the number of toxicities was also not previously described. All patients treated with nivolumab for advanced NSCLC, in the second line setting, were retrospectively reviewed in a single-center from March 2015 to March 2017. Sixty-nine patients were identified. After a median follow-up of 13 months (95% CI: 10.8; 15.3), there were 46 tumor progressions and 37 deaths. The 6-month and one-year progression-free survival (PFS) and overall survival (OS) rates were 29%/61% and 24%/49%, respectively. Thirty-one patients (44.9%) presented irAEs. Patients presenting tumor response to previous chemotherapy had a higher rate of irAEs ($P=0.01$) and a better OS (HR=2, $P=0.04$). Occurrence of irAEs correlated with OS in multivariate analysis (HR=0.4, 95% CI [0.19; 0.8], $P=0.02$). The number of irAEs correlated with tumor response, PFS and OS in univariate analysis. Having ≥ 2 irAEs correlated with better outcome compared with one irAE, which correlated with better tumor response and PFS in comparison with 0 irAE, in multivariate analysis. In this study, irAEs was associated with a better outcome in patients treated with nivolumab for advanced NSCLC in the second line setting. Interestingly, the number of irAEs correlated with tumor response and PFS.

[A serum protein classifier identifying patients with advanced non-small cell lung cancer who derive clinical benefit from treatment with immune checkpoint inhibitors](#)

Clin Cancer Res. 2020 Jul 6;clincanres.0538.2020. doi: 10.1158/1078-0432.CCR-20-0538. Online ahead of print. Mirte Muller 1 , Karlijn Hummelink 2 , Daan P Hurkmans 3 , Anna-Larissa N Niemeijer 4 , Kim Monkhorst 5 , Joanna Roder 6 , Carlos Oliveira 6 , Heinrich Roder 7 , Joachim G Aerts 8 , Egbert F Smit 9

PURPOSE: Pretreatment selection of non-small-cell lung cancer (NSCLC) patients who derive clinical benefit from treatment with immune checkpoint inhibitors would fulfill an unmet clinical need by reducing unnecessary toxicities from treatment and result in substantial health care savings.

PATIENTS AND METHODS: In a retrospective study, mass spectrometry (MS) based proteomic analysis was performed on pretreatment sera derived from advanced NSCLC patients treated with nivolumab as part of routine clinical care (n=289). Machine learning combined spectral and clinical data to stratify patients into three groups with good ("sensitive"), intermediate and poor ("resistant") outcomes following treatment in the second-line setting. The test was applied to three independent patient cohorts and its biology investigated using protein set enrichment analyses (PSEA). **RESULTS:** A signature consisting of 274 MS features derived from a development set of 116 patients was associated with progression free survival (PFS) and overall survival (OS) across 2 validation cohorts (n=98 and n=75). In pooled analysis, significantly better OS was demonstrated for "sensitive" relative to "not sensitive" patients treated with nivolumab, HR 0.58 (95% CI 0.38-0.87, p=0.009). There was no significant association with clinical factors including PD-L1 expression, available from 133/289 patients. The test demonstrated no significant association with PFS or OS in a historical cohort (n=68) of second-line NSCLC patients treated with docetaxel. PSEA revealed proteomic classification to be significantly associated with complement and wound healing cascades. **CONCLUSIONS:** This serum-derived protein signature successfully stratified outcomes in cohorts of advanced NSCLC patients treated with second line PD-1 checkpoint inhibitors and deserves further prospective study.

NSCLC - RADIOTHERAPY

[Practice Recommendations for Lung Cancer Radiotherapy During the COVID-19 Pandemic: An ESTRO-ASTRO Consensus Statement](#) Int J Radiat Oncol Biol Phys. 2020 Jul 15;107(4):631-640. doi: 10.1016/j.ijrobp.2020.05.012. Matthias Guckenberger 1 , Claus Belka 2 , Andrea Bezjak 3 , et al.

BACKGROUND: The COVID-19 pandemic has caused radiotherapy resource pressures and led to increased risks for lung cancer patients and healthcare staff. An international group of experts in lung cancer radiotherapy established this practice recommendation pertaining to whether and how to adapt radiotherapy for lung cancer in the COVID-19 pandemic. **METHODS:** For this ESTRO & ASTRO endorsed project, 32 experts in lung cancer radiotherapy contributed to a modified Delphi consensus process. We assessed potential adaptations of radiotherapy in two pandemic scenarios. The first, an early pandemic scenario of risk mitigation, is characterized by an altered risk-benefit ratio of radiotherapy for lung cancer patients due to their increased susceptibility for severe COVID-19 infection, and minimization of patient travelling and exposure of radiotherapy staff. The second, a later pandemic scenario, is characterized by reduced radiotherapy resources requiring patient triage. Six common lung cancer cases were assessed for both scenarios: peripherally located stage I NSCLC, locally advanced NSCLC, postoperative radiotherapy after resection of pN2 NSCLC, thoracic radiotherapy and prophylactic cranial irradiation for limited stage SCLC and palliative thoracic radiotherapy for stage IV NSCLC. **RESULTS:** In a risk-mitigation pandemic scenario, efforts should be made not to compromise the prognosis of lung cancer patients by departing from guideline-recommended radiotherapy practice. In that same scenario, postponement or interruption of radiotherapy treatment of COVID-19 positive patients is generally recommended to avoid exposure of cancer patients and staff to an increased risk of COVID-19 infection. In a severe pandemic scenario characterized by reduced resources, if patients must be triaged, important factors for triage include potential for cure, relative benefit of radiation, life

expectancy, and performance status. Case-specific consensus recommendations regarding multimodality treatment strategies and fractionation of radiotherapy are provided. **CONCLUSION:** This joint ESTRO-ASTRO practice recommendation established pragmatic and balanced consensus recommendations in common clinical scenarios of radiotherapy for lung cancer in order to address the challenges of the COVID-19 pandemic.

[Practice Recommendations for Lung Cancer Radiotherapy During the COVID-19 Pandemic: An ESTRO-ASTRO Consensus Statement](#) Int J Radiat Oncol Biol Phys. 2020 Jul 15;107(4):631-640. doi: 10.1016/j.ijrobp.2020.05.012.

BACKGROUND: The COVID-19 pandemic has caused radiotherapy resource pressures and led to increased risks for lung cancer patients and healthcare staff. An international group of experts in lung cancer radiotherapy established this practice recommendation pertaining to whether and how to adapt radiotherapy for lung cancer in the COVID-19 pandemic. **METHODS:** For this ESTRO & ASTRO endorsed project, 32 experts in lung cancer radiotherapy contributed to a modified Delphi consensus process. We assessed potential adaptations of radiotherapy in two pandemic scenarios. The first, an early pandemic scenario of risk mitigation, is characterized by an altered risk-benefit ratio of radiotherapy for lung cancer patients due to their increased susceptibility for severe COVID-19 infection, and minimization of patient travelling and exposure of radiotherapy staff. The second, a later pandemic scenario, is characterized by reduced radiotherapy resources requiring patient triage. Six common lung cancer cases were assessed for both scenarios: peripherally located stage I NSCLC, locally advanced NSCLC, postoperative radiotherapy after resection of pN2 NSCLC, thoracic radiotherapy and prophylactic cranial irradiation for limited stage SCLC and palliative thoracic radiotherapy for stage IV NSCLC. **RESULTS:** In a risk-mitigation pandemic scenario, efforts should be made not to compromise the prognosis of lung cancer patients by departing from guideline-recommended radiotherapy practice. In that same scenario, postponement or interruption of radiotherapy treatment of COVID-19 positive patients is generally recommended to avoid exposure of cancer patients and staff to an increased risk of COVID-19 infection. In a severe pandemic scenario characterized by reduced resources, if patients must be triaged, important factors for triage include potential for cure, relative benefit of radiation, life expectancy, and performance status. Case-specific consensus recommendations regarding multimodality treatment strategies and fractionation of radiotherapy are provided. **CONCLUSION:** This joint ESTRO-ASTRO practice recommendation established pragmatic and balanced consensus recommendations in common clinical scenarios of radiotherapy for lung cancer in order to address the challenges of the COVID-19 pandemic.

[Application and limitation of radiomics approach to prognostic prediction for lung stereotactic body radiotherapy using breath-hold CT images with random survival forest: A multi-institutional study](#) Med Phys. 2020 Jul 9. doi: 10.1002/mp.14380. Online ahead of print. Ryo Kakino 1 2 3 , Mitsuhiro Nakamura 1 2 , Takamasa Mitsuyoshi 2 4 , et al.

PURPOSE: To predict local recurrence (LR) and distant metastasis (DM) in early-stage non-small-cell lung cancer (NSCLC) patients after stereotactic body radiotherapy (SBRT) in multiple institutions using breath-hold CT-based radiomic features with random survival forest. **METHODS:** A total of 573 primary early-stage NSCLC patients who underwent SBRT between January 2006 and March 2016 and met the eligibility criteria were included in this study. Patients were divided into two datasets: training (464 patients in ten institutions) and test (109 patients in one institution) dataset. A total of 944 radiomic features were extracted from manually segmented gross tumor volumes (GTVs). Feature selection was performed by analyzing inter-segmentation reproducibility, GTV correlation, and inter-feature redundancy. Nine clinical factors, including histology and GTV size, were also used. Three prognostic models (clinical, radiomic, and combined) for LR and DM were constructed using random survival forest

(RSF) to deal with total death as a competing risk in the training dataset. Robust models with optimal hyper-parameters were determined using 5-fold cross validation. The patients were dichotomized into two groups based on the median value of the patient-specific risk scores (high- and low-risk score groups). Gray's test was used to evaluate the statistical significance between the two risk score groups. The prognostic power was evaluated by the C-index with the 95% confidence intervals (CI) via bootstrapping (2,000 iterations). **RESULTS:** The concordance indices at 3 years of clinical, radiomic, and combined models for LR were 0.57 [CI: 0.39-0.75], 0.55 [CI: 0.38-0.73], and 0.61 [CI: 0.43-0.78], respectively, whereas those for DM were 0.59 [CI: 0.54-0.79], 0.67 [CI: 0.54-0.79], and 0.68 [CI: 0.55-0.81], respectively, in the test dataset. The combined DM model significantly discriminated its cumulative incidence between high- and low-risk score groups ($p < 0.05$). The variable importance of RSF in the combined model for DM indicated that two radiomic features were more important than other clinical factors. The feature maps generated on the basis of the most important radiomic feature had visual difference between high- and low-risk score groups. **CONCLUSIONS:** The radiomics approach with RSF for competing risks using breath-hold CT-based radiomic features might predict DM in early-stage NSCLC patients who underwent SBRT although that may not have potential to predict LR.

Tumor volume shrinkage during stereotactic body radiotherapy is related to better prognoses in patients with stage I non-small-cell lung cancer J Radiat Res. 2020 Jul 13;rraa040. doi:

10.1093/jrr/rraa040. Online ahead of print. Nam Vu ^{1 2}, Hiroshi Onishi ¹, Masahide Saito ¹, et al. The purpose of the study was to investigate the association between tumor volume changes during stereotactic body radiation therapy (SBRT) and prognoses in stage I non-small-cell lung cancer (NSCLC). This retrospective review included stage I NSCLC patients in whom SBRT was performed at a total dose of 48.0-50.5 Gy in four or five fractions. The tumor volumes observed on computed tomography (CT) simulation and on the CT performed at the last treatment session using a CT-on-rails system were measured and compared. Then, the tumor volume changes during the SBRT period were measured and assessed for their association with prognoses (overall survival, local control, lymph node metastases and distant metastases). A total of 98 patients with a mean age of 78.6 years were enrolled in the study. The T-stage was T1a in 42%, T1b in 32% and T2a in 26% of the cases. The gross tumor volume (GTV) shrank and increased $\geq 10\%$ in 23 (23.5%) and 36 (36.7%) of the cases, respectively. The 5-year local control and overall survival rates in the groups with a tumor shrinkage of $\geq 10\%$ vs the group with a shrinkage of $< 10\%$ were 94.7 vs 70.8% and 85.4 vs 47.6%, respectively; these differences were significant, with a P-value < 0.05 . During a short SBRT period, the tumor shrank or enlarged in a small number of cases. A decrease of $\geq 10\%$ in the GTV during SBRT was significantly related to better overall survival and local control.

Identification of patterns of tumour change measured on CBCT images in NSCLC patients during radiotherapy Phys Med Biol. 2020 Jul 21. doi: 10.1088/1361-6560/aba7d3. Online ahead of print.

Lameck Mbangula Amugongo ¹, Eliana Vasquez Osorio ², Andrew Frederick Green ³, David Cobben ⁴, Marcel van Herk ⁵, Alan McWilliam ⁶

In this study, we propose a novel approach to investigate changes in the visible tumour and surrounding tissues with the aim of distinguishing modes of tumour change (elastic versus non-elastic) without segmentation on the follow-up images. On-treatment cone-beam computed tomography (CBCT) images of 240 non-small cell lung cancer (NSCLC) patients who received 55 Gy of radiotherapy were included. CBCTs were aligned onto planning computed tomography (planning CT) scan using a two-step rigid registration process. To explore density changes across the lung-tumour boundary, eight shells confined to the shape of the gross tumour volume (GTV) were created. The shells extended 6 mm inside and outside of the GTV border, and each shell is 1.5 mm thick. After applying intensity correction on CBCTs, the mean intensity was extracted from each shell across all CBCTs. Thereafter, linear fits were created,

indicating density change over time in each shell during treatment. The slopes of all eight shells were clustered to explore patterns in the slopes that show how tumours change. Seven clusters were obtained, 97% of the patients were clustered into three groups. After visual inspection, we found that these clusters represented patients with little or no density change, progression and regression. For the three groups, the survival curves were not significantly different between the groups, p-value=0.51. However, the results show that definite patterns of tumour changes exist, suggesting that it may be possible to identify modes of tumour changes from on-treatment CBCT images.

SMALL CELL LUNG CANCER - SCLC

[Opportunities and obstacles of targeted therapy and immunotherapy in small cell lung cancer](#)

J Drug Target. 2020 Jul 23;1-29. doi: 10.1080/1061186X.2020.1797050. Online ahead of print.

Lin Yu ^{1 2}, Qinhuai Lai ², Lantu Gou ², Jiafu Feng ¹, Jinliang Yang ²

Small cell lung cancer (SCLC) is an aggressive malignant tumour which accounts for approximately 13-15% of all newly diagnosed lung cancer cases. To date, platinum-based chemotherapy are still the first-line treatments for SCLC. However, chemotherapy resistance and systemic toxicity limit the long-term clinical outcome of first-line treatment in SCLC. Recent years, targeted therapy and immunotherapy have made great breakthrough in cancer therapy, and researchers aim to exploit both as a single agent or in combination with chemotherapy to improve the survival of SCLC patients, but limited effectiveness and the adverse events remain the major obstacles in the treatment of SCLC. To overcome these challenges for SCLC therapies, prevention and early diagnosis for this refractory disease is very important. At the same time, we should reveal more information about the pathogenesis of SCLC and the mechanism of drug resistance. Finally, new treatment strategies should also be taken into considerations, such as repurposing drug, optimizing of targets, combination therapy strategies or prognostic biomarkers to enhance therapeutic effects and decrease the adverse events rates in SCLC patients. This article will review the molecular biology characteristics of SCLC and discuss the opportunities and obstacles of the current therapy for SCLC patients.

[Twice-daily vs higher-dose once-daily thoracic radiotherapy for limited-disease small-cell lung cancer: A PRISMA-compliant meta-analysis](#)

Medicine (Baltimore). 2020 Jul 2;99(27):e20518. doi: 10.1097/MD.00000000000020518. Lin Yang ¹, Libo Liu ², Yanjie Yang ³, Yao Lei ⁴, Tianyi Wang ⁵, Xiaocui Wu ¹, Xiaoling Guo ⁶

INTRODUCTION: The optimal dose and fractionation of thoracic radiotherapy (RT) for limited-disease small-cell lung cancer (LD-SCLC) remain controversial. This meta-analysis was performed to compare the efficacy and RT toxicity between twice-daily thoracic RT (45 Gy with 1.5 Gy twice daily) and higher-dose once-daily RT (60-72 Gy with 1.8 Gy/2 Gy once daily) administered with chemotherapy in LD-SCLC patients. **METHODS:** PubMed, EMBASE, Web of Science, and the Cochrane Library were searched up to March 19, 2020 for studies that compared twice-daily thoracic RT (45 Gy with 1.5 Gy twice daily over 3 weeks) with higher-dose once-daily RT (60-72 Gy with 1.8 Gy/2 Gy once daily over 6-8 weeks) in LD-SCLC patients. **RESULTS:** Five studies involving 13,726 patients were included in this analysis. Compared with the once-daily thoracic RT group, the 1-year overall survival (OS) rate ($P < .001$), the 2-year OS rate ($P < .001$), the 5-year OS rate ($P < .001$), the mOS ($P < .001$), and the 1-year LRFS rate ($P = .048$) were significantly improved in the twice-daily RT group. The toxic effects of RT (esophagitis: $P = .293$; pneumonitis: $P = .103$) were similar in both groups. **CONCLUSION:** Compared with the higher-dose once-daily regimen, the twice-daily thoracic radiotherapy regimen improved efficacy but did not increase RT toxicity in LD-SCLC patients.

[ASXL3 bridges BRD4 to BAP1 complex and governs enhancer activity in small cell lung cancer](#)

Genome Med. 2020 Jul 15;12(1):63. doi: 10.1186/s13073-020-00760-3. Aileen Patricia Szczepanski 1 2 , Zibo Zhao 1 2 , Tori Sosnowski 3 , Young Ah Goo 1 2 3 , Elizabeth Thomas Bartom 1 2 , Lu Wang 4 5

BACKGROUND: Small cell lung cancer (SCLC) is a more aggressive subtype of lung cancer that often results in rapid tumor growth, early metastasis, and acquired therapeutic resistance. Consequently, such phenotypical characteristics of SCLC set limitations on viable procedural options, making it difficult to develop both screenings and effective treatments. In this study, we examine a novel mechanistic insight in SCLC cells that could potentially provide a more sensitive therapeutic alternative for SCLC patients.

METHODS: Biochemistry studies, including size exclusion chromatography, mass spectrometry, and western blot analysis, were conducted to determine the protein-protein interaction between additional sex combs-like protein 3 (ASXL3) and bromodomain-containing protein 4 (BRD4). Genomic studies, including chromatin immunoprecipitation sequencing (ChIP-seq), RNA sequencing, and genome-wide analysis, were performed in both human and mouse SCLC cells to determine the dynamic relationship between BRD4/ASXL3/BAP1 epigenetic axis in chromatin binding and its effects on transcriptional activity. **RESULTS:** We report a critical link between BAP1 complex and BRD4, which is bridged by the physical interaction between ASXL3 and BRD4 in an SCLC subtype (SCLC-A), which expresses a high level of ASXL1. We further showed that ASXL3 functions as an adaptor protein, which directly interacts with BRD4's extra-terminal (ET) domain via a novel BRD4 binding motif (BBM), and maintains chromatin occupancy of BRD4 to active enhancers. Genetic depletion of ASXL3 results in a genome-wide reduction of histone H3K27Ac levels and BRD4-dependent gene expression in SCLC.

Pharmacologically induced inhibition with BET-specific chemical degrader (dBET6) selectively inhibits cell proliferation of a subtype of SCLC that is characterized with high expression of ASXL3.

CONCLUSIONS: Collectively, this study provides a mechanistic insight into the oncogenic function of BRD4/ASXL3/BAP1 epigenetic axis at active chromatin enhancers in SCLC-A subtype, as well as a potential new therapeutic option that could become more effective in treating SCLC patients with a biomarker of ASXL3-highly expressed SCLC cells.

[Use of Immunotherapy in Extensive-Stage Small Cell Lung Cancer](#)

Oncology. 2020 Jul 14;1-6. doi: 10.1159/000508516. Online ahead of print. Venu Madhav Konala 1 , Bhaskar Reddy Madhira 2 , Sara Ashraf 3 , Stephen Graziano 2

Lung cancer is a leading cause of cancer death in the United States and around the world. Approximately 13% of lung cancers are small cell lung cancer (SCLC). SCLC is generally classified as a limited-stage and extensive-stage disease depending on the extent of involvement. For patients with the extensive-stage disease, until recently, chemotherapy alone has been the recommended treatment, although radiotherapy could be used in select patients for palliation of symptoms. The standard of care for extensive-stage SCLC is platinum doublet chemotherapy with either cisplatin or carboplatin in combination with etoposide.

Even though first-line therapy has an initial response rate of 60-80%, the prognosis is poor, with overall survival of 10-12 months. The only FDA-approved second line of therapy is topotecan, approved both as an intravenous formulation as well as an oral formulation, with response rates of 6-12% in chemorefractory disease and 15-37% in chemosensitive disease. Immunotherapy has recently been approved as a first-line agent in metastatic SCLC in combination with chemotherapy. It is also approved as a third-line agent in metastatic SCLC after the failure of two chemotherapy regimens. The FDA approved four drugs, two of them being PD-1 inhibitors (pembrolizumab, nivolumab), and two of them being PD-L1 inhibitors (atezolizumab and durvalumab) in SCLC. This review article summarizes the significance of immunotherapy in the treatment of extensive-stage SCLC, its side effects, and limitations.

[Lifestyle behaviors and intervention preferences of early-stage lung cancer survivors and their family caregivers](#) Support Care Cancer. 2020 Jul 20. doi: 10.1007/s00520-020-05632-5. Online ahead of print. McKenzie K Roddy 1 , Raja M Flores 2 , Brian Burt 1 , Hoda Badr 3

PURPOSE: Lung cancer (LC) is a highly prevalent disease with more survivors diagnosed and treated at earlier stages. There is a need to understand psychological and lifestyle behavior needs to design interventions for this population. Furthermore, understanding the needs and role of family caregivers, especially given the risks associated with second-hand smoke, is needed. **METHODS:** Thirty-one early-stage (stages I or IIA) LC survivors of (52% men) and 22 (50% women) caregivers (N = 53 total) completed surveys after surgery (baseline) and at 3- and 6-month follow-ups. Participants reported on psychological functioning, smoking, and physical activity (PA) as well as intervention preferences. **RESULTS:** Survivors reported low levels of psychological distress and 3% were current smokers during the study. Approximately 79% were sedentary and not meeting national PA guidelines. Caregivers also reported minimal psychological distress and were sedentary (62% not meeting guidelines), but a larger proportion continued to smoke following the survivor's cancer diagnosis (14%). Both survivors and caregivers expressed interest in home-based PA interventions but differed regarding preferred format for delivery. Most (64%) caregivers preferred a dyadic format, where survivors and caregivers participate in the intervention together. However, most survivors preferred an individual or group format (57%) for intervention delivery. **CONCLUSION:** Both LC survivors and family caregivers could benefit from PA interventions, and flexible, dyadic interventions could additionally support smoking cessation for family caregivers.

[A Mindfulness-Based Intervention as a Supportive Care Strategy for Patients with Metastatic Non-Small Cell Lung Cancer and their Spouses: Results of a 3-Arm Pilot Randomized Controlled Trial](#)

Oncologist. 2020 Jul 4. doi: 10.1634/theoncologist.2020-0125. Online ahead of print. Kathrin Milbury 1 , Yisheng Li 2 , Sania Durrani 1 , Zhongxing Liao 3 , Anne S Tsao 4 , Cindy Carmack 5 , Lorenzo Cohen 5 , Eduardo Bruera 5

BACKGROUND: Although mindfulness-based interventions have been widely examined in patients with non-metastatic cancer, the feasibility and efficacy of these types of programs are largely unknown for those with advanced disease. We pilot-tested a couple-based mediation (CBM) relative to a supportive-expressive (SE) and a usual care (UC) arm targeting psycho-spiritual distress in patients with metastatic lung cancer and their spousal caregivers. **PATIENTS AND METHODS:** Seventy-five patient-caregiver dyads completed baseline self-report measures and were then randomized to one of the three arms. Couples in the CBM and SE groups attended four, 60 min. sessions that were delivered via videoconference. All dyads were reassessed 1 and 3 months later. **RESULTS:** A priori feasibility benchmarks were met. Although attendance was high in both groups, dyads in the CBM group indicated greater benefit of the sessions than those in the SE group (patients, CBM mean=2.63, SE mean=2.20, P=.003; spouse, CBM mean=2.71, SE mean=2.00, P=.005). Compared with the UC group, patients in the CBM group reported significantly lower depressive symptoms (P=.05; d=.53) and marginally reduced cancer-related stress (P=.07; d=.68). Medium effect sizes in favor of the CBM compared with the SE group for depressive symptoms (d=.59) and cancer-related stress (d=.54) were found. Spouses in the CBM group reported significantly lower depressive symptoms (P<.01; d=.74) compared with those in the UC group. **CONCLUSION:** It seems feasible and possibly efficacious to deliver dyadic interventions via videoconference to couples coping with metastatic lung cancer. Mindfulness-based interventions may be of value to managing psychological symptoms in the palliative care setting.

Relationship Between Perceptions of Treatment Goals and Psychological Distress in Patients With Advanced Cancer J Natl Compr Canc Netw. 2020 Jul;18(7):849-855. doi: 10.6004/jnccn.2019.7525.

Areej El-Jawahri 1 2 , Deborah Forst 1 2 , Alyssa Fenech 1 2 , et al.

BACKGROUND: Studies have shown gaps in prognostic understanding among patients with cancer. However, few studies have explored patients' perceptions of their treatment goals versus how they perceive their oncologist's goals, and the association of these views with their psychological distress.

METHODS: We conducted a cross-sectional study of 559 patients with incurable lung, gastrointestinal, breast, and brain cancers. The Prognosis and Treatment Perception Questionnaire was used to assess patients' reports of their treatment goal and their oncologist's treatment goal, and the Hospital Anxiety and Depression Scale was used to assess patients' psychological symptoms. **RESULTS:** We found that 61.7% of patients reported that both their treatment goal and their oncologist's treatment goal were noncurative, whereas 19.3% reported that both their goal and their oncologist's goal were to cure their cancer, 13.9% reported that their goal was to cure their cancer whereas their oncologist's goal was noncurative, and 5% reported that their goal was noncurative whereas their oncologist's goal was curative. Patients who reported both their goal and their oncologist's goal as noncurative had higher levels of depression (B=0.99; P=.021) and anxiety symptoms (B=1.01; P=.015) compared with those who reported that both their goal and their oncologist's goal was curative. Patients with discordant perceptions of their goal and their oncologist's goal reported higher anxiety symptoms (B=1.47; P=.004) compared with those who reported that both their goal and their oncologist's goal were curative. **CONCLUSIONS:** One-fifth of patients with incurable cancer reported that both their treatment goal and their oncologist's goal were to cure their cancer. Patients who acknowledged the noncurative intent of their treatment and those who perceived that their treatment goal was discordant from that of their oncologist reported greater psychological distress.

Outcomes of Patients With Cancer Discharged to a Skilled Nursing Facility After Acute Care Hospitalization J Natl Compr Canc Netw. 2020 Jul;18(7):856-865. doi: 10.6004/jnccn.2020.7534.

Sarguni Singh 1 , Megan Eguchi 2 , Sung-Joon Min 3 , Stacy Fischer 4

BACKGROUND: After discharge from an acute care hospitalization, patients with cancer may choose to pursue rehabilitative care in a skilled nursing facility (SNF). The objective of this study was to examine receipt of anticancer therapy, death, readmission, and hospice use among patients with cancer who discharge to an SNF compared with those who are functionally able to discharge to home or home with home healthcare in the 6 months after an acute care hospitalization. **METHODS:** A population-based cohort study was conducted using the SEER-Medicare database of patients with stage II-IV colorectal, pancreatic, bladder, or lung cancer who had an acute care hospitalization between 2010 and 2013. A total of 58,770 cases were identified and patient groups of interest were compared descriptively using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Logistic regression was used to compare patient groups, adjusting for covariates.

RESULTS: Of patients discharged to an SNF, 21%, 17%, and 2% went on to receive chemotherapy, radiotherapy, and targeted chemotherapy, respectively, compared with 54%, 28%, and 6%, respectively, among patients discharged home. Fifty-six percent of patients discharged to an SNF died within 6 months of their hospitalization compared with 36% discharged home. Thirty-day readmission rates were 29% and 28% for patients discharged to an SNF and home, respectively, and 12% of patients in hospice received <3 days of hospice care before death regardless of their discharge location. **CONCLUSIONS:** Patients with cancer who discharge to an SNF are significantly less likely to receive subsequent oncologic treatment of any kind and have higher mortality compared with patients who discharge to home after an acute care hospitalization. Further research is needed to understand and address patient goals of care before discharge to an SNF.

[Incidence of thrombosis and hemorrhage in hospitalized cancer patients with COVID-19](#) J Thromb Haemost. 2020 Jul 21. doi: 10.1111/jth.15018. Online ahead of print. Rushad Patell 1, Thomas Bogue 1, Poorva Bindal 1, Anita Koshy 1, Mwanasha Merrill 2, William C Aird 1, Kenneth A Bauer 1, Jeffrey I Zwicker 1

OBJECTIVES: To evaluate cumulative incidences of thrombotic and hemorrhagic events in hospitalized COVID-19 patients with and without active cancer at 28 days. **METHODS:** A retrospective cohort analyses of consecutive adults hospitalized with COVID-19 was performed. Active cancer required cancer-directed therapy within last 6 months. The cumulative incidences of thrombosis or hemorrhage were estimated considering death as a competing risk. **RESULTS:** Patients without cancer (n=353) and active cancer (n=45) were comparable in terms of age, sex, antibiotics administered, length of hospitalization, and critical care. The most common malignancies were lymphoid (17.8%), gastrointestinal (15.6%), lung (13.3%), and genitourinary (13.3%). At day 28, the cumulative incidence of thrombotic events was 18.2% (95% CI, 10.2% to 27.9%) in non-cancer cohort and 14.2% (95% CI, 4.7% to 28.7%) in the cancer cohort. The cumulative incidence of major and fatal bleeding at day 28 was 20.8% (95% CI, 12.1 to 31.0%) in the non-cancer group and 19.5% (95% CI, 5.5% to 39.8%) in the cancer cohort. Three patients experienced fatal bleeds, all of whom were in the non-cancer cohort. Survival was significantly shorter in the group with active cancer (P=0.038). **CONCLUSIONS:** We observed a similarly high incidence of thrombosis and bleeding among patients admitted with COVID-19 with or without active cancer.

[Pneumonitis associated with immune checkpoint inhibitors among patients with non-small cell lung cancer](#) Curr Opin Pulm Med. 2020 Jul;26(4):326-340. doi: 10.1097/MCP.0000000000000689.

Vickie R Shannon 1

PURPOSE OF REVIEW: Patients with lung cancer are particularly vulnerable to lung injury associated with immune checkpoint inhibition and often present with more frequent and more severe manifestations of lung disease compared to patients with other tumor types. The present review explores the reasons for increased susceptibility to immune checkpoint-related lung injury among this group of patients and focuses on the current knowledge of the clinical and radiologic manifestations of lung injury associated with immune checkpoint blockade and current treatment strategies. **RECENT FINDINGS:** Recent investigations have shown that pneumonitis risk associated with immune checkpoint blockade may be stratified according to the tumor type that is being targeted. Patients with lung cancer have the highest rates of pneumonitis associated with this class of agents. **SUMMARY:** Pneumonitis associated with immune checkpoint blockade among patients with lung cancer has the highest prevalence of all cancer types. In this patient population, the additional insult to the lungs imposed by immune-checkpoint therapies is often poorly tolerated because of tumor burden within the lung, sequelae from prior treatment and frequent comorbid lung diseases, such as chronic obstructive pulmonary disease. Thus, early recognition and treatment is critical in this patient population to successful outcome.

[Atypical skin manifestations during immune checkpoint blockade in COVID19-infected lung cancer patients](#) J Thorac Oncol. 2020 Jul 9;S1556-0864(20)30543-8. doi: 10.1016/j.jtho.2020.06.019. Online ahead of print. Christian Rolfo 1, Andrés F Cardona 2, Alejandro Ruiz-Patiño 3,

A new coronavirus, named SARS-CoV-2 by the World Health Organization (WHO), has rapidly spread around the world since its first reported case in late December of 2019 from Wuhan, China. As of mid-April 2020, this virus has affected more than 180 countries and territories, infecting more than 1,650,000 individuals and causing over 100,000 deaths. With ≈20 million new cases per year globally, cancer affects a significant portion of the population. Individuals affected by cancer are more susceptible to infections due to coexisting chronic diseases (cardiovascular, pulmonary and diabetes), overall poor health status, and systemic immunosuppressive states caused by both cancer and anticancer treatments. As a

consequence, patients with malignancies, and especially with lung cancer who develop COVID19 experience more difficult outcomes. A recent multicenter study developed by the Hubei Anti-Cancer Association also documented that lung cancer patients had an increased risk of death, ICU requirement, risk of presenting severe or critical symptoms, and use of invasive mechanical ventilation. Here we present two representative cases of patients with lung cancer and COVID19 without respiratory compromise and with atypical and severe skin manifestations, findings that could be influenced by the chronic use of anti-PD1 antibodies.

COMPLEMENTARY & ALTERNATIVE THERAPY

MISCELLANEOUS WORKS

[Treatment Guidance for Patients With Lung Cancer During the Coronavirus 2019 Pandemic](#)

J Thorac Oncol. 2020 Jul;15(7):1119-1136. doi: 10.1016/j.jtho.2020.05.001. Epub 2020 May 15.

Anne-Marie C Dingemans ¹, Ross A Soo ², Abdul Rahman Jazieh ³, et al.

The global coronavirus disease 2019 pandemic continues to escalate at a rapid pace inundating medical facilities and creating substantial challenges globally. The risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients with cancer seems to be higher, especially as they are more likely to present with an immunocompromised condition, either from cancer itself or from the treatments they receive. A major consideration in the delivery of cancer care during the pandemic is to balance the risk of patient exposure and infection with the need to provide effective cancer treatment. Many aspects of the SARS-CoV-2 infection currently remain poorly characterized and even less is known about the course of infection in the context of a patient with cancer. As SARS-CoV-2 is highly contagious, the risk of infection directly affects the cancer patient being treated, other cancer patients in close proximity, and health care providers. Infection at any level for patients or providers can cause considerable disruption to even the most effective treatment plans. Lung cancer patients, especially those with reduced lung function and cardiopulmonary comorbidities are more likely to have increased risk and mortality from coronavirus disease 2019 as one of its common manifestations is as an acute respiratory illness. The purpose of this manuscript is to present a practical multidisciplinary and international overview to assist in treatment for lung cancer patients during this pandemic, with the caveat that evidence is lacking in many areas. It is expected that firmer recommendations can be developed as more evidence becomes available.

[Genetic determinants of lung cancer prognosis in never smokers: A pooled analysis in the International Lung Cancer Consortium](#)

Cancer Epidemiol Biomarkers Prev. 2020 Jul

22;cebp.0248.2020. doi: 10.1158/1055-9965.EPI-20-0248. Online ahead of print. Yonathan Brhane ¹,

Ping Yang ², David C Christiani ³, et al.

BACKGROUND: Lung cancer remains the leading cause of cancer death worldwide with 15-20% 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 1569 never-smoking lung cancer patients of European ancestry from 10 ILCCO studies were included. Hazard ratios(HRs) and 95% confidence intervals of overall survival were estimated. We assessed whether the associations were mediated through mRNA expression based 1553 normal lung tissues from the Lung expression quantitative trait loci(eQTL) dataset and 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=3.60x10⁻⁸),

and altered mRNA expression of LMO7DN in lung tissue(GTE_x, $p=9.40 \times 10^{-7}$; Lung eQTL dataset, $p=0.003$). Furthermore, two of 11 independent loci that reached the suggestive significance level($p < 10^{-6}$) were significant eQTL affecting mRNA expression of nearby gene 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), $p=6.92 \times 10^{-7}$) 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.

[COVID-19 in patients with thoracic malignancies \(TERAVOLT\): first results of an international, registry-based, cohort study](#) Lancet Oncol. 2020 Jul;21(7):914-922. doi: 10.1016/S1470-2045(20)30314-4. Epub 2020 Jun 12 Marina Chiara Garassino ¹, Jennifer G Whisenant ², Li-Ching Huang ³, et al.

BACKGROUND: Early reports on patients with cancer and COVID-19 have suggested a high mortality rate compared with the general population. Patients with thoracic malignancies are thought to be particularly susceptible to COVID-19 given their older age, smoking habits, and pre-existing cardiopulmonary comorbidities, in addition to cancer treatments. We aimed to study the effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on patients with thoracic malignancies. **METHODS:** The Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry is a multicentre observational study composed of a cross-sectional component and a longitudinal cohort component. Eligibility criteria were the presence of any thoracic cancer (non-small-cell lung cancer [NSCLC], small-cell lung cancer, mesothelioma, thymic epithelial tumours, and other pulmonary neuroendocrine neoplasms) and a COVID-19 diagnosis, either laboratory confirmed with RT-PCR, suspected with symptoms and contacts, or radiologically suspected cases with lung imaging features consistent with COVID-19 pneumonia and symptoms. Patients of any age, sex, histology, or stage were considered eligible, including those in active treatment and clinical follow-up. Clinical data were extracted from medical records of consecutive patients from Jan 1, 2020, and will be collected until the end of pandemic declared by WHO. Data on demographics, oncological history and comorbidities, COVID-19 diagnosis, and course of illness and clinical outcomes were collected. Associations between demographic or clinical characteristics and outcomes were measured with odds ratios (ORs) with 95% CIs using univariable and multivariable logistic regression, with sex, age, smoking status, hypertension, and chronic obstructive pulmonary disease included in multivariable analysis. This is a preliminary analysis of the first 200 patients. The registry continues to accept new sites and patient data. **FINDINGS:** Between March 26 and April 12, 2020, 200 patients with COVID-19 and thoracic cancers from eight countries were identified and included in the TERAVOLT registry; median age was 68.0 years (61.8-75.0) and the majority had an Eastern Cooperative Oncology Group performance status of 0-1 (142 [72%] of 196 patients), were current or former smokers (159 [81%] of 196), had non-small-cell lung cancer (151 [76%] of 200), and were on therapy at the time of COVID-19 diagnosis (147 [74%] of 199), with 112 (57%) of 197 on first-line treatment. 152 (76%) patients were hospitalised and 66 (33%) died. 13 (10%) of 134 patients who met criteria for ICU admission were admitted to ICU; the remaining 121 were hospitalised, but were not admitted to ICU. Univariable analyses revealed that being older than 65 years (OR 1.88, 95% 1.00-3.62), being a current or former smoker (4.24, 1.70-12.95), receiving treatment with chemotherapy alone (2.54, 1.09-6.11), and the presence of any comorbidities (2.65, 1.09-7.46) were associated with increased risk of death. However, in multivariable analysis, only smoking history (OR 3.18, 95% CI 1.11-9.06) was associated with increased risk of death. **INTERPRETATION:** With an ongoing global pandemic of COVID-19, our data suggest high mortality and low admission to intensive

care in patients with thoracic cancer. Whether mortality could be reduced with treatment in intensive care remains to be determined. With improved cancer therapeutic options, access to intensive care should be discussed in a multidisciplinary setting based on cancer specific mortality and patients' preference.

[Alternative Multidisciplinary Management Options for Locally Advanced NSCLC During the Coronavirus Disease 2019 Global Pandemic](#) J Thorac Oncol. 2020 Jul;15(7):1137-1146. doi:

10.1016/j.jtho.2020.04.016. Epub 2020 Apr 28. Sameera Kumar ¹, Steven Chmura ², Clifford Robinson ³, et al.

The coronavirus disease 2019 (COVID-19) pandemic is currently accelerating. Patients with locally advanced NSCLC (LA-NSCLC) may require treatment in locations where resources are limited, and the prevalence of infection is high. Patients with LA-NSCLC frequently present with comorbidities that increase the risk of severe morbidity and mortality from COVID-19. These risks may be further increased by treatments for LA-NSCLC. Although guiding data is scarce, we present an expert thoracic oncology multidisciplinary (radiation oncology, medical oncology, surgical oncology) consensus of alternative strategies for the treatment of LA-NSCLC during a pandemic. The overarching goals of these approaches are the following: (1) reduce the number of visits to a health care facility, (2) reduce the risk of exposure to severe acute respiratory syndrome-coronavirus-2, (3) attenuate the immunocompromising effects of lung cancer therapies, and (4) provide effective oncologic therapy. Patients with resectable disease can be treated with definitive nonoperative management if surgical resources are limited or the risks of perioperative care are high. Nonoperative options include chemotherapy, chemoimmunotherapy, and radiation therapy with sequential schedules that may or may not affect long-term outcomes in an era in which immunotherapy is available. The order of treatments may be on the basis of patient factors and clinical resources. Whenever radiation therapy is delivered without concurrent chemotherapy, hypofractionated schedules are appropriate. For patients who are confirmed to have COVID-19, usually, cancer therapies may be withheld until symptoms have resolved with negative viral test results. The risk of severe treatment-related morbidity and mortality is increased for patients undergoing treatment for LA-NSCLC during the COVID-19 pandemic. Adapting alternative treatment strategies as quickly as possible may save lives and should be implemented through communication with the multidisciplinary cancer team.

[Expanding Access to Lung Cancer Clinical Trials by Reducing the Use of Restrictive Exclusion Criteria: Perspectives of a Multistakeholder Working Group](#) Clin Lung Cancer. 2020 Jul;21(4):295-

307. doi: 10.1016/j.clc.2020.02.008. Epub 2020 Feb 26. Patrick M Forde ¹, Phil Bonomi ², Alice Shaw ³, et al.

Low rates of adult patient participation have been a persistent problem in cancer clinical trials and have continued to be a barrier to efficient drug development. The routine use of significant exclusion criteria has contributed to this problem by limiting participation in studies and creating significant clinical differences between the study cohorts and the real-world cancer patient populations. These routine exclusions also unnecessarily restrict opportunities for many patients to access potentially promising new therapies during clinical development. Multiple efforts are underway to broaden eligibility criteria, allowing more patients to enroll in studies and generating more robust data regarding the effect of novel therapies in the population at large. Focusing specifically on lung cancer as an example, a multi-stakeholder working group empaneled by the LUNGeVity Foundation identified 14 restrictive and potentially outdated exclusion criteria that appear frequently in lung cancer clinical trials. As a part of the project, the group evaluated data from multiple recent lung cancer studies to ascertain the extent to which these 14 criteria appeared in study protocols and played a role in excluding patients (screen failures). The present report describes the working group's efforts to limit the use of these routine exclusions and presents clinical justifications for reducing the use of 14 criteria as routine exclusions in lung cancer

studies, potentially expanding trial eligibility and improving the generalizability of the results from lung cancer trials.

[Comprehensive mapping of immune perturbations associated with severe COVID-19](#)

Sci Immunol. 2020 Jul 15;5(49):eabd7114. doi: 10.1126/sciimmunol.abd7114. Leticia Kuri-Cervantes # 1 2 , M Betina Pampena # 1 2 , Wenzhao Meng 3 , et al.

Although critical illness has been associated with SARS-CoV-2-induced hyperinflammation, the immune correlates of severe COVID-19 remain unclear. Here, we comprehensively analyzed peripheral blood immune perturbations in 42 SARS-CoV-2 infected and recovered individuals. We identified extensive induction and activation of multiple immune lineages, including T cell activation, oligoclonal plasmablast expansion, and Fc and trafficking receptor modulation on innate lymphocytes and granulocytes, that distinguished severe COVID-19 cases from healthy donors or SARS-CoV-2-recovered or moderate severity patients. We found the neutrophil to lymphocyte ratio to be a prognostic biomarker of disease severity and organ failure. Our findings demonstrate broad innate and adaptive leukocyte perturbations that distinguish dysregulated host responses in severe SARS-CoV-2 infection and warrant therapeutic investigation.

[Physical activity does not lower the risk of lung cancer](#) Cancer Res. 2020 Jul 9;canres.1127.2020. doi: 10.1158/0008-5472.CAN-20-1127. Online ahead of print. Sebastian-Edgar Baumeister 1 , Michael F Leitzmann 2 , et al.

Observational studies have suggested that physical activity might lower the risk of lung cancer in former and current smokers but not in never smokers. Using genetic instruments for self-reported and accelerometer-measured physical activity traits implemented through two-sample Mendelian randomization (MR), we sought to strengthen the evidence for causality. We used 18 genome-wide significant ($P < 5 \times 10^{-8}$) single nucleotide polymorphisms (SNP) for self-reported moderate-to-vigorous physical activity and seven SNP for accelerometer-measured ('average acceleration') physical activity from up to 377,234 UK Biobank participants and evaluated these in relation to risk using 29,266 lung cancer cases (including 11,273 adenocarcinomas, 7,426 squamous cell carcinoma and 2,664 small cell carcinoma cases) and 56,450 controls. MR analysis suggested no effect of self-reported physical activity (odds ratio (OR) [95% confidence interval (CI)] = 0.67 [0.42-1.05], P-value = 0.081, Q-value = 0.243) and accelerometer-measured activity (OR [95% CI] = 0.98 [0.93-1.03], P-value = 0.372, Q-value = 0.562) on lung cancer. There was no evidence for associations of physical activity with histologic types and lung cancer in ever and never smokers. Replication analysis using genetic instruments from a different genome-wide study and sensitivity analysis to address potential pleiotropic effects led to no substantive change in estimates. Collectively, these findings do not support a protective relationship between physical activity and the risk of lung cancer.

[The Associations of Interstitial Lung Abnormalities with Cancer Diagnoses and Mortality](#)

Eur Respir J. 2020 Jul 9;1902154. doi: 10.1183/13993003.02154-2019. Online ahead of print. Gisli T Axelsson 1 , Rachel K Putman 2 , Thor Aspelund 3 4 , et al.

An increased incidence of lung cancer is well-known among patients with idiopathic pulmonary fibrosis. It is unknown whether interstitial lung abnormalities, early fibrotic changes of the lung, are a risk factor for lung cancer in the general population. The study's objective was to assess whether interstitial lung abnormalities were associated with diagnoses of, and mortality from, lung cancer and other cancers. Data from the AGES-Reykjavik study, a cohort of 5764 elderly Icelanders, were used. Outcome data were ascertained from electronic medical records. Gray's tests, Cox proportional hazards models and proportional subdistribution hazards models were used to analyse associations of interstitial lung

abnormalities with lung cancer diagnoses and lung cancer mortality as well as diagnoses and mortality from all cancers. Participants with interstitial lung abnormalities had greater cumulative incidence of lung cancer diagnoses ($p < 0.001$) and lung cancer mortality ($p < 0.001$) than others. Interstitial lung abnormalities were associated with an increased hazard of lung cancer diagnosis ($HR = 2.77$) and lung cancer mortality ($HR = 2.89$) in adjusted Cox models. Associations of interstitial lung abnormalities with all cancers were found in models including lung cancers but not in models excluding lung cancers. People with interstitial lung abnormalities are at increased risk of lung cancer and lung cancer mortality, but not of other cancers. This implies that an association between fibrotic and neoplastic lung diseases of the lung exists from the early stages of lung fibrosis and suggests interstitial lung abnormalities as a risk factor in lung cancer screening efforts.

[The effect of Medicaid expansion among adults from low-income communities on stage at diagnosis in those with screening-amenable cancers](#) Cancer. 2020 Jul 6. doi: 10.1002/cncr.32895. Online ahead of print. Uriel Kim ^{1 2}, Siran Koroukian ^{2 3 4}, Abby Statler ^{2 5}, Johnie Rose ^{1 2 4}

BACKGROUND: Several states have opted to expand Medicaid under the Patient Protection and Affordable Care Act (ACA), which offers insurance coverage to low-income individuals up to 138% of the federal poverty level. This expansion of Medicaid to a medically vulnerable population potentially can reduce cancer outcome disparities, especially among patients with screening-amenable cancers. The objective of the current study was to estimate the effect of Medicaid expansion on the percentage of adults from low-income communities with screening-amenable cancers who present with metastatic disease. **METHODS:** Using state cancer registry data linked with block group-level income data, a total of 12,760 individuals aged 30 to 64 years who were diagnosed with incident invasive breast (female), cervical, colorectal, or lung cancer from 2011 through 2016 and who were uninsured or had Medicaid insurance at the time of diagnosis were identified. This sample was probability weighted based on income to reflect potential Medicaid eligibility under the ACA's Medicaid expansion. A multivariable logistic model then was fitted to examine the independent association between the exposure (pre-expansion [years 2011-2013] vs postexpansion [years 2014-2016]) and the outcome (metastatic vs nonmetastatic disease at the time of diagnosis). **RESULTS:** After adjusting for potential confounders, individuals who were diagnosed postexpansion were found to have 15% lower odds of having metastatic disease compared with those who were diagnosed pre-expansion (adjusted odds ratio, 0.85; 95% confidence interval, 0.77-0.93). As a control, a separate analysis that focused on individuals with private insurance who resided in high-income communities found nonsignificant postexpansion (vs pre-expansion) changes in the outcome (adjusted odds ratio, 1.02; 95% confidence interval, 0.96-1.09). **CONCLUSIONS:** Medicaid expansion is associated with a narrowing of a critical cancer outcome disparity in adults from low-income communities.

[Does Medicare Coverage Improve Cancer Detection and Mortality Outcomes?](#) J Policy Anal Manage. Summer 2020;39(3):577-604. doi: 10.1002/pam.22199. Epub 2020 Jan 12.

Rebecca M Myerson, Reginald D Tucker-Seeley, Dana P Goldman, Darius N Lakdawalla Medicare is a large government health insurance program in the United States that covers about 60 million people. This paper analyzes the effects of Medicare insurance on health for a group of people in urgent need of medical care: people with cancer. We used a regression discontinuity design to assess impacts of near-universal Medicare insurance at age 65 on cancer detection and outcomes, using population-based cancer registries and vital statistics data. Our analysis focused on the three tumor sites for which screening is recommended both before and after age 65: breast, colorectal, and lung cancer. At age 65, cancer detection increased by 72 per 100,000 population among women and 33 per 100,000 population among men; cancer mortality also decreased by nine per 100,000 population for women but did not significantly change for men. In a placebo check, we found no comparable changes at age 65 in

Canada. This study provides the first evidence to our knowledge that near-universal access to Medicare at age 65 is associated with improvements in population-level cancer mortality.