



## Caring Ambassadors Lung Cancer Program Literature Review, April 2020

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### **BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES**

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#### **[Immunization against ROS1 by DNA Electroporation Impairs K-Ras-Driven Lung](#)**

**[Adenocarcinomas](#)** . Riccardo F1, Barutello G1, Petito A1, et al. Vaccines (Basel). 2020 Apr 6;8(2). pii: E166. doi: 10.3390/vaccines8020166.

Non-small cell lung cancer (NSCLC) is still the leading cause of cancer death worldwide. Despite the introduction of tyrosine kinase inhibitors and immunotherapeutic approaches, there is still an urgent need for novel strategies to improve patient survival. ROS1, a tyrosine kinase receptor endowed with oncoantigen features, is activated by chromosomal rearrangement or overexpression in NSCLC and in several tumor histotypes. In this work, we have exploited transgenic mice harboring the activated K-Ras oncogene (K-RasG12D) that spontaneously develop metastatic NSCLC as a preclinical model to test the efficacy of ROS1 immune targeting. Indeed, qPCR and immunohistochemical analyses revealed ROS1 overexpression in the autochthonous primary tumors and extrathoracic metastases developed by K-RasG12D mice and in a derived transplantable cell line. As proof of concept, we have evaluated the effects of the intramuscular electroporation (electrovaccination) of plasmids coding for mouse- and human-ROS1 on the progression of these NSCLC models. A significant increase in survival was observed in ROS1-electrovaccinated mice challenged with the transplantable cell line. It is worth noting that tumors were completely rejected, and immune memory was achieved, albeit only in a few mice. Most importantly, ROS1 electrovaccination was also found to be effective in slowing the development of autochthonous NSCLC in K-RasG12D mice.

#### **[Inhibition of MEK alone and in combination with ALK inhibition suppresses tumor growth in a mouse model of ALK positive lung cancer](#)**.

Shrestha N1, Bland AR1, Bower RL1, Rosengren R2, Ashton J3. J Pharmacol Exp Ther. 2020 Apr 13. pii: jpet.120.266049. doi: 10.1124/jpet.120.266049. [Epub ahead of print]

Anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer most commonly arises through EML4-ALK chromosomal fusion. We have previously demonstrated that combination of the ALK inhibitor crizotinib with the MEK inhibitor selumetinib was highly effective at reducing cell viability of ALK-positive NSCLC (H3122) cells. In this study, we further investigated the efficacy of crizotinib and

selumetinib combination therapy in an in vivo xenograft model of ALK-positive lung cancer. Crizotinib decreased tumor volume by 52% compared to control, and the drug combination reduced tumor growth compared to crizotinib. In addition, MEK inhibition alone reduced tumor growth by 59% compared to control. Crizotinib, selumetinib, alone and in combination were non-toxic at the dose of 25 mg/kg with values for ALT (< 80 U/L) and creatinine (<2 mg/dL) within the normal range. Our results support the combined use of crizotinib with selumetinib in ALK-positive lung cancer but raise the possibility that a sufficient dose of a MEK inhibitor alone may be as effective as adding a MEK inhibitor to an ALK inhibitor. SIGNIFICANCE STATEMENT: This study contains in vivo evidence supporting the use of combination MEK inhibitors in ALK+ lung cancer research, both singularly and in combination with ALK inhibitors. Contrary to previously published reports, our results suggest that is possible to gain much of the benefit from combination treatment with a MEK inhibitor alone, at a tolerable dose.

**Specific gut microbiome signature predicts the early-stage lung cancer.** Zheng Y1, Fang Z1, Xue Y1, et al. Gut Microbes. 2020 Apr 2:1-13. doi: 10.1080/19490976.2020.1737487. [Epub ahead of print] Alterations of gut microbiota have been implicated in multiple diseases including cancer. However, the gut microbiota spectrum in lung cancer remains largely unknown. Here we profiled the gut microbiota composition in a discovery cohort containing 42 early-stage lung cancer patients and 65 healthy individuals through the 16S ribosomal RNA (rRNA) gene sequencing analysis. We found that lung cancer patients displayed a significant shift of microbiota composition in contrast to the healthy populations. To identify the optimal microbiota signature for noninvasive diagnosis purpose, we took advantage of Support-Vector Machine (SVM) and found that the predictive model with 13 operational taxonomic unit (OTU)-based biomarkers achieved a high accuracy in lung cancer prediction (area under curve, AUC = 97.6%). This signature performed reasonably well in the validation cohort (AUC = 76.4%), which contained 34 lung cancer patients and 40 healthy individuals. To facilitate potential clinical practice, we further constructed a 'patient discrimination index' (PDI), which largely retained the prediction efficiency in both the discovery cohort (AUC = 92.4%) and the validation cohort (AUC = 67.7%). Together, our study uncovered the microbiota spectrum of lung cancer patients and established the specific gut microbial signature for the potential prediction of the early-stage lung cancer.

**KMT2D Deficiency Impairs Super-Enhancers to Confer a Glycolytic Vulnerability in Lung Cancer.**

Alam H1, Tang M2, Maitituoheti M2, et al. Cancer Cell. 2020 Apr 13;37(4):599-617.e7. doi: 10.1016/j.ccell.2020.03.005. Epub 2020 Apr 2.

Epigenetic modifiers frequently harbor loss-of-function mutations in lung cancer, but their tumor-suppressive roles are poorly characterized. Histone methyltransferase KMT2D (a COMPASS-like enzyme, also called MLL4) is among the most highly inactivated epigenetic modifiers in lung cancer. Here, we show that lung-specific loss of Kmt2d promotes lung tumorigenesis in mice and upregulates pro-tumorigenic programs, including glycolysis. Pharmacological inhibition of glycolysis preferentially impedes tumorigenicity of human lung cancer cells bearing KMT2D-inactivating mutations. Mechanistically, Kmt2d loss widely impairs epigenomic signals for super-enhancers/enhancers, including the super-enhancer for the circadian rhythm repressor Per2. Loss of Kmt2d decreases expression of PER2, which regulates multiple glycolytic genes. These findings indicate that KMT2D is a lung tumor suppressor and that KMT2D deficiency confers a therapeutic vulnerability to glycolytic inhibitors.

**CLEC3B as a potential diagnostic and prognostic biomarker in lung cancer and association with the immune microenvironment.** Sun J#1,2, Xie T#1,2, Jamal M2, Tu Z2, Li X3, Wu Y4, Li J2, Zhang Q2, Huang X1. Cancer Cell Int. 2020 Apr 1;20:106. doi: 10.1186/s12935-020-01183-1. eCollection 2020.

**BACKGROUND:** Lung cancer is the leading cause of cancer-related mortality globally. Discovering effective biomarkers for early diagnosis and prognosis is important to reduce the mortality rate and ensure

efficient therapy for lung cancer patients. C-type lectin domain family 3 member B (CLEC3B) has been reported in various cancers, but its correlation with lung cancer remains elusive. **METHODS:** The GEO, TCGA and Oncomine databases were analyzed to examine the expression of CLEC3B in lung cancer. The CLEC3B mRNA levels in 15 patient tissue samples were detected by real-time PCR and the CLEC3B protein levels in 34 patient tissue samples were detected by immunohistochemistry. A Chi-square test was performed to analyze the correlation of CLEC3B expression and clinicopathological factors. The diagnostic value of CLEC3B was revealed by receiver operating characteristic (ROC) curves. Univariate and multivariate Cox proportional hazards regression models and Kaplan-Meier plots were used to evaluate the prognostic value of CLEC3B in lung cancer. The TIMER database was used to evaluate the correlation of CLEC3B and immune infiltration. Gene set enrichment analysis revealed tumor-associated biological processes related to CLEC3B. **RESULTS:** CLEC3B is significantly downregulated in lung cancer patients compared with nontumor controls according to database analysis and patient tissue sample detection ( $p < 0.001$ ). Specifically, CLEC3B is significantly downregulated in stage IA lung cancer patients ( $p < 0.001$ ) and has a high diagnostic accuracy (area under the receiver operating characteristic curve  $> 0.9$ ). Moreover, low expression of CLEC3B is related to poor progression-free survival (HR = 0.60, 95% CI 0.49-0.74,  $p = 8.3e-07$ ) and overall survival (HR = 0.66, 95% CI 0.58-0.75,  $p = 2.1e-10$ ), indicating it as a risk factor for lung cancer. Multivariate analysis value showed that low expression of CLEC3B may be an independent risk factor for disease-free survival in lung cancer patients (HR = 0.655, 95% CI 0.430-0.996, Cox  $p = 0.048$ ). In addition, we also investigated the potential role of CLEC3B in tumor-immune interactions and found that CLEC3B might be associated with the immune infiltration and immune activation of lung cancer, especially in squamous cell carcinoma. **CONCLUSIONS:** Our findings indicate that CLEC3B expression is downregulated in lung cancer and reveal the diagnostic and prognostic potential of CLEC3B in lung cancer and its potential as an immune-related therapeutic target in lung cancer.

[Aspirin-targeted PD-L1 in lung cancer growth inhibition.](#) Zhang Y1, Lv C1, Dong Y2, Yang Q3. Thorac Cancer. 2020 Apr 15. doi: 10.1111/1759-7714.13433. [Epub ahead of print]

**BACKGROUND:** Aspirin is a classic anti-inflammatory drug and its anticancer effect has been previously explored in many types of cancer including colorectal cancer therapy. Programmed cell death-ligand 1 (PD-L1) is widely expressed in tumor cells and displays an inhibitory role in antitumor immunity. This study aimed to clarify the role of PD-L1 in aspirin-suppressed lung cancer. **METHODS:** The inhibitory effect of aspirin on lung cancer cell proliferation was assessed using an MTT cell viability assay. The role of aspirin in the modulation of PD-L1 expression was analyzed by western blot or RT-PCR assays. In lung cancer cells, the influence of aspirin on PD-L1 promoter activity was detected using a luciferase reporter assay. The interaction of TAZ with PD-L1 promoter in the cells, with or without aspirin administration, was tested via chromatin immunoprecipitation (ChIP) analysis. The function of PD-L1 in aspirin-mediated growth inhibition of lung cancer was examined using a cell viability assay. **RESULTS:** Following treatment with aspirin, lung cancer cell growth was markedly suppressed. Aspirin was able to markedly decrease the expression of PD-L1 at the mRNA and protein levels in lung cancer cells. For the mechanism study, we found that the promoter of PD-L1 was inactivated by aspirin via TAZ transcriptional coactivator in the cells. With regard to the functional investigation, aspirin was capable of resisting cell proliferation and PD-L1 overexpression abolished aspirin-depressed cell proliferation in lung cancer. **CONCLUSIONS:** Aspirin suppressed the growth of lung cancer cells via targeting the TAZ/PD-L1 axis.

[RAD51Bme Levels as a Potential Predictive Biomarker for PD-1 Blockade Response in Non-Small Cell Lung Cancer.](#) Guerreiro IM1, Barros-Silva D2, Lopes P2,3, Cantante M2,3, et al. J Clin Med. 2020 Apr 2;9(4). pii: E1000. doi: 10.3390/jcm9041000.

Lung cancer (LC) cells frequently express high levels of programmed death-ligand 1 (PD-L1). Although these levels grossly correlate with the likelihood of response to specific checkpoint inhibitors, the response prediction is rather imperfect, and more accurate predictive biomarkers are mandatory. We examined the methylation profile of RAD51B (RAD51Bme) as a candidate predictive biomarker for anti-PD-1 therapy efficacy in non-small cell lung cancer (NSCLC), correlating with patients' outcome. PD-L1 immunoexpression and RAD51Bme levels were analysed in NSCLC samples obtained from patients not treated with anti-PD-1 (Untreated Cohort (#1)) and patients treated with PD-1 blockade (Treated Cohort (#2)). Of a total of 127 patients assessed, 58.3% depicted PD-L1 positivity (PD-L1+). RAD51Bme levels were significantly associated with PD-L1 immunoexpression. Patients with PD-1 blockade clinical benefit disclosed higher RAD51Bme levels ( $p = 0.0390$ ) and significantly lower risk of disease progression (HR 0.37; 95% CI: 0.15-0.88;  $p = 0.025$ ). Combining RAD51Bme+ with PD-L1+ improved the sensitivity of the test to predict immunotherapy response. PD-L1+ was also associated with lower risk of death (HR 0.35; 95% CI: 0.15-0.81;  $p = 0.014$ ). Thus, RAD51Bme levels might be combined with validated predictive biomarker PD-L1 immunostaining to select patients who will most likely experience clinical benefit from PD-1 blockade. The predictive value of RAD51Bme should be confirmed in prospective studies.

[Preclinical model of stereotactic ablative lung irradiation using arc delivery in the mouse: effect of beam size changes and dose effect at constant collimation.](#) Bertho A1, Santos MD2, Buard V1, Paget V1, Guipaud O1, Tarlet G1, Milliat F1, François A3. Int J Radiat Oncol Biol Phys. 2020 Apr 9. pii: S0360-3016(20)30934-2. doi: 10.1016/j.ijrobp.2020.03.011. [Epub ahead of print]

**PURPOSE:** Stereotactic body radiation therapy is a therapeutic option offered to high surgical risk cancer patients with lung cancer. Focal lung irradiation in mice is a new preclinical model to help understand the development of lung damage in this context. Here we developed a mouse model of lung stereotactic therapy using arc delivery and monitored the development of lung damage while varying beam size and dose delivered. **METHODS AND MATERIALS:** C57BL/6JRj mice were exposed to 90 Gy focal irradiation on the left lung, using 1 mm diameter, 3 x 3 mm<sup>2</sup>, 7 x 7 mm<sup>2</sup> or 10 x 10 mm<sup>2</sup> beam collimation for beam size effect, and using 3 x 3 mm<sup>2</sup> beam collimation delivering 20 to 120 Gy for dose effect. Long-term lung damage was monitored with micro-CT imaging together with anatomopathological and gene expression measurements in the injured patch and the ipsilateral and contralateral lungs. **RESULTS:** Both 1 mm diameter and 3 x 3 mm<sup>2</sup> beam collimation allow long-term studies, but only 3 mm beam collimation generates lung fibrosis when delivering 90 Gy. Dose-effect studies with constant 3 mm beam collimation revealed a dose of 60 Gy as the minimum to obtain lung fibrosis 6 months post-exposure. Lung fibrosis development was associated with club cell depletion and increased type II pneumocyte numbers. Lung injury developed with ipsilateral and contralateral consequences such as parenchymal thickening and gene expression modifications. **CONCLUSIONS:** Arc therapy allows long-term studies and dose escalation without lethality. In our dose-delivering conditions, dose-effect studies revealed that 3 x 3 mm<sup>2</sup> beam collimation to a minimum single dose of 60 Gy enables preclinical models for the assessment of lung injury within a 6-month period. This model of lung tissue fibrosis in a time length compatible with mouse life span may offer good prospects for future mechanistic studies.

[Transcription factor c-Maf is a checkpoint that programs macrophages in lung cancer.](#) Liu M1, Tong Z1, Ding C1, et al. J Clin Invest. 2020 Apr 1;130(4):2081-2096. doi: 10.1172/JCI131335. Macrophages have been linked to tumor initiation, progression, metastasis, and treatment resistance. However, the transcriptional regulation of macrophages driving the protumor function remains elusive. Here, we demonstrate that the transcription factor c-Maf is a critical controller for immunosuppressive macrophage polarization and function in cancer. c-Maf controls many M2-related genes and has direct binding sites within a conserved noncoding sequence of the Csf-1r gene and promotes M2-like



macrophage-mediated T cell suppression and tumor progression. c-Maf also serves as a metabolic checkpoint regulating the TCA cycle and UDP-GlcNAc biosynthesis, thus promoting M2-like macrophage polarization and activation. Additionally, c-Maf is highly expressed in tumor-associated macrophages (TAMs) and regulates TAM immunosuppressive function. Deletion of c-Maf specifically in myeloid cells results in reduced tumor burden with enhanced antitumor T cell immunity. Inhibition of c-Maf partly overcomes resistance to anti-PD-1 therapy in a subcutaneous LLC tumor model. Similarly, c-Maf is expressed in human M2 and tumor-infiltrating macrophages/monocytes as well as circulating monocytes of human non-small cell lung carcinoma (NSCLC) patients and critically regulates their immunosuppressive activity. The natural compound  $\beta$ -glucan downregulates c-Maf expression on macrophages, leading to enhanced antitumor immunity in mice. These findings establish a paradigm for immunosuppressive macrophage polarization and transcriptional regulation by c-Maf and suggest that c-Maf is a potential target for effective tumor immunotherapy.

[Suppression of the SLC7A11/glutathione axis causes synthetic lethality in KRAS-mutant lung adenocarcinoma.](#) Hu K1,2, Li K1, Lv J1, et al. J Clin Invest. 2020 Apr 1;130(4):1752-1766. doi: 10.1172/JCI124049.

Oncogenic KRAS is a major driver in lung adenocarcinoma (LUAD) that has yet to be therapeutically conquered. Here we report that the SLC7A11/glutathione axis displays metabolic synthetic lethality with oncogenic KRAS. Through metabolomics approaches, we found that mutationally activated KRAS strikingly increased intracellular cystine levels and glutathione biosynthesis. SLC7A11, a cystine/glutamate antiporter conferring specificity for cystine uptake, was overexpressed in patients with KRAS-mutant LUAD and showed positive association with tumor progression. Furthermore, SLC7A11 inhibition by either genetic depletion or pharmacological inhibition with sulfasalazine resulted in selective killing across a panel of KRAS-mutant cancer cells in vitro and tumor growth inhibition in vivo, suggesting the functionality and specificity of SLC7A11 as a therapeutic target. Importantly, we further identified a potent SLC7A11 inhibitor, HG106, that markedly decreased cystine uptake and intracellular glutathione biosynthesis. Furthermore, HG106 exhibited selective cytotoxicity toward KRAS-mutant cells by increasing oxidative stress- and ER stress-mediated cell apoptosis. Of note, treatment of KRAS-mutant LUAD with HG106 in several preclinical lung cancer mouse models led to marked tumor suppression and prolonged survival. Overall, our findings reveal that KRAS-mutant LUAD cells are vulnerable to SLC7A11 inhibition, offering potential therapeutic approaches for this currently incurable disease.

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## SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

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[Protocol and Rationale for the International Lung Screening Trial.](#) Lim KP1,2, Marshall H3, Tammemägi M4, et al. Ann Am Thorac Soc. 2020 Apr;17(4):503-512. doi: 10.1513/AnnalsATS.201902-102OC.

**RATIONALE:** The NLST (National Lung Screening Trial) reported a 20% reduction in lung cancer mortality with low-dose computed tomography screening; however, important questions on how to optimize screening remain, including which selection criteria are most accurate at detecting lung cancers and what nodule management protocol is most efficient. The PLCOm2012 (Prostate, Lung, Colorectal and Ovarian) Cancer Screening Trial 6-year and PanCan (Pan-Canadian Early Detection of Lung Cancer) nodule malignancy risk models are two of the better validated risk prediction models for screenee selection and nodule management, respectively. Combined use of these models for participant selection and nodule management could significantly improve screening efficiency. **OBJECTIVES:** The ILST (International Lung Screening Trial) is a prospective cohort study with two primary aims: 1) Compare the accuracy of the PLCOm2012 model against U.S. Preventive Services Task Force (USPSTF) criteria for detecting lung cancers and 2) evaluate nodule management efficiency using the PanCan nodule

probability calculator-based protocol versus Lung-RADS. **METHODS:** ILST will recruit 4,500 participants who meet USPSTF and/or PLCom2012 risk  $\geq 1.51\%$ /6-year selection criteria. Participants will undergo baseline and 2-year low-dose computed tomography screening. Baseline nodules are managed according to PanCan probability score. Participants will be followed up for a minimum of 5 years. Primary outcomes for aim 1 are the proportion of individuals selected for screening, proportion of lung cancers detected, and positive predictive values of either selection criteria, and outcomes for aim 2 include comparing distributions of individuals and the proportion of lung cancers in each of three management groups: next surveillance scan, early recall scan, or diagnostic evaluation recommended. Statistical powers to detect differences in the four components of primary study aims were  $\geq 82\%$ . **CONCLUSIONS:** ILST will prospectively evaluate the comparative accuracy and effectiveness of two promising multivariable risk models for screenee selection and nodule management in lung cancer screening. Clinical trial registered with [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT02871856).

**Circulating tumour DNA: A new biomarker to monitor resistance in NSCLC patients treated with EGFR-TKIs.** Diao Z1, Han Y2, Zhang R2, Li J3. *Biochim Biophys Acta Rev Cancer*. 2020 Apr 8;1873(2):188363. doi: 10.1016/j.bbcan.2020.188363. [Epub ahead of print]

Targeted molecular therapies have markedly improved the therapeutic management of lung cancer, while the discovery of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) has revolutionized the treatment of non-small cell lung cancer (NSCLC). However, the clinical benefit of targeted therapies is limited by the eventual emergence of resistance. Identifying and monitoring the underlying mechanism of EGFR-TKI resistance could lead to more precise therapy and advances in treatment. Presently, tissue biopsy remains the gold standard for genotyping but it is limited by sampling bias, lack of available tissue, and potential complications. Analysis of circulating tumour DNA (ctDNA) may overcome the current limitations of tissue biopsies and provide a comprehensive landscape of the resistance mechanisms in a minimally invasive manner. Well-developed, analytically valid detection technologies are prerequisites for integrating ctDNA detection into clinical cancer management. Here, we provide an overview of available methodologies for ctDNA detection and we also discuss the potential clinical applications of ctDNA to monitor the resistance mechanisms.

**Examining Gender Differences in Lung Cancer Screening.** Randhawa S1, Sferra SR2, Das C3, Kaiser LR4, Ma GX5, Erkmen CP6. *J Community Health*. 2020 Apr 22. doi: 10.1007/s10900-020-00826-8. [Epub ahead of print]

It is unknown if gender influences outcome of lung cancer screening with Low Dose CT (LDCT), especially with frequent and continued underrepresentation of women in clinical trials. We examined a balanced cohort of men and women with the hypothesis that there would be no difference in participation or results between men and women undergoing lung cancer screening. In an urban, academic medical center, we prospectively collected data on patients referred for lung cancer screening from October 2015 to August 2018. We studied gender, age, ethnicity, level of education and smoking history. We measured results of LDCT using Lung-RADS reporting system. 546 patients underwent LDCT between October 2015 and August 2018. 279 (51%) were female and 267 (49%) were males. Age, education status or smoking patterns did not significantly differ between females and males. There was a significant difference between males and females in the distribution of LDCT results ( $p = 0.05$ ). 81 females and 105 males were diagnosed with Lung-RADS 1; 99 females and 92 males with Lung-RADS 2; 15 females and 8 males with Lung-RADS 3; 19 females and 11 males with Lung-RADS 4. Overall, 10 females (3.5%) and 3 males (1.1%) were diagnosed with lung cancer (risk difference 2.4, 95% CI-0.0006-0.05,  $p = 0.09$ ). Women are often underrepresented in clinical trials. Preliminary results from our lung cancer screening program demonstrate equal participation and equal benefit from the screening program. Long term data is needed to study survival benefit.

**Meeting ACR Dose Guidelines for CT Lung Cancer Screening in an Overweight and Obese Population.**

Peng R1, Mardakhaev E2, Shmukler A2, Levsky JM2, Haramati LB2. Acad Radiol. 2020 Apr 10. pii: S1076-6332(20)30095-7. doi: 10.1016/j.acra.2020.02.009. [Epub ahead of print]

**RATIONALE AND OBJECTIVES:** Lung cancer screening adoption coincides with a growing obesity epidemic. Maintaining high-quality imaging at low radiation dose is challenging in obesity. We investigate the feasibility of meeting American College of Radiology (ACR) dose guidelines for lung cancer screening in a predominantly overweight and obese population. **MATERIALS AND METHODS:** Radiation dose (Volumetric CT dose index [CTDI<sub>vol</sub>], dose-length product), and body mass index (BMI) were collected for baseline screening CTs December, 2012-December, 2017. Dose metrics were analyzed according to BMI classification (normal <25, overweight 25-29, obese ≥30 kg/m<sup>2</sup>), using  $k = 0.014 \text{ mSv/mGy*cm}$ . Results were compared to ACR dose guidelines and mean national 2017 Lung Cancer Screening Registry dose metrics. Analysis used Kruskal-Wallis (SPSS, version 24.0.0, IBM corp, Armonk, NY). **RESULTS:** Study population comprised 1478 patients (49.2% [727] women: mean BMI  $28.1 \pm 6.5 \text{ kg/m}^2$ , 26.9% [397] normal weight, 35.9% [530] overweight, 37.2% [551] obese). ACR dose requirements were met for both genders in all BMI classifications. Dose metrics were higher in men than in women; median effective dose and CTDI<sub>vol</sub> were 1.39 (0.8-1.58) mSv and 2.78 (1.41-2.80) mGy in men versus 1.16 (0.71-1.43) mSv and 2.70 (1.4-2.78) mGy in women. There were significant differences in dose metrics between men and women in the same BMI classification and between BMI classifications ( $p < 0.001$ ). Mean dose metrics in our program were considerably lower than 2017 national average- mean CTDI<sub>vol</sub> and effective dose  $2.45 \pm 1.14 \text{ mGy}$  and  $1.26 \pm 0.59 \text{ mSv}$  versus  $3.24 \text{ mGy}$  and  $1.35 \text{ mSv}$ , respectively for our program and nationally. Mean dose metrics were also lower in our obese patients versus obese patients nationally. **CONCLUSION:** ACR dose metrics for lung cancer screening were met and can be appropriately tailored in a predominantly overweight and obese population clinical program.

**Lung Cancer Staging at Diagnosis in the Veterans Health Administration: Is Rurality an Influencing Factor? A Cross-sectional Study.**

Sanchez R1,2,3, Zhou Y4, Sarrazin MSV2,3,5, et al. J Rural Health. 2020 Apr 3. doi: 10.1111/jrh.12429. [Epub ahead of print]

**PURPOSE:** To evaluate the association between rurality and lung cancer stage at diagnosis. **METHODS:** We conducted a cross-sectional study using Veterans Health Administration (VHA) data to identify veterans newly diagnosed with lung cancer between 10/1/11 and 9/30/15. We defined rurality, based on place of residence, using Rural-Urban Commuting Area (RUCA) codes with the subcategories of urban, large rural, small rural, and isolated. We used multivariable logistic regression models to determine associations between rurality and stage at diagnosis, adjusting for sociodemographic and clinical characteristics. We also analyzed data using the RUCA code for patients' assigned primary care sites and driving distances to primary care clinics and medical centers. **FINDINGS:** We identified 4,220 veterans with small cell lung cancer (SCLC) and 25,978 with non-small cell lung cancer (NSCLC). Large rural residence (compared to urban) was associated with early stage diagnosis of NSCLC (OR = 1.12; 95% CI: 1.00-1.24) and SCLC (OR = 1.73; 95% CI: 1.18-1.55). However, the finding was significant only in the southern and western regions of the country. White race, female sex, chronic lung disease, higher comorbidity, receiving primary care, being a former tobacco user, and more recent year of diagnosis were also associated with diagnosing early stage NSCLC. Driving distance to medical centers was inversely associated with late-stage NSCLC diagnoses, particularly for large rural areas. **CONCLUSIONS:** We did not find clear associations between rurality and lung cancer stage at diagnosis. These findings highlight the complex relationship between rurality and lung cancer within VHA, suggesting access to care cannot be fully captured by current rurality codes.

### [Lung Cancer Screening Knowledge Among Internal Medicine Residents in a University Program.](#)

Urrutia Argueta S1, Hanna N2. J Cancer Educ. 2020 Apr 19. doi: 10.1007/s13187-020-01747-9. [Epub ahead of print]

Lung cancer remains the main cause of cancer-related death. Even though several societies recommend that certain populations may benefit from lung cancer screening with low-dose computed tomography (LDCT), its nationwide adoption has been slow. Practices in primary care are closely linked to residency training. Recognizing gaps in knowledge during training may translate into increased utilization of life-saving measures. Sixty internal medicine residents training at a university-based program were presented with an anonymous online-based survey designed to measure their knowledge about lung cancer screening. In the second phase, residents were presented with an infographic containing the answers to the initial survey. They were surveyed again 30 days after this intervention. The average correct response rate among all years was 42%. PGY-1 residents performed better compared with PGY-2 and PGY-3 residents ( $p = 0.015$ ). Ninety-two percent of residents did not think screening improved all-cause mortality. Less than half thought screening had a lung cancer-specific mortality benefit. Fifty-three percent rated their self-perceived knowledge above 50%. There was no difference in knowledge after the intervention. Specific populations may benefit from LDCT screening. Even if these benefits do not directly translate to population settings, the burden and mortality of lung cancer calls for urgent measures to attempt an earlier diagnosis. Internal medicine residents in this program may have several concerns about lung cancer screening including coverage, benefit, and false positive rate. Educational methods such as infographics may not be effective in improving knowledge among residents. Lung cancer screening should be a priority in medical education, especially in states with high smoking rates and lung cancer mortality.

[Assessment of Lung Cancer Screening Program Websites.](#) Clark SD1,2, Reuland DS1,2,3, Enyioha C4, Jonas DE1,2. AMA Intern Med. 2020 Apr 13. doi: 10.1001/jamainternmed.2020.0111. [Epub ahead of print]

**IMPORTANCE:** The US Preventive Services Task Force recommends that individuals at high risk for lung cancer consider benefits and harms before pursuing lung cancer screening. Medical centers develop websites for their lung cancer screening programs, but to date little is known about the websites' portrayal of benefits and harms or what next steps they recommend for individuals considering screening.

**OBJECTIVE:** To assess the presentation of potential benefits and harms and recommended next steps on lung cancer screening program websites. **DESIGN, SETTING, AND PARTICIPANTS:** Cross-sectional content analysis of 162 lung cancer screening program websites of academic medical centers ( $n = 81$ ) and state-matched community medical centers ( $n = 81$ ) that were randomly selected from American College of Radiology lung cancer screening-designated centers was conducted. The study was performed from December 1, 2018, to January 31, 2019. **MAIN OUTCOMES AND MEASURES:** Website presentation of screening-associated benefits and harms was the primary outcome. Benefit was defined as any description related to the potential reduction in lung cancer mortality. Harms were based on the US Preventive Services Task Force recommendations and included false positives, false negatives, overdiagnosis, radiation exposure, and incidental findings. The secondary outcome was next steps that are recommended by websites. **RESULTS:** Overall, the 162 lung cancer screening program websites described the potential benefits more frequently than they described any potential harms (159 [98%] vs 78 [48%],  $P < .01$ ). False-positive findings were the most frequently reported (72 [44%]) potential harm. Community centers were less likely than academic centers to report any potential harm (32 [40%] vs 46 [57%],  $P = .03$ ), potential harm from radiation (20 [25%] vs 35 [43%],  $P = .01$ ), and overdiagnosis (0% vs 11 [14%],  $P < .01$ ). One hundred nineteen websites (73%) did not explicitly recommend that individuals personally consider the potential benefits and harms of screening; community centers were less likely than academic centers to give this recommendation (15 [19%] vs 28 [35%],  $P = .02$ ). Most institutions (157 [97%]) listed follow-up steps for screening, but few institutions (35 [22%]) recommended that individuals



discuss benefits and harms with a health care professional. **CONCLUSIONS AND RELEVANCE:** Information on public-facing websites of US lung cancer screening programs appears to lack balance with respect to portrayal of potential benefits and harms of screening. Important harms, such as overdiagnosis, were commonly ignored in the sites evaluated, and most of the centers did not explicitly guide individuals toward a guideline-recommended, shared decision-making discussion of harms and benefits.

**[Diagnostic Accuracy of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration \(EBUS-TBNA\) in Real Life.](#)** Murthi M1, Donna E1, Arias S1, Villamizar NR2, Nguyen DM2, Holt GE1, Mirsaeidi MS1. *Front Med (Lausanne)*. 2020 Apr 7;7:118. doi: 10.3389/fmed.2020.00118. eCollection 2020.

**BACKGROUND:** EBUS-TBNA is an integral tool in the diagnosis and staging of lung cancer and other diseases involving mediastinal lymphadenopathy. Most studies attesting to the performance of EBUS-TBNA are prospective analyses performed under strict protocols. The objective of our study was to compare the accuracy of EBUS-TBNA to surgery in diagnosing hilar and mediastinal pathologies in a tertiary hospital, staffed by pulmonologists with and without formal interventional pulmonary training. **METHODS:** We retrospectively analyzed subjects who underwent EBUS-TBNA followed by a confirmatory surgical procedure from January 2012 to December 2018. The primary outcome was to evaluate the accuracy of EBUS-TBNA in the diagnosis of all mediastinal disease. Secondary analyses determined the accuracy of EBUS-TBNA in cancer, NSCLC, and non-malignant lesions individually. **RESULTS:** One hundred and forty-three subjects had an EBUS-TBNA procedure followed by surgery. EBUS-TBNA for all pathologies had an accuracy of 81.2% (CI 95% 73.8-87.4) and sensitivity of 55.1% (CI 95% 41.5-68.3). The accuracy and sensitivity of individual groups were: cancer (81.7, 48.8%), NSCLC (84, 48.3%), and non-malignancy (78.9, 60%). The NSCLC group had 15 false negatives and 5 (33.3%) of them were due to non-sampling of EBUS accessible nodes. Missed sampling led to a change in the final staging in 8.6% of NSCLC subjects. **CONCLUSION:** The accuracy of EBUS-TBNA across all groups was comparable to those reported previously. However, the sensitivity was comparatively lower. This was primarily due to the large number of EBUS-TBNA accessible lymph nodes that were not sampled. This data highlights the need for guidelines outlining the best sampling approach and lymph node selection.

**[ELISA-based detection of Open Reading Frame protein 1 in patients at risk of developing lung cancer.](#)** Sharp CN1, Korte EA1, Hosseinejad K1, Pitman J1, Lavasanifar A2, Eichenberger DJ3, Sephton S4, Cash E5, Jortani SA6.

**BACKGROUND:** Early detection of lung cancer significantly improves survival outcomes. Thus, lung cancer screening for high-risk individuals using low-dose CT scan (LDCT) is recommended. LDCT has several limitations, and often requires invasive follow up. Previously, we have developed an ELISA for measurement of Open Reading Frame 1 protein (ORF1p) in serum. We assessed whether ORF1p can be used as a risk assessment biomarker for patients at high risk for developing lung cancer. **PATIENTS:** Patients with risk factors for lung cancer were enrolled in our study with consent under IRB approval. A total of 122 patients were included. The lung cancer cohort consisted of 38 patients with varying stages of cancer undergoing treatment. **METHODS:** ORF1p quantification was performed using our ELISA assay on serum samples. **RESULTS:** ORF1p was significantly increased in the serum of patients with identified lung nodules compared to those without nodules ( $P = 0.0007$ ). ORF1p was also significantly increased in patients who were recommended for follow up ( $P = 0.0004$ ). When comparing the at-risk cohort to patients with lung cancer, there was not a significant difference in ORF1p levels. **CONCLUSION:** ORF1p can be used to identify patients at high risk of developing lung cancer and may provide an effective, non-invasive risk assessment marker to complement LDCT screening.

**Identification of circulating tumor cells using 4-color fluorescence in situ hybridization: Validation of a noninvasive aid for ruling out lung cancer in patients with low-dose computed tomography-detected lung nodules.** Katz RL1, Zaidi TM1, Pujara D2, et al. *Cancer Cytopathol.* 2020 Apr 22. doi: 10.1002/ency.22278. [Epub ahead of print]

**BACKGROUND:** Approximately one third of needle biopsies that are performed to rule out malignancy of indeterminate pulmonary nodules detected radiologically during lung cancer screening are negative, thus exposing cancer-free patients to risks of pneumothorax, bleeding, and infection. A noninvasive confirmatory tool (eg, liquid biopsy) is urgently needed in the lung cancer diagnosis setting to stratify patients who should receive biopsy versus those who should be monitored. **METHODS:** A novel antigen-independent, 4-color fluorescence in situ hybridization (FISH)-based method was developed to detect circulating tumor cells (CTCs) with abnormalities in gene copy numbers in mononuclear cell-enriched peripheral blood samples from patients with (n = 107) and without (n = 100) lung cancer. **RESULTS:** Identification of CTCs using FISH probes at 10q22.3/CEP10 and 3p22.1/3q29 detected lung cancer cases with 94.2% accuracy, 89% sensitivity, and 100% specificity compared with biopsy. **CONCLUSION:** The high accuracy of this liquid biopsy method suggests that it may be used as a noninvasive decision tool to reduce the frequency of unnecessary needle biopsy in patients with benign pulmonary lesions.

**Analysis of Out-of-Pocket Cost of Lung Cancer Screening for Uninsured Patients Among ACR-Accredited Imaging Centers.** Febbo J1, Little B2, Fischl-Lanzoni N1, Narayan AK3, Tiersma KM1, Glover M3, Shepard JO3, Flores EJ4. *J Am Coll Radiol.* 2020 Apr 9. pii: S1546-1440(20)30248-9. doi: 10.1016/j.jacr.2020.03.001. [Epub ahead of print]

**PURPOSE:** To determine the variability in out-of-pocket costs of lung cancer screening (LCS) for uninsured patients and assess accessibility of this information by telephone or Internet. **METHODS:** LCS centers from the ACR's LCS database were randomly selected. Centers were called between July and August 2019 to determine out-of-pocket cost. Telephone call variables, accessibility of cost information on screening centers' website, screening centers' chargemaster, and publicly available facility and state insurance coverage variables were obtained. Cost information was summarized using descriptive analyses. Multiple variable linear regression analyses were conducted to evaluate effects of facility and state-level characteristics on out-of-pocket costs. **RESULTS:** Fifty-five ACR-accredited LCS centers were included with 78% (43 of 55) willing to provide out-of-pocket cost. Average out-of-pocket cost was \$583 ± \$607 (mean ± standard deviation), range \$49 to \$2,409. Average telephone call length 6 ± 3.8 min. Two of 55 screening centers' websites provided out-of-pocket cost information and 1 matched cost given over the telephone. A chargemaster was found for 30 of 55 screening centers. No statistically significant differences in out-of-pocket costs were found by geographic region, state percentages of uninsured residents, state percentages of residents with public insurance, or facility safety net hospital affiliation. **DISCUSSION:** Out-of-pocket LCS costs for uninsured patients and availability of this information is highly variable. Radiology practices should be aware of this variability that may influence participation rates among uninsured patients.

**Development of Decisional Values Statements for Lung Cancer Screening Among African American Smokers.** Williams RM1, Beck KH2, Butler J 3rd2, Lee S2, Wang MQ2, Taylor KL3, Knott CL2. *J Cancer Educ.* 2020 Apr;35(2):412-418. doi: 10.1007/s13187-020-01687-4.

Lung cancer screening via low-dose computed tomography (LDCT) has been underutilized by high-risk current and former smokers since its approval in 2013. Further, lower use of other evidence-based cancer screening tests (e.g., colorectal cancer, breast cancer) has been noted among African Americans when compared with other racial and ethnic groups. Reasons for low uptake are multilayered but include the need for consideration of patients' personal values about the screening decision. The goal of the present study was to (1) identify positive and negative factors specific to lung cancer screening via LDCT and (2)

develop statements to capture values about the screening test for use in a new measure of decisional values. Key informant interviews (n = 9) identified several benefits and risks of lung cancer screening that may be important to African American smokers. Based on these interviews, a pool of items with the values statements was administered to a convenience sample of 119 African Americans [aged 55-80 years, current or former smokers (who quit < 15 years), and without lung cancer]. An exploratory factor analysis revealed two components explaining 64% of the variance: cons of screening (e.g., "make you feel badly about your smoking history") and pros of screening (e.g., "lowering your risk of dying from lung cancer"). The final 12-item measure had very good internal consistency ( $\alpha = 0.89$  overall;  $\alpha = 0.86$  and  $0.88$  for subscales, respectively). This tool provides a promising values measure for lung cancer screening among African Americans and could inform future values clarification tools promoting informed and shared decision-making.

**[Invasive Staging Procedures Do Not Prevent Nodal Metastases from Being Missed In Stage I Lung Cancer.](#)** Resio BJ1, Canavan M2, Mase V1, Dhanasopon AP1, Blasberg JD1, Boffa DJ3. *Ann Thorac Surg.* 2020 Apr 10. pii: S0003-4975(20)30536-1. doi: 10.1016/j.athoracsur.2020.03.026. [Epub ahead of print]

**BACKGROUND:** Up to 20% of clinical stage I lung cancer patients harbor lymph node metastases that go undetected (missed) during the clinical staging evaluation. We investigated to what degree the addition of invasive nodal staging procedures to imaging, as currently practiced, prevents radiographically-occult nodal metastases from being missed during the clinical staging evaluation. **METHODS:** Treatment-naïve patients, imaged by PET and CT scanning, that underwent lobectomy for clinical stage I lung cancer from 2012-17 in the Society of Thoracic Surgeons General Thoracic Surgery Database were studied. Rates of missed nodal metastases (MNM) (i.e. nodal metastases in lobectomy specimens - undetected during clinical staging evaluation) were determined. Risk factors were assessed with multivariable modeling. **RESULTS:** Of the 30,685 clinical stage I patients identified, 3,895 (12.7%) underwent preoperative EBUS and 3,341 (10.9%) underwent mediastinoscopy. Invasive staging was more common with tumors >2cm (66.4% vs 50.2%,  $p < 0.001$ ), and squamous histology (26.9% vs. 16.9%  $p < 0.001$ ). MNM were discovered in 14.7% of patients, including 20.1% (95% CI:18.8-21.5%) of patients that had undergone EBUS and 18.2% (95% CI:16.7-19.6%) of mediastinoscopy patients. Hilar nodes were most often "missed" (9.5%). Using cut-points in tumor size, histology, laterality and age, patients could be stratified into particularly high (25% MNM) and low (6% MNM) risk cohorts. **CONCLUSIONS:** Substantial risk of occult lymph node metastases persists in patients with clinical stage I lung cancer despite negative invasive nodal staging, PET and CT scans. In the absence of a thorough surgical nodal evaluation, early-stage lung cancer patients are at risk of undertreatment.

## CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

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### NSCLC - SURGERY

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**[Racial Disparities in Resection of Early Stage Non-Small Cell Lung Cancer: Variability Among Surgeons.](#)** Ezer N1,2, Mhango G2, Bagiella E3, Goodman E2, Flores R4, Wisnivesky JP2,5. *Med Care.* 2020 Apr;58(4):392-398. doi: 10.1097/MLR.0000000000001280.

**BACKGROUND:** Racial disparities in resection of non-small cell lung cancer (NSCLC) are well documented. Patient-level and system-level factors only partially explain these findings. Although physician-related factors have been suggested as mediators, empirical evidence for their contribution is limited. **OBJECTIVE:** To determine if racial disparities in receipt of thoracic surgery persisted after patients had a surgical consultation and whether there was a physician contribution to disparities in care.

**METHODS:** The authors identified 19,624 patients with stage I-II NSCLC above 65 years of age from the Surveillance-Epidemiology and End-Results-Medicare database. They studied black and white patients evaluated by a surgeon within 6 months of diagnosis. They assessed for racial differences in resection rates among surgeons using hierarchical linear modeling. Our main outcome was receipt of NSCLC resection. A random intercept was included to test for variability in resection rates across surgeons. Interaction between patient race and the random surgeon intercept was used to evaluate for heterogeneity between surgeons in resection rates for black versus white patients. **RESULTS:** After surgical consultation, black patients were less likely to undergo resection (adjusted odds ratio, 0.57; 95% confidence interval, 0.47-0.69). Resection rates varied significantly between surgeons ( $P < 0.001$ ). A significant interaction between the surgeon intercept and race ( $P < 0.05$ ) showed variability beyond chance across surgeons in resection rates of black versus white patients. When the model included thoracic surgery specialization the physician contribution to disparities in care was decreased. **CONCLUSIONS:** Racial disparities in resection of NSCLC exist even among patients who had access to a surgeon. Heterogeneity between surgeons in resection rates between black and white patients suggests a physician's contribution to observed racial disparities. Specialization in thoracic surgery attenuated this contribution.

**Morbidity and mortality of lobectomy or pneumonectomy after neoadjuvant treatment: an analysis from the ESTS database.** Brunelli A1, Rocco G2, Szanto Z3, Thomas P4, Falcoz PE5. Eur J Cardiothorac Surg. 2020 Apr 1;57(4):740-746. doi: 10.1093/ejcts/ezz287.

**OBJECTIVES:** To evaluate the postoperative complications and 30-day mortality rates associated with neoadjuvant chemotherapy before major anatomic lung resections registered in the European Society of Thoracic Surgeons (ESTS) database. **METHODS:** Retrospective analysis on 52 982 anatomic lung resections registered in the ESTS database (July 2007-31 December 2017) (6587 pneumonectomies and 46 395 lobectomies); 5143 patients received neoadjuvant treatment (9.7%) (3993 chemotherapy alone and 1150 chemoradiotherapy). To adjust for possible confounders, a propensity case-matched analysis was performed. The postoperative outcomes (morbidity and 30-day mortality) of matched patients with and without induction treatment were compared. **RESULTS:** 8.2% of all patients undergoing lobectomies and 20% of all patients undergoing pneumonectomies received induction treatment. Lobectomy analysis: propensity score analysis yielded 3824 pairs of patients with and without induction treatment. The incidence of cardiopulmonary complications was higher in the neoadjuvant group (626 patients, 16% vs 446 patients, 12%,  $P < 0.001$ ), but 30-day mortality rates were similar (71 patients, 1.9% vs 75 patients, 2.0%,  $P = 0.73$ ). The incidence of bronchopleural fistula and prolonged air leak  $> 5$  days were similar between the 2 groups (neoadjuvant: 0.5% vs 0.4%,  $P = 0.87$ ; 9.2% vs 9.9%,  $P = 0.27$ ). Pneumonectomy analysis: propensity score analysis yielded 1312 pairs of patients with and without induction treatment. The incidence of cardiopulmonary complications was higher in the treated patients compared to those without neoadjuvant treatment (neoadjuvant 275 cases, 21% vs 18%,  $P = 0.030$ ). However, the 30-day mortality was similar between the matched groups (neoadjuvant 68 cases, 5.2% vs 5.3%,  $P = 0.86$ ). Finally, the incidence of bronchopleural fistula was also similar between the 2 groups (neoadjuvant 1.8% vs 1.4%,  $P = 0.44$ ). **CONCLUSIONS:** Neoadjuvant chemotherapy is not associated with an increased perioperative risk after either lobectomy or pneumonectomy, warranting a more liberal use of this approach for patients with locally advanced operable lung cancer.

**Prognostic value of the advanced lung cancer inflammation index in early-stage non-small cell lung cancer patients undergoing video-assisted thoracoscopic pulmonary resection.** Wang Y1, Lin L1, Ji Y1, Mei X1, Zhao C1, Chen Y1, Che G2. Ann Palliat Med. 2020 Apr 13. pii: apm.2020.03.18. doi: 10.21037/apm.2020.03.18. [Epub ahead of print]



**BACKGROUND:** The aim of this study was to assess the prognostic value of the preoperative advanced lung cancer inflammation index (ALI) in early stage non-small lung cancer (NSCLC) patients who received videoassisted thoracoscopic surgery (VATS) pulmonary surgery as their only therapy.

**METHODS:** We retrospectively reviewed the medical records of patients who were diagnosed with early-stage NSCLC and received a VATS pulmonary resection from January 2014 to June 2016 in the Department of Thoracic Surgery, West China Hospital. A receiver operating characteristic (ROC) curve analysis was conducted to determine the optimal cut-off values, and patients were divided into low and high ALI groups. The Kaplan-Meier method and Cox proportional hazards model were used to evaluate potential predictors of overall survival (OS) and disease-free survival (DFS). **RESULTS:** A total of 292 patients were enrolled in our analysis. Then, 155 and 137 patients were assigned to the low ALI (ALI <50) and high (ALI >50) groups, respectively. The multivariate analyses revealed that preoperative ALI <50 was an independent prognostic factor for both OS [hazard ratio (HR) = 2.603, 95% confidence interval (95% CI): 1.128-6.006, P=0.025] and DFS (HR =2.372, 95% CI: 1.141-4.935, P=0.021), and patients with a low preoperative ALI had worse OS (P<0.001) and DFS (P<0.001) compared with those with a high preoperative ALI. **CONCLUSIONS:** A low preoperative ALI was significantly correlated with poor survival, and the ALI might serve as a promising marker of prognosis in early-stage NSCLC patients who received a VATS pulmonary resection as their only therapy.

**Closing the gap: Contribution of surgical best practices to outcome differences between high- and low-volume centers for lung cancer resection.** von Itzstein MS1, Lu R2, Kernstine KH3, Halm

EA1,4,5, Wang S2, Xie Y2,5, Gerber DE1,4,5. Cancer Med. 2020 Apr 21. doi: 10.1002/cam4.3055.

[Epub ahead of print]

**BACKGROUND:** Clinical outcomes for resected early-stage non-small cell lung cancer (NSCLC) are superior at high-volume facilities, but reasons for these differences remain unclear. Understanding these differences and optimizing outcomes across institutions are critical to the management of the increasing incidence of these cases. We evaluated the extent to which surgical best practices account for resected early-stage NSCLC outcome differences between facilities according to case volume. **METHODS:** We performed a retrospective cohort study for clinical stage 1 or 2 NSCLC undergoing surgical resection from 2004 to 2013 using the National Cancer Database (NCDB). Surgical best practices (negative surgical margins, lobar or greater resection, lymph node (LN) dissection, and examination of > 10 LNs) were compared between the highest and lowest quartile volumes. **RESULTS:** A total of 150,179 patients were included in the cohort (89% white, 53% female, median age 68 years). In a multivariate model, superior overall survival (OS) was observed at highest volume centers compared to lowest volume centers (hazard ratio (HR) = 0.89; 95% CI, 0.82-0.96; P = .002). After matching for surgical best practices, there was no significant OS difference (HR = 0.95; 95% CI, 0.87-1.05; P = .32). Propensity score-adjusted HR estimates indicated that surgical best practices accounted for 54% of the numerical OS difference between low-volume and high-volume centers. Each surgical best practice was independently associated with improved OS (all P ≤ .001). **CONCLUSION:** Quantifiable and potentially modifiable surgical best practices largely account for resected early-stage NSCLC outcome differences observed between low- and high-volume centers. Adherence to these guidelines may reduce and potentially eliminate these differences.

**Survival Value of Primary Tumor Resection for Stage IV Non-small-cell lung cancer: a Population Based Study of 6466 Patients.** Xu J1, Fan L1, Yu H1, Lu D2, Peng W1, Sun G1. Clin Respir J. 2020 Apr

16. doi: 10.1111/crj.13194. [Epub ahead of print]

**INTRODUCTION:** For stage IV non-small-cell lung cancer (NSCLC) patients, surgical resection of primary tumor was rarely recommended. **OBJECTIVES:** We conducted this population based study to demonstrate the survival value of primary tumor resection (PTR) for stage IV (NSCLC). **METHODS:**

The Surveillance, Epidemiology and End Results (SEER) database was searched for selecting stage IV NSCLC patients. The patients were matched according to age, gender, grade, primary tumor site, histopathological type, tumor size and regional lymph nodes metastasis by propensity score matching (PSM) analysis. Kaplan-Meier curves were presented to show the survival differences between resection group and non-resection group. Risk factors which were supposed to influence survival outcome were investigated using a Cox proportional hazard regression model. And a nomogram was performed to present prognostic factors for stage IV NSCLC patients. **RESULTS:** 6466 patients diagnosed from 2004 to 2015 were included in survival analyses after PSM. The median overall survival (OS) for overall patients with resection was 27 months, much longer than those without resection (8 months). And this trend remained in subgroup analyses, including different histopathological types and distant metastases (All P values < 0.001). Younger age, race other than white and black, female, grade1/2 (G1/G2), PTR, chemotherapy, no other distant metastases, smaller tumor size, and no regional lymph node metastases were favorable prognostic factors for stage IV NSCLC. A predictive nomogram was conducted based on above risk factors. **CONCLUSION:** PTR prolonged survival of stage IV NSCLC patients. And PTR should be considered in clinical practice for stage IV NSCLC.

[Immune Checkpoint Inhibitors for Brain Metastases: A Primer for Neurosurgeons.](#) Aquilanti E1,2,3,4,5, Brastianos PK1,2,4,5. Neurosurgery. 2020 Apr 17. pii: nyaa095. doi: 10.1093/neuros/nyaa095. [Epub ahead of print]

Immune checkpoint inhibitors enhance immune recognition of tumors by interfering with the cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and programmed death 1 (PD1) pathways. In the past decade, these agents brought significant improvements to the prognostic outlook of patients with metastatic cancers. Recent data from retrospective analyses and a few prospective studies suggest that checkpoint inhibitors have activity against brain metastases from melanoma and nonsmall cell lung cancer, as single agents or in combination with radiotherapy. Some studies reported intracranial response rates that were comparable with systemic ones. In this review, we provide a comprehensive summary of clinical data supporting the use of anti-CTLA4 and anti-PD1 agents in brain metastases. We also touch upon specific considerations on the assessment of intracranial responses in patients and immunotherapy-specific toxicities. We conclude that a subset of patients with brain metastases benefit from the addition of checkpoint inhibitors to standard of care therapeutic modalities, including radiotherapy and surgery.

[Increased reporting but decreased mortality associated with adverse events in patients undergoing lung cancer surgery: Competing forces in an era of heightened focus on care quality?](#) von Itzstein MS1, Gupta A1, Kernstine KH2, Mara KC3, Khanna S4, Gerber DE1,5,6. PLoS One. 2020 Apr 9;15(4):e0231258. doi: 10.1371/journal.pone.0231258. eCollection 2020.

**INTRODUCTION:** Advances in surgical techniques have improved clinical outcomes and decreased complications. At the same time, heightened attention to care quality has resulted in increased identification of hospital-acquired adverse events. We evaluated these divergent effects on the reported safety of lung cancer resection. **METHODS AND MATERIALS:** We analyzed hospital-acquired adverse events in patients undergoing lung cancer resection using the National Hospital Discharge Survey (NHDS) database from 2001-2010. Demographics, diagnoses, and procedures data were abstracted using ICD-9 codes. We used the Agency for Healthcare Research and Quality (AHRQ) Patient Safety Indicators (PSI) to identify hospital-acquired adverse events. Weighted analyses were performed using t-tests and chi-square. **RESULTS:** A total of 302,444 hospitalizations for lung cancer resection and were included in the analysis. Incidence of PSI increased over time (28% in 2001-2002 vs 34% in 2009-2010; P<0.001). Those with one or more PSI had increased in-hospital mortality (aOR = 11.1; 95% CI, 4.7-26.1; P<0.001) and prolonged hospitalization (12.5 vs 7.8 days; P<0.001). However, among those with PSI, in-hospital mortality decreased over time, from 17% in 2001-2002 to 2% in 2009-2010. **CONCLUSIONS:** In a

recent ten-year period, documented rates of adverse events associated with lung cancer resection increased. Despite this increase in safety events, we observed that mortality decreased. Because such metrics may be incorporated into hospital rankings and reimbursement considerations, adverse event coding consistency and content merit further evaluation.

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

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[\*\*Atezolizumab in Combination With Carboplatin and Nab-Paclitaxel in Advanced Squamous Non-Small-Cell Lung Cancer \(IMpower131\): Results From a Randomized Phase III Trial.\*\*](#) Jotte R1, Cappuzzo F2, Vynnychenko I3, et al. *J Thorac Oncol.* 2020 Apr 7. pii: S1556-0864(20)30292-6. doi: 10.1016/j.jtho.2020.03.028. [Epub ahead of print]

**INTRODUCTION:** Cytotoxic agents have immunomodulatory effects, providing rationale for combining atezolizumab (anti-programmed death-ligand 1 [PD-L1]) with chemotherapy. The randomized phase III IMpower131 study (NCT02367794) evaluated atezolizumab with platinum-based chemotherapy in stage IV squamous non-small cell lung cancer (NSCLC). **METHODS:** 1021 patients were randomized 1:1:1 to receive atezolizumab+carboplatin+paclitaxel (A+CP) (n=338), atezolizumab+carboplatin+nab-paclitaxel (A+CnP) (n=343), or carboplatin+nab-paclitaxel (CnP) (n=340) for four or six 21-day cycles; patients randomized to A+CP or A+CnP received atezolizumab maintenance therapy until progressive disease or loss of clinical benefit. Coprimary endpoints were investigator-assessed progression-free survival (PFS) and overall survival (OS) in the intention-to-treat (ITT) population. Secondary endpoints included PFS and OS in PD-L1 subgroups and safety. Primary PFS (January 22, 2018) and final OS (October 3, 2018) for A+CnP vs CnP are reported. **RESULTS:** PFS improvement with A+CnP vs CnP was seen in the ITT population (median, 6.3 vs 5.6 months; hazard ratio [HR]=0.71, 95% CI: 0.60-0.85; P=0.0001). Median OS in the ITT population was 14.2 and 13.5 months in the A+CnP and CnP arms, (HR=0.88, 95% CI: 0.73-1.05; P=0.16), not reaching statistical significance. OS improvement with A+CnP vs CnP was observed in the PD-L1-high subgroup (HR=0.48, 95% CI: 0.29-0.81), despite not being formally tested. Treatment-related grade 3-4 adverse events (AEs) and serious AEs occurred in 68.0% and 47.9% (A+CnP) and 57.5% and 28.7% (CnP) of patients. **CONCLUSIONS:** Adding atezolizumab to platinum-based chemotherapy significantly improved PFS in patients with first-line squamous NSCLC; OS was similar between arms. (Funding: F. Hoffmann-La Roche Ltd/Genentech, Inc.).

[\*\*Response to Checkpoint Inhibition in Non-Small Cell Lung Cancer with Molecular Driver Alterations.\*\*](#) Kauffmann-Guerrero D1, Tufman A2, et al. *Oncol Res Treat.* 2020 Apr 8:1-9. doi: 10.1159/000506842. [Epub ahead of print]

**AIMS:** Non-small cell lung cancer (NSCLC) patients with EGFR mutations do not respond well to checkpoint inhibitors. However, little is known about the activity of immunotherapy in NSCLC with other driver mutations. The increasing use of next-generation sequencing (NGS) leads to molecular findings that face the clinician with problems while choosing the best treatment. This study aims at analyzing response of NSCLC with driver mutations to immunotherapy. **PATIENTS AND METHODS:** We retrospectively included 84 NSCLC patients diagnosed and treated at 2 German tertiary-care lung cancer centers using NGS and treatment with immunotherapy. Response to immunotherapy was analyzed in correlation to molecular findings. **RESULTS:** 51 patients harbored at least 1 driver mutation. PIK3CA, EGFR, and STK11 mutations did not respond to immunotherapy. KRAS, TP53, and MET exon 14 skipping mutations responded well. One patient with NF-1 mutation showed durable response. **CONCLUSIONS:** Molecular testing may be of use in guiding treatment decision making in NSCLC.

[Assessment of Immune-Related Interstitial Lung Disease in Non-Small Cell Lung Cancer Patients Treated with Immune Checkpoint Inhibitors: A Multi-Center Prospective Study.](#) Suzuki Y1, Karayama M2, Uto T3, et al. *J Thorac Oncol.* 2020 Apr 11. pii: S1556-0864(20)30297-5. doi: 10.1016/j.jtho.2020.04.002. [Epub ahead of print]

**INTRODUCTION:** Programmed death-1 immune checkpoint inhibitors (ICIs) have been shown to improve survival of non-small cell lung cancer (NSCLC) patients. Upon expansion of clinical administration for a variety of cancers, immune-related adverse events (ir-AEs) have been typically recognized to be associated with ICIs therefore, necessitating the monitoring and management of these patients. Among ir-AEs, immune-related interstitial lung disease (ir-ILD) is a serious complication which interrupts treatment and occasionally, is fatal. However, no prospective studies have investigated incidences of ir-ILD and associated risk factors for its development in the clinical setting. **METHODS:** This was a prospective cohort study consisting of NSCLC patients treated with ICIs. Baseline characteristics, including laboratory data, pulmonary function tests (PFTs), daily dyspnea defined by the modified Medical Research Council (mMRC), and anti-tumor response were assessed. **RESULTS:** Among the 138 NSCLC patients that received anti-PD-1 monotherapy, 20 patients (14.5%) developed ir-ILD within median 51.5 days [29-147: interquartile]. This was approximately three-times higher than those in clinical trials. Eleven patients (55.0%), including all of eight patients with high-grade ir-ILD ( $\geq$ Grade 3), developed ir-ILD within 60 days. Impaired spirometry, decreased forced vital capacity (%FVC) and forced expiratory volume in 1.0 second (%FEV1), and daily dyspnea measured by mMRC were identified as risk factors for ir-ILD development. Additionally, combination assessment of %FVC and %FEV1 successfully classified patients at risk for ir-ILD development. **CONCLUSION:** The incidences of ir-ILD were substantially higher in clinical setting. Assessment of spirometry and daily dyspnea before ICI treatment may be useful to monitor and manage NSCLC patients.

[Is there a role for dacomitinib, a second-generation irreversible inhibitor of the epidermal-growth factor receptor tyrosine kinase, in advanced non-small cell lung cancer?](#) Bergonzini C1, Leonetti A1,2, Tiseo M2,3, Giovannetti E1,4, Peters GJ1,5. *Expert Opin Pharmacother.* 2020 Apr 15:1-11. doi: 10.1080/14656566.2020.1746269. [Epub ahead of print]

**INTRODUCTION:** Non-small cell lung cancer (NSCLC) is a highly lethal disease. During the past 20 years, the epidermal growth factor receptor (EGFR) has been a relevant target for anticancer drug-design, and a large family of EGFR tyrosine kinase inhibitors (TKI) were designed, which improved therapeutic outcomes compared to conventional chemotherapy in NSCLC patients with specific EGFR mutations. However, resistance to these inhibitors occurs; therefore, the debate on which inhibitor should be used first is still open. Dacomitinib was approved in 2018 for the first-line treatment of NSCLC with EGFR activating mutations. **AREAS COVERED:** This manuscript reviews the properties of dacomitinib, including the current information from clinical trials and its potential application as stand-alone therapy, or in combination. **EXPERT OPINION:** Dacomitinib is a second-generation EGFR-TKI that has demonstrated significant improvement in overall survival in a phase III randomized study compared with gefitinib, a first-generation TKI. However, the rapid development and approval of a new generation of TKIs (osimertinib), with better clinical profiles, raises the question of which role can dacomitinib play in NSCLC. Further studies are required to evaluate the efficacy of this drug on brain metastases, as a second-line treatment after third-generation TKIs, or in combination with other types of treatments.

[Comparative study of intratracheal and oral gefitinib for the treatment of primary lung cancer.](#) Zhang T1, Wang R2, Li M3, Bao J4, Chen Y3, Ge Y5, Jin Y6. *Eur J Pharm Sci.* 2020 Apr 18:105352. doi: 10.1016/j.ejps.2020.105352. [Epub ahead of print]

Oral gefitinib tablets are widely clinically applied for the treatment of non-small cell lung cancer (NSCLC) though its broad distribution in the body may result in weak therapeutic efficiency and



unexpected side effects. Here, liposomal gefitinib dry powder inhalers (LGDs) were prepared using the injection-lyophilization method. LGDs were rough porous particles under the scanning electron microscope, which can be rapidly rehydrated to liposomes. LGDs and gefitinib powders were separately intratracheally (i.t.) administered into the lungs of primary lung cancer rats, while powdered gefitinib tablets were orally administered. Gefitinib was rapidly absorbed from the lung after i.t. administration of LGDs. The maximal gefitinib concentration in the circulation and the area under curve (AUC) of i.t. LGDs were higher than those of i.t. gefitinib powders and oral gefitinib. More importantly, much higher concentration and longer retention of gefitinib in the lung were shown after i.t. administration of LGDs and gefitinib powders but remarkably less drug distribution in the liver compared to oral gefitinib. LGDs showed higher therapeutic effect on primary lung cancer than i.t. gefitinib powders and oral gefitinib with reduction of inflammation, weak lung injury, and high apoptosis. Combination of inhalation and liposomes of anticancer drugs is a promising strategy for treatment of primary lung cancer.

[Durvalumab in frail and elderly patients with stage four non-small cell lung cancer: Study protocol of the randomized phase II DURATION trial.](#) Kuon J1, Hommertgen A2, Krisam J3, et al. *Trials*. 2020 Apr 22;21(1):352. doi: 10.1186/s13063-020-04280-8.

**BACKGROUND:** Elderly patients represent a major fraction of non-small cell lung cancer (NSCLC) patients in routine clinical practice, but they are still underrepresented in clinical trials. In particular, data regarding efficacy and safety in frail or elderly patients with respect to immunotherapy are lacking. Importantly, immunosenescence in elderly patients might interfere with activities of immune-modulating drugs such as PD-1/PD-L1 inhibitors. Thus, there is an urgent need to assess safety and efficacy of such inhibitors in this group. **METHODS/DESIGN:** This prospective, open label, treatment stratified, randomized phase II study will enroll 200 patients with stage IV NSCLC amenable at least to single-agent chemotherapy (CT). Eligible patients must be aged 70 years or older and/or "frail" (Charlson Comorbidity Index > 1) or have a restricted performance status (Eastern Cooperative Oncology Group, ECOG > 1). Patients are stratified according to modified Cancer and Age Research Group (CARG) score: "fit" patients are allocated to combination CT (carboplatin/nab-paclitaxel) and "less fit" patients receive single-agent CT (gemcitabine or vinorelbine). After allocation to strata, patients are randomized 1:1 to receive either four cycles of CT or two cycles of CT followed by two cycles of durvalumab and subsequent maintenance treatment with durvalumab every 4 weeks. The primary endpoint is the rate of treatment-related grade III/IV adverse events (Common Terminology Criteria for Adverse Events (CTCAE) V4.03). As secondary endpoints, progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, response rate (RR), overall survival (OS), descriptive subgroup analyses according to PD-L1 expression, and quality of life are addressed. Geriatric screening assessments and functional tests will be performed to complete the phenotyping of a potential "frail" and "elderly" patient cohort. The trial is accompanied by a biomaterial repository to explore potential biomarkers. **DISCUSSION:** The DURATION trial will prospectively investigate the safety and tolerability of anti-PD-L1 treatment with durvalumab after chemotherapy in elderly and frail patients and thereby provide new insights into the effect of PD-L1 blockade and the impact of immunosenescence in this cohort of patients.

[Durvalumab With or Without Tremelimumab vs Standard Chemotherapy in First-line Treatment of Metastatic Non-Small Cell Lung Cancer: The MYSTIC Phase 3 Randomized Clinical Trial.](#)

Rizvi NA1, Cho BC2, Reinmuth N3, et al. *JAMA Oncol*. 2020 Apr 9. doi: 10.1001/jamaoncol.2020.0237. [Epub ahead of print]

**IMPORTANCE:** Checkpoint inhibitors targeting programmed cell death 1 or its ligand (PD-L1) as monotherapies or in combination with anti-cytotoxic T-lymphocyte-associated antigen 4 have shown clinical activity in patients with metastatic non-small cell lung cancer. **OBJECTIVE:** To compare

durvalumab, with or without tremelimumab, with chemotherapy as a first-line treatment for patients with metastatic non-small cell lung cancer. **DESIGN, SETTING, AND PARTICIPANTS:** This open-label, phase 3 randomized clinical trial (MYSTIC) was conducted at 203 cancer treatment centers in 17 countries. Patients with treatment-naïve, metastatic non-small cell lung cancer who had no sensitizing EGFR or ALK genetic alterations were randomized to receive treatment with durvalumab, durvalumab plus tremelimumab, or chemotherapy. Data were collected from July 21, 2015, to October 30, 2018. **INTERVENTIONS:** Patients were randomized (1:1:1) to receive treatment with durvalumab (20 mg/kg every 4 weeks), durvalumab (20 mg/kg every 4 weeks) plus tremelimumab (1 mg/kg every 4 weeks, up to 4 doses), or platinum-based doublet chemotherapy. **MAIN OUTCOMES AND MEASURES:** The primary end points, assessed in patients with  $\geq 25\%$  of tumor cells expressing PD-L1, were overall survival (OS) for durvalumab vs chemotherapy, and OS and progression-free survival (PFS) for durvalumab plus tremelimumab vs chemotherapy. Analysis of blood tumor mutational burden (bTMB) was exploratory. **RESULTS:** Between July 21, 2015, and June 8, 2016, 1118 patients were randomized. Baseline demographic and disease characteristics were balanced between treatment groups. Among 488 patients with  $\geq 25\%$  of tumor cells expressing PD-L1, median OS was 16.3 months (95% CI, 12.2-20.8) with durvalumab vs 12.9 months (95% CI, 10.5-15.0) with chemotherapy (hazard ratio [HR], 0.76; 97.54% CI, 0.56-1.02;  $P = .04$  [nonsignificant]). Median OS was 11.9 months (95% CI, 9.0-17.7) with durvalumab plus tremelimumab (HR vs chemotherapy, 0.85; 98.77% CI, 0.61-1.17;  $P = .20$ ). Median PFS was 3.9 months (95% CI, 2.8-5.0) with durvalumab plus tremelimumab vs 5.4 months (95% CI, 4.6-5.8) with chemotherapy (HR, 1.05; 99.5% CI, 0.72-1.53;  $P = .71$ ). Among 809 patients with evaluable bTMB, those with a bTMB  $\geq 20$  mutations per megabase showed improved OS for durvalumab plus tremelimumab vs chemotherapy (median OS, 21.9 months [95% CI, 11.4-32.8] vs 10.0 months [95% CI, 8.1-11.7]; HR, 0.49; 95% CI, 0.32-0.74). Treatment-related adverse events of grade 3 or higher occurred in 55 (14.9%) of 369 patients who received treatment with durvalumab, 85 (22.9%) of 371 patients who received treatment with durvalumab plus tremelimumab, and 119 (33.8%) of 352 patients who received treatment with chemotherapy. These adverse events led to death in 2 (0.5%), 6 (1.6%), and 3 (0.9%) patients, respectively. **CONCLUSIONS AND RELEVANCE:** The phase 3 MYSTIC study did not meet its primary end points of improved OS with durvalumab vs chemotherapy or improved OS or PFS with durvalumab plus tremelimumab vs chemotherapy in patients with  $\geq 25\%$  of tumor cells expressing PD-L1. Exploratory analyses identified a bTMB threshold of  $\geq 20$  mutations per megabase for optimal OS benefit with durvalumab plus tremelimumab.

### [Natural Killer Cells as a Potential Biomarker for Predicting Immunotherapy Efficacy in Patients with Non-Small Cell Lung Cancer.](#)

Cho YH1, Choi MG2, Kim DH1, et al. Target Oncol. 2020 Apr;15(2):241-247. doi: 10.1007/s11523-020-00712-2.

**BACKGROUND:** Immunotherapy with immune checkpoint inhibitors for non-small cell lung cancer (NSCLC) has emerged as an important treatment option. Although immunotherapy may significantly improve survival and quality of life, response rates are as low as 20% in NSCLC patients. **OBJECTIVE:** The identification of reliable biomarkers predicting response to immunotherapy is required urgently to determine patient selection guidelines. **PATIENTS AND METHODS:** Peripheral blood mononuclear cells (PBMCs) from nine NSCLC patients were collected pre- and post-treatment with immunotherapy. The immune cell composition of PBMCs was analyzed using CyTOF with an optimized 32-marker panel. The natural killer (NK) cell activity was assessed with the measurement of interferon (INF)- $\gamma$  using an NK Vue™ kit. **RESULTS:** We found that the percentages of NK cell populations in the immune cells of PBMCs were prominently elevated in the immunotherapy responder group when compared with non-responders. While no meaningful differences were observed in other populations of immune cells, consistent with these results, the overall activity of NK cells in responders was highly elevated compared with that of non-responders. From the analysis of NK subsets, although differences in the population of

early NK cells were not observed, the functionally differentiated late NK cells were prominently high in responders. **CONCLUSIONS:** The overall activity or number of NK cells may be a useful biomarker to predict immunotherapy response in patients with NSCLC.

[Association of metastatic pattern and molecular status in stage IV non-small cell lung cancer adenocarcinoma.](#) Dormieux A1, Mezquita L2, Courneade PH3, et al. Eur Radiol. 2020 Apr 23. doi: 10.1007/s00330-020-06784-y. [Epub ahead of print]

**OBJECTIVES:** The aim of our study was to investigate the association between driver oncogene alterations and metastatic patterns on imaging assessment, in a large cohort of metastatic lung adenocarcinoma patients. **METHODS:** From January 2010 to May 2017, 550 patients with stage IV lung adenocarcinoma with molecular analysis were studied retrospectively including 135 EGFR-mutated, 81 ALK-rearrangement, 47 BRAF-mutated, 141 KRAS-mutated, and 146 negative tumors for these 4 mutations (4N). After review of the complete imaging report by two radiologists (junior and senior) to identify metastatic sites, univariate correlation analyzes were performed. **RESULTS:** We found differences in metastatic tropism depending on the molecular alteration type when compared with the non-mutated 4N group: in the EGFR group, pleural metastases were more frequent (32% versus 20%;  $p = 0.021$ ), and adrenal and node metastases less common (6% versus 23%;  $p < 0.001$  and 11% versus 23%;  $p = 0.011$ ). In the ALK group, there were more brain and lung metastases (respectively 42% versus 29%;  $p = 0.043$  and 37% versus 24%;  $p = 0.037$ ). In the BRAF group, pleural and pericardial metastases were more common (respectively 47% versus 20%;  $p < 0.001$  and 11% versus 3%;  $p = 0.04$ ) and bone metastases were rarer (21% versus 42%;  $p = 0.011$ ). Lymphangitis was more frequent in EGFR, ALK, and BRAF groups (respectively 6%, 7%, and 15% versus 1%);  $p = 0.016$ ;  $p = 0.009$ ; and  $p < 0.001$ .

**CONCLUSION:** The application of these correlations between molecular status and metastatic tropism in clinical practice may lead to earlier and more accurate identification of patients for targeted therapy.

**KEY POINTS:** • Bone and brain metastasis are the most common organs involved in lung adenocarcinoma but the relative incidence of each metastatic site depends on the molecular alteration. • EGFR-mutated tumors preferentially spread to the pleura and less commonly to adrenals, ALK-rearrangement tumors usually spread to the brain and the lungs, whereas BRAF-mutated tumors are unlikely to spread to bones and have a serous (pericardial ad pleural) tropism. • These correlations could help in the clinical management of patients with metastatic lung adenocarcinoma.

[Consolidation treatment of durvalumab after chemoradiation in real-world patients with stage III unresectable non-small cell lung cancer.](#) Chu CH1,2, Chiu TH1,2, et al. Thorac Cancer. 2020 Apr 13. doi: 10.1111/1759-7714.13426. [Epub ahead of print]

**BACKGROUND:** Treatment for stage III non-small cell lung cancer (NSCLC) of unresectable disease mainly involves concurrent chemoradiation (CRT). Post-CRT consolidation treatment with durvalumab is a major therapeutic advance that provides survival benefit in this group of patients. However, the performance of this treatment strategy remains to be studied in a real-world setting. **METHODS:** A total of 31 patients who had disease control post-CRT were included in the durvalumab early access program (EAP) as an intent-to-treat cohort and retrospectively reviewed for post-CRT progression-free survival (PFS) and time to metastatic disease or death (TMDD). The neutrophil-to-lymphocyte ratio (NLR) at the initiation of durvalumab was analyzed in 29 patients. **RESULTS:** The median time from the completion of concurrent CRT to the initiation of durvalumab was 2.8 months. The objective response was 25.8% and the 12 month PFS and TMDD-free rate were 56.4% and 66.9%, respectively. The low NLR patients showed a significantly longer post-CRT PFS (not reach vs. 12.0 months [95% CI: 5.5-not estimable];  $P = 0.040$ ; the hazard ratio for disease progression or death, 0.23 [95% CI: 0.05-1.00];  $P = 0.048$ ) and the 12 month post-CRT PFS rate (82.5 vs. 42.6%). The post-CRT TMDD (not reach vs. 12.6 months, [95% CI: 10.8-not estimable];  $P = 0.010$ ; the hazard ratio for distant metastasis or death, 0.11 [95% CI: 0.01-0.88];

P = 0.037) and 12 month post-CRT TMDD-free rate (90.9 vs. 57.1%) were also significantly higher in the low NLR patients. **CONCLUSIONS:** Durvalumab consolidation treatment in real-world patients showed substantial efficacy and the correlation with the NLR level warrants further investigation.

**Healthcare resource utilization in advanced non-small-cell lung cancer: post hoc analysis of the randomized phase 3 REVEL study.** Garon EB1, Winfree KB2, Molife C2, Cui ZL2, Arriola E3, Levy B4, Mekhail T5, Pérol M6. Support Care Cancer. 2020 Apr 21. doi: 10.1007/s00520-020-05459-0. [Epub ahead of print]

**PURPOSE:** In REVEL, patients with advanced non-small-cell lung cancer (aNSCLC) and patients with increased tumor aggressiveness (rapid disease progression (RDP), platinum-refractory disease (PRD), and high symptom burden (HSB)) benefited from second-line treatment with ramucirumab plus docetaxel over placebo plus docetaxel. This post hoc analysis describes healthcare resource utilization (HCRU) associated with the treatment. **METHODS:** aNSCLC patients who had progressed during or after first-line platinum-based chemotherapy were randomized to receive docetaxel and either ramucirumab or placebo until disease progression, unacceptable toxicity, withdrawal, or death. HCRU included hospitalizations, transfusions, and concomitant medications. Categorical variables (counts and percentages) were compared using Fisher's exact test. Continuous variables (mean, standard deviation (SD), median, minimum, and maximum) were compared using the Wilcoxon rank sum test. **RESULTS:** Patient characteristics were largely similar between treatment arms. Within the intent-to-treat (ITT) population (n = 1253), the mean treatment duration was 19.7 and 16.9 weeks in the ramucirumab and control arms, respectively; 51.0% versus 54.9% of patients received subsequent anticancer therapy, respectively. Hospitalization rates were 41.9% versus 42.6% (p = 0.863), mean length of hospital stay was 14.5 days versus 11.3 days (p = 0.066), transfusion rates were 9.9% versus 12.3% (p = 0.206), and use of granulocyte colony-stimulating factors was 41.8% versus 36.6% (p = 0.063), respectively. No significant difference was observed in HCRU between treatment arms in both ITT population and in aggressive disease subgroups including RDP (n = 209), PRD (n = 360), and HSB (n = 497). **CONCLUSION:** In REVEL, the addition of ramucirumab to docetaxel did not increase HCRU among patients with aggressive aNSCLC disease. These results may help inform economic evaluation of treatment for patients with aNSCLC.

**The efficacy and safety of ramucirumab plus docetaxel in older patients with advanced non-small cell lung cancer.** Sakaguchi T1,2, Furuya N1, Ito K2, Hida N3, Morikawa K1, Komase Y3, Inoue T1, Hataji O2, Mineshita M1. Thorac Cancer. 2020 Apr 14. doi: 10.1111/1759-7714.13429. [Epub ahead of print]

**BACKGROUND:** Ramucirumab plus docetaxel (RAM+DOC) is expected to prolong survival in patients with advanced non-small cell lung cancer (NSCLC); however, the efficacy and safety for older patients remains unknown. The objective of this study was to evaluate the efficacy and safety of RAM+DOC in patients 75 years and older. **METHODS:** We retrospectively reviewed consecutive patients with advanced NSCLC who had received RAM+DOC treatment at three institutions. We compared the efficacy and safety in patients 75 years and older to those under 75 years of age. **RESULTS:** A total of 114 patients were identified. The median progression-free survival, time to treatment failure and overall survival was 3.6 (95% CI: 0.4-6.7), 3.1 (95% CI: 2.4-3.9) and 11.2 months (95% CI: 5.6-16.8) in the older group (N = 23), and 4.2 (95% CI: 3.3-5.0), 3.4 (95% CI: 3.3-5.0) and 12.2 months (95% CI: 9.1-15.4) in the younger group (N = 91), respectively. Survival curves were similar for each group, while the objective response rate was 30.4% (95% CI: 13.2-52.9%) in older patients and 35.2% (95% CI: 25.4-45.9%) for the younger group. A total of 22 older patients (95.7%) and 73 (80.2%) younger patients received primary prophylactic pegylated-granulocyte-colony stimulating factor (PEG-G-CSF). Four older patients (17.3%) and 14 younger patients (15.3%) discontinued RAM+DOC due to adverse events. **CONCLUSIONS:**



RAM+DOC is expected to be efficacious and tolerable in older patients when supported with prophylactic PEG-G-CSF therapy. **KEY POINTS:** Significant findings of the study • PFS, OS, and ORR in older patients were similar to those under 75 years of age. • Safety of RAM+DOC was well tolerated in older patients with prophylactic PEG-G-CSF. • Prophylactic PEG-G-CSF with RAM+DOC may contribute to better efficacy. What this study adds • This study suggests that RAM+DOC with prophylactic PEG-G-CSF is expected to be a useful option in older patients with advanced NSCLC.

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## NSCLC - RADIOTHERAPY

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### [Survival and Toxicity of Hypofractionated Intensity-Modulated Radiotherapy in 4-Gy Fractions for Unresectable Stage III Non-Small-Cell Lung Cancer.](#)

Kong C1, Zhu X2, Shi M3, Wang L3, et al. Int J Radiat Oncol Biol Phys. 2020 Apr 7. pii: S0360-3016(20)30979-2. doi: 10.1016/j.ijrobp.2020.03.038. [Epub ahead of print]

**PURPOSE:** To assess the survival, local and distant control and toxicity in patients with unresectable locally advanced non-small-cell lung cancer (LA-NSCLC) treated with radical-intent hypofractionated radiotherapy delivering approximately 60 Gy in 4-Gy fractions. **METHODS AND MATERIALS:** Consecutive patients with unresectable stage III NSCLC (n=42) who received hypofractionated intensity-modulated radiotherapy (hypoIMRT) were retrospectively analyzed (2012-2016). Treatments consisted of first-line platinum-based doublet induction chemotherapy followed by an intended dose of 60 Gy in 15 fractions. **RESULTS:** During a median follow-up period of 46 months (95% CI: 41 to 59) the median overall survival (OS) was 47 months (95% CI: 31 to not reached). The 1-, 2-, 3-, and 5-year OS rates were 81%, 69%, 64%, and 32%, respectively. The 1-, 2-, 3-, and 5-year progression free survival rates were 58%, 35%, 25%, and 25%, respectively. An isolated local-regional recurrence was seen in 12% of the patients (n = 5). The incidence of grade (G) 3 or higher treatment-related lung toxicity was 14% (n=6), among which G3 toxicity was 9.5% (n=4) and G5 toxicity was 4.8% (n=2). Twelve percent of patients (n=5) experienced G3 radiation esophagitis and 2% (n=1) had G4 esophageal toxicity. **CONCLUSIONS:** Patients with unresectable LA-NSCLC treated with hypoIMRT in doses up to 60 Gy at 4 Gy per fraction had promising survival although high grade esophageal and lung toxicities were seen. Our findings deserve further evaluation in prospective studies.

### [Exploiting tumor position differences between deep inspiration and expiration in lung stereotactic body radiation therapy planning.](#)

Huang C1, Shiue K1, Bartlett G1, Agrawal N1, et al. Med Dosim. 2020 Apr 2. pii: S0958-3947(20)30024-8. doi: 10.1016/j.meddos.2020.02.002. [Epub ahead of print]

**PURPOSE:** We demonstrate proof of principle that normal tissue doses can be greatly reduced in lung stereotactic body radiation therapy (SBRT) for mobile tumors, if the delivered dose is split between opposite respiratory states. **METHODS:** Patients that underwent 5 fraction lung SBRT at our institution and had deep inspiration breath hold (DIBH) and free breathing 4D computed tomography scans were included. Volumetric modulated arc therapy plans were generated on both respiratory phases and a third composite plan was generated delivering half the dose using the DIBH plan and the other half using the expiratory phase plan for each fraction. Computed tomography scans for the composite plan were fused based on ribs adjacent to the tumor to evaluate the dose volume histogram of critical structures. **RESULTS:** Four patients with 4 total tumors had requisite planning scans available. Tumor size was between 0.7 to 2.9 cm and tumor movement 1.4 to 2.9 cm. Median reduction in the chest wall (CW) V30Gy for the composite plan was 74.6% (range 33.7 to 100%), 76.9% (range 32.9 to 100%), and 89.3% (range 69.5 to 100%) compared to the DIBH, expiration phase, and free breathing plans, respectively. Median reduction in CW maximum dose for the composite plan was 23.3% (range 0.27% to 46.4%), 23.5% (range 3.2 to 48.2%), and 23.4% (range 0.27% to 48.4%) compared to the DIBH, expiration phase, and free breathing plans, respectively. Greater reduction in CW maximum dose was observed when

patients had no overlap in planning target volumes between DIBH and expiration phases (median reduction 43.9% for no overlap vs 2.7% with overlap). Between all plans, lung V20Gy absolute differences were within 1.3%. For 2 of 4 patients, the composite plan met constraints for 3 fraction SBRT, while standard plans did not. **CONCLUSIONS:** We conclude that composite DIBH-expiration SBRT planning has the potential to improve organ at risk sparing.

**[Radiotherapy for local recurrence of non-small-cell lung cancer after lobectomy and lymph node dissection-can local recurrence be radically cured by radiation?](#)** Terada Y1, Isaka M1, Harada H2, et al. *Jpn J Clin Oncol.* 2020 Apr 7;50(4):425-433. doi: 10.1093/jjco/hyz188.

**BACKGROUND:** There is no standard therapeutic approach for local recurrence of non-small cell lung cancer (NSCLC) after complete resection. We investigated the outcomes of radiotherapy (RT) for patients with local recurrence. **METHODS:** We reviewed 46 patients who underwent curative-intent RT for local recurrence after lobectomy or pneumonectomy accompanied with mediastinal lymph node dissection between 2002 and 2014. We analyzed overall survival (OS), progression-free survival (PFS), local control, tumour response and the re-recurrence pattern. **RESULTS:** Among the 46 patients, 16 received concurrent chemotherapy. The median follow-up period was 48 months. The response rate was 91%. The 5-year OS and local control rates were 47.9 and 65.3%, respectively, and the 5-year PFS rate was 22.8%. Female sex and complete response to radiation were favourable prognostic factors. Of the 33 patients with recurrence after radiation, 32 (97%) had distant metastasis. **CONCLUSIONS:** Although RT for local recurrence has high efficacy, distant relapse after radiation remains a major issue. Therefore, combination systemic therapy for local recurrence at any site should be further investigated. Since it is difficult to achieve a radical cure for local recurrence using RT, further study, for the administration of post-operative adjuvant therapy, is recommended.

**[Hospitalization and definitive radiotherapy in lung cancer: incidence, risk factors and survival impact.](#)** Hazell SZ1, Mai N1, Fu W2, et al. *BMC Cancer.* 2020 Apr 19;20(1):334. doi: 10.1186/s12885-020-06843-z.

**BACKGROUND:** Unplanned hospitalization during cancer treatment is costly, can disrupt treatment, and affect patient quality of life. However, incidence and risks factors for hospitalization during lung cancer radiotherapy are not well characterized. **METHODS:** Patients treated with definitive intent radiation ( $\geq 45$  Gy) for lung cancer between 2008 and 2018 at a tertiary academic institution were identified. In addition to patient, tumor, and treatment related characteristics, specific baseline frailty markers (Charlson comorbidity index, ECOG, patient reported weight loss, BMI, hemoglobin, creatinine, albumin) were recorded. All cancer-related hospitalizations during or within 30 days of completing radiation were identified. Associations between baseline variables and any hospitalization, number of hospitalizations, and overall survival were identified using multivariable linear regression and multivariable Cox proportional-hazards models, respectively. **RESULTS:** Of 270 patients included: median age was 66.6 years (31-88), 50.4% of patients were male ( $n = 136$ ), 62% were Caucasian ( $n = 168$ ). Cancer-related hospitalization incidence was 17% ( $n = 47$ ), of which 21% of patients hospitalized ( $n = 10/47$ ) had  $> 1$  hospitalization. On multivariable analysis, each 1 g/dL baseline drop in albumin was associated with a 2.4 times higher risk of any hospitalization (95% confidence interval (CI) 1.2-5.0,  $P = 0.01$ ), and baseline hemoglobin  $\leq 10$  was associated with, on average, 2.7 more hospitalizations than having pre-treatment hemoglobin  $> 10$  (95% CI 1.3-5.4,  $P = 0.01$ ). After controlling for baseline variables, cancer-related hospitalization was associated with 1.8 times increased risk of all-cause death (95% CI: 1.02-3.1,  $P = 0.04$ ). **CONCLUSIONS:** Our data show baseline factors can predict those who may be at increased risk for hospitalization, which was independently associated with increased mortality. Taken together, these data support the need for developing further studies aimed at early and aggressive interventions to decrease hospitalizations during treatment.

### [Stereotactic Radiotherapy for Ultra-Central Lung Oligometastases in Non-Small-Cell Lung Cancer.](#)

Loi M1, Franceschini D1, Dominici L2, et al. *Cancers (Basel)*. 2020 Apr 5;12(4). pii: E885. doi: 10.3390/cancers12040885.

**BACKGROUND:** Stereotactic body radiotherapy (SBRT) in ultra-central (UC) lung tumors, defined in the presence of planning target volume (PTV) overlap or direct tumor abutment to the central bronchial tree or esophagus, may be correlated to a higher incidence of severe adverse events. Outcome and toxicity in oligometastatic ( $\leq 3$  metastases) non-small-cell lung cancer (NSCLC) patients receiving SBRT for UC tumors were evaluated. **METHODS:** Oligometastatic NSCLC patients treated with SBRT for UC were retrospectively reviewed. Local control (LC), distant metastasis-free survival (DMFS), progression-free survival (PFS) and overall survival (OS) were calculated. Incidence and grade of toxicity were evaluated. Statistical analysis was performed to assess the impact of clinical and treatment-related variables on outcome and toxicity occurrence. **RESULTS:** Seventy-two patients were treated to a median biologically effective dose (BED) of 105 (75-132) Gy<sub>10</sub>. Two-year LC, DMFS, PFS, and OS were 83%, 46%, 43%, and 49%. BED $>75$  Gy<sub>10</sub> was correlated to superior LC ( $p = 0.02$ ), PFS ( $p = 0.036$ ), and OS ( $p < 0.001$ ). Grade  $\geq 3$  toxicity rate was 7%, including one fatal esophagitis. No variables were correlated to DMFS or to occurrence of overall and grade  $\geq 3$  toxicity. **CONCLUSIONS:** SBRT using dose-intensive schedules improves outcome in NSCLC patients. Overall toxicity is acceptable, although rare but potentially fatal toxicities may occur.

### [A simple, yet novel hybrid-dynamic conformal arc therapy planning via flattening filter-free beam for lung stereotactic body radiotherapy.](#)

Pokhrel D1, Halfman M1, Sanford L1. *J Appl Clin Med Phys*. 2020 Apr 3. doi: 10.1002/acm2.12868. [Epub ahead of print]

**PURPOSE:** Due to multiple beamlets in the delivery of highly modulated volumetric arc therapy (VMAT) plans, dose delivery uncertainties associated with small-field dosimetry and interplay effects can be concerns in the treatment of mobile lung lesions using a single-dose of stereotactic body radiotherapy (SBRT). Herein, we describe and compare a simple, yet clinically useful, hybrid 3D-dynamic conformal arc (h-DCA) planning technique using flattening filter-free (FFF) beams to minimize these effects.

**MATERIALS AND METHODS:** Fifteen consecutive solitary early-stage I-II non-small-cell lung cancer (NSCLC) patients who underwent a single-dose of 30 Gy using 3-6 non-coplanar VMAT arcs with 6X-FFF beams in our clinic. These patients' plans were re-planned using a non-coplanar hybrid technique with 2-3 differentially-weighted partial dynamic conformal arcs (DCA) plus 4-6 static beams. About 60-70% of the total beam weight was given to the DCA and the rest was distributed among the static beams to maximize the tumor coverage and spare the organs-at-risk (OAR). The clinical VMAT and h-DCA plans were compared via RTOG-0915 protocol for conformity and dose to OAR. Additionally, delivery efficiency, accuracy, and overall h-DCA planning time were recorded. **RESULTS:** All plans met RTOG-0915 requirements. Comparison with clinical VMAT plans h-DCA gave better target coverage with a higher dose to the tumor and exhibited statistically insignificant differences in gradient index, D2cm, gradient distance and OAR doses with the exception of maximal dose to skin ( $P = 0.015$ ). For h-DCA plans, higher values of tumor heterogeneity and tumor maximum, minimum and mean doses were observed and were 10%, 2.8, 1.0, and 2.0 Gy, on average, respectively, compared to the clinical VMAT plans. Average beam on time was reduced by a factor of 1.51. Overall treatment planning time for h-DCA was about an hour. **CONCLUSION:** Due to no beam modulation through the target, h-DCA plans avoid small-field dosimetry and MLC interplay effects and resulting in enhanced target coverage by improving tumor dose (characteristic of FFF-beam). The h-DCA simplifies treatment planning and beam on time significantly compared to clinical VMAT plans. Additionally, h-DCA allows for the real time target verification and eliminates patient-specific VMAT quality assurance; potentially offering cost-effective,

same or next day SBRT treatments. Moreover, this technique can be easily adopted to other disease sites and small clinics with less extensive physics or machine support.

**Prognostic factors of local control and disease free survival in centrally located non-small cell lung cancer treated with stereotactic body radiation therapy.** Duijm M1, van der Voort van Zyp NC2, Granton PV1, van de Vaart P2, Mast ME2, Oomen-de Hoop E1, Hoogeman MS1, Nuyttens JJ1. Acta Oncol. 2020 Apr 14:1-9. doi: 10.1080/0284186X.2020.1750693. [Epub ahead of print]

**BACKGROUND:** Stereotactic body radiation therapy (SBRT) results in high local control (LC) rates in patients with non-small cell lung cancer (NSCLC). For central lung tumors, risk-adapted fractionation schedules are used and underdosage to the Planned Target Volume (PTV) is often accepted to respect the dose constraints of the organs at risk in order to avoid high rates of toxicity. The purpose of this study was to analyze the effect of PTV underdosage and other possible prognostic factors on local- and disease control after SBRT in patients with central lung tumors. **MATERIAL AND METHODS:** Patients with centrally located NSCLC treated with SBRT were included. The doses were converted into biologically equivalent dose using  $\alpha/\beta$ -value of 10 Gy (BED10). Underdosage to the PTV was defined as the (percentage of) PTV receiving less than 100 Gy BED10; (%PTV < 100 BED10. Potential prognostic factors for LC and Disease Free Survival (DFS) were evaluated using Cox regression analysis.

**RESULTS:** Two hundred and twenty patients received  $\leq 12$  fractions of SBRT. LC-rates were 88% at 2 years and 81% at 3 years. Twenty-seven patients developed a local recurrence. Both the PTV < 100 BED10 and %PTV < 100 BED10 were not prognostic for LC. Tumor size and forced expiratory volume in 1 second (FEV1) were independently prognostic for LC. Disease progression was reported in 75 patients with DFS-rates of 66% at 2 years and 56% at 3 years. Disease recurrence was independent significantly associated with larger tumor diameter, lower lobe tumor location and decreased FEV1. Grade 4-5 toxicity was reported in 10 patients (8 with ultra-central tumors) and was fatal in at least 3 patients. **CONCLUSION:** Decrease in tumor coverage was not correlated with the local recurrence probability. The LC and DFS were promising after SBRT of centrally located NSCLC with tumor size, FEV1 and tumor location (for DFS only) as prognostic factors.

**Predictors of Distant Recurrence Following Stereotactic Body Radiation Therapy for Stage I Non-Small Cell Lung Cancer.** Wong JK1, Shaikh T1, DeMora L2, Zhang E1, Borghaei H3, Hayes SB1, Kumar S1, Meyer JE1, Hallman MA1. Am J Clin Oncol. 2020 Apr;43(4):243-248. doi: 10.1097/COC.0000000000000662.

**OBJECTIVE:** The objective of this study was to characterize patients at an increased risk of distant metastasis (DM) following stereotactic body radiation therapy (SBRT) for stage I non-small cell lung cancer (NSCLC). **MATERIALS AND METHODS:** We identified patients undergoing SBRT for stage I NSCLC between 2005 and 2016. Patients with a prior lung cancer diagnosis, receiving a biological effective dose <100 Gy, or receiving chemotherapy were excluded. Patients underwent pretreatment staging and were classified according to the American Joint Committee for Cancer (AJCC) 8th edition staging. The primary endpoint was DM. The Kaplan-Meier method and the Cox proportional hazards model were used for survival analysis and to identify predictors of DM. **RESULTS:** A total of 174 patients were included, with a median age 75 years (range, 49 to 96 y) and a median follow-up of 24 months (range, 3 to 123 mo). The 2- and 4-year cumulative incidences of DM were 14.2% and 19.1%, respectively. Patients who developed DM had worse overall survival versus patients developing a locoregional recurrence ( $P=0.023$ ). On multivariable analysis, having stage IB disease (hazard ratio: 2.95; 95% confidence interval: 1.06-8.23;  $P=0.039$ ) or a lower/middle lobe tumor (hazard ratio: 2.67; 95% confidence interval: 1.07-6.69;  $P=0.036$ ) was associated with increased risk of DM. The 2-year cumulative incidences of DM were 10.9% and 35.7% ( $P=0.002$ ) for patients with stage IA versus IB tumors, respectively, and 11.3% and 19.7% ( $P=0.049$ ) for patients with upper lobe versus lower/middle



lobe tumors, respectively. **CONCLUSIONS:** Patients with stage IB disease or lower/middle lobe tumors may have an increased risk of DM following SBRT. Randomized controlled trials are needed to further identify patients who may benefit from adjuvant systemic therapy after SBRT for stage I NSCLC.

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## SMALL CELL LUNG CANCER - SCLC

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### [Outcomes with immune checkpoint inhibitors for relapsed small-cell lung cancer in a Swiss cohort.](#)

Schmid S1,2, Mauti LA3, Friedlaender A4, et al. Cancer Immunol Immunother. 2020 Apr 19. doi: 10.1007/s00262-020-02565-0. [Epub ahead of print]

**OBJECTIVES:** Early clinical trials showed promising outcomes with immune-checkpoint inhibitors (ICI) in a subset of patients with relapsed small-cell lung carcinoma (SCLC). The aim of this retrospective analysis was to assess the efficacy and safety of ICI for relapsed SCLC in a real-world patient population. **METHODS:** Nine cancer centres in Switzerland contributed data to this cohort. Responses were assessed by the local investigators using standard RECIST v1.1 criteria. Progression-free survival (PFS) and overall survival (OS) were analysed by the Kaplan-Meier method. Associations between potential predictive markers and survival endpoints were probed by Cox proportional hazards. **RESULTS:** Forty-five patients were included in the analysis. Median age was 63 years, 73% were males and 18% had an ECOG performance status (PS)  $\geq 2$ . ICIs were given as second-line treatment in 60%. Twenty-four patients (53%) received ipilimumab with nivolumab. Twenty-eight patients (62%) had undergone irradiation (RT) prior to or during ICI. Overall response rate (ORR) was 29% and median PFS and OS were 2.3 and 6.5 months, respectively. Median duration of response was 9 months (95% CI 2.8-NA). Five patients maintained their response for  $> 6$  months, all of them receiving combination treatment. There were no new safety signals. **CONCLUSION:** This is the first report of "real-world" data on ICI in relapsed SCLC also including patients with poor PS. Promising durable responses were observed. No biological prognostic marker could be identified.

### [A Prospective Study of Apatinib in Patients with Extensive-Stage Small Cell Lung Cancer After Failure of Two or More Lines of Chemotherapy.](#)

Liu Y1, Hu X1, Jiang J2, Yang L3, Zhou S1, Liu P1, Li J1, Wang Y1, Hao X1, Shi Y1. Oncologist. 2020 Apr 6. doi: 10.1634/theoncologist.2019-0391. [Epub ahead of print]

**BACKGROUND:** Because of rapid disease progression and lack of optimal treatment strategies beyond the second-line, the prognosis of patients with extensive-stage (ES) small cell lung cancer (SCLC) still remains depressing. Alternative treatment strategies are required to improve their prognosis. In this prospective clinical study, we aimed to evaluate the feasibility of single-agent apatinib, a vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor, as a treatment option for patients with ES-SCLC after failure of at least two prior chemotherapy regimens. **MATERIALS AND METHODS:** Twenty-two patients with ES-SCLC treated with 500 mg single-agent apatinib as subsequent-line regimen in our institution from November 2016 to August 2018 were enrolled in the study. The primary endpoint was progression-free survival (PFS). The secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and adverse events (AEs). **RESULTS:** Clinical outcomes included partial response in 3 patients (13.6%), stable disease in 18 patients (81.8%), and disease progression in 1 patient (4.5%), with an ORR of 13.6% and DCR of 95.5%. The median PFS and OS were 5.4 and 10.0 months, respectively. Apatinib demonstrated a manageable toxicity profile, with grade I-III secondary hypertension and proteinuria as the most common AEs. No grade IV and V AEs were observed among the patients. Multivariate analysis revealed secondary hypertension as an independent predictor of OS ( $p = .047$ ); however, the association became insignificant after Q correction ( $p = .455$ ). **CONCLUSIONS:** Apatinib was safe and effective in the management of patients with ES-SCLC and can be considered as a treatment option after failure of at least two prior chemotherapy

regimens. ClinicalTrials.gov identifier. NCT02995187 IMPLICATIONS FOR PRACTICE: This study indicated the acceptable toxicity profile and promising efficacy of apatinib in the management of patients with extensive-stage small cell lung cancer after failure from at least two prior chemotherapy regimens. Secondary hypertension can be a potential prognostic factor for apatinib treatment.

**[Comprehensive bioinformatics analysis identifies tumor microenvironment and immune-related genes in small cell lung cancer.](#)** Song Y1, Sun Y2, Sun T1, Tang R1. Comb Chem High Throughput Screen. 2020 Apr 6. doi: 10.2174/1386207323666200407075004. [Epub ahead of print]

**BACKGROUND:** Tumor microenvironment (TME) cells play important roles in tumor progression. Accumulating evidence show that they can be exploited to predict the clinical outcomes and therapeutic responses of tumor. However, the role of immune genes of TME in small cell lung cancer (SCLC) is currently unknown. **OBJECTIVE:** To determine the role of immune genes in SCLC. **METHODS:** We downloaded the expression profile and clinical follow-up data of SCLC patients from Gene Expression Omnibus (GEO), and TME infiltration profile data of 158 patients using CIBERSORT. The correlation between TME phenotypes, genomic features, and clinicopathological features of SCLC was examined. A gene signature was constructed based on TME genes to further evaluate the relationship between molecular subtypes of SCLC with the prognosis and clinical features. **RESULTS:** We identified a group of genes that are highly associated with TME. Several immune cells in TME cells were significantly correlated with SCLC prognosis ( $p < 0.0001$ ). These immune cells displayed diverse immune patterns. Three molecular subtypes of SCLC (TMEC1-3) were identified on the basis of enrichment of immune cell components, and these subtypes showed dissimilar prognosis profiles ( $p = 0.03$ ). The subtype with the best prognosis, TMEC3, was enriched with immune activation factors such as oncogene M0, oncogene M2, T cells follicular helper, and T cells CD8 ( $p < 0.001$ ). The TMEC1 subtype with the worst prognosis was enriched with T cells CD4 naive, B cells memory and Dendritic cells activated cells ( $p < 0.001$ ). Further analysis showed that the TME was significantly enriched with immune checkpoint genes, immune genes, and immune pathway genes ( $p < 0.01$ ). From the gene expression data, we identified four TME-related genes, GZMB, HAVCR2, PRF1 and TBX2, which were significantly associated with poor prognosis in both the training set and the validation set ( $p < 0.05$ ). These genes may serve as markers for monitoring tumor responses to immune checkpoint inhibitors. **CONCLUSION:** This study shows that TME features may serve as markers for evaluating response of SCLC cells to immunotherapy.

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## PALLIATIVE AND SUPPORTIVE CARE

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**[Patient-reported symptom burden and supportive care needs at cancer diagnosis: a retrospective cohort study.](#)** Cuthbert CA1, Boyne DJ2, Yuan X2,3, Hemmelgarn BR4,5, Cheung WY3,6. Support Care Cancer. 2020 Apr 8. doi: 10.1007/s00520-020-05415-y. [Epub ahead of print]

**PURPOSE:** Patient-reported outcomes (PROs) are used to assess patients' symptoms and supportive care needs. While PROs are increasingly employed in clinical practice, research utilizing these data remains limited. Our goal was to evaluate PROs from a provincial cancer program. **METHODS:** A retrospective, population-based cohort study using administrative health data of patients in Alberta, Canada, diagnosed with cancer between January 1, 2016, and October 23, 2017. Adults who completed PROs (Edmonton Symptom Assessment System, ESAS) and supportive care needs inventory (Canadian Problem Checklist)) within  $\pm 60$  days of diagnosis were included. Patients were stratified by tumor types (breast, colorectal, lung, prostate, hematological, or other). Descriptive statistics were used to characterize symptom burden and supportive care needs. Multivariate logistic regression was used to evaluate factors associated with higher symptom severity. **RESULTS:** We included 1310 patients (mean age 64 years; 51% female), the majority of whom had breast (19%), lung (25%), or other cancers (26%). For the cohort, severity of symptoms based on ESAS was low, but prevalence of specific symptoms was high including

tiredness (84%), anxiety (60%), pain (60%), and low well-being (80%). Seventy percent of the cohort reported at least one supportive care need. The highest-ranking problems were fears and worries and needing information about illness/treatment. There were differences across tumor types with respect to symptoms and supportive care needs. Comorbidity and having a high number of supportive care needs were associated with higher symptom severity. **DISCUSSION:** Our results underscore the need to develop and implement tumor-specific supportive care interventions.

### [Tumor Mutation Burden and Depression in Lung Cancer: Association With Inflammation.](#)

McFarland DC1, Jutagir DR1, Miller AH2, Breitbart W1, Nelson C1, Rosenfeld B3. *J Natl Compr Canc Netw.* 2020 Apr;18(4):434-442. doi: 10.6004/jnccn.2019.7374.

**BACKGROUND:** Patients with lung cancer with greater systemic inflammation have higher rates of depression. Tumor mutation burden (TMB) predicts immunotherapy response in patients with lung cancer and is associated with intratumoral inflammation, which may contribute to systemic inflammation and depression. This study evaluated whether higher TMB was associated with increased depression and systemic inflammation in patients with lung cancer. **PATIENTS AND METHODS:** Patients with metastatic lung cancers were evaluated for depression severity using the Hospital Anxiety and Depression Scale. TMB was measured using the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets. Inflammation was evaluated using C-reactive protein (CRP) level and neutrophil-to-lymphocyte ratio (NLR). **RESULTS:** A total of 96 patients with adequate TMB testing were evaluated. The average number of mutations (TMB) was 10.8 (SD, 10.9). A total of 19% of patients endorsed clinically significant depression symptoms. TMB was significantly correlated with depression severity ( $r = 0.34$ ;  $P = .001$ ) and NLR ( $r = 0.37$ ;  $P = .002$ ) but not CRP level ( $r = 0.19$ ;  $P = .07$ ). TMB was also higher in patients receiving chemotherapy (mean, 12.0) and immunotherapy (mean, 14.4) versus targeted therapy (mean, 4.8). A multivariate model found that TMB ( $\beta = 0.30$ ;  $P = .01$ ) and CRP level ( $\beta = 0.31$ ;  $P = .01$ ) were independently associated with depression; there was no significant interaction effect of  $TMB \times CRP$  and depression. A similar multivariate model showed no independent effect for NLR and depression ( $\beta = 0.16$ ;  $P = .17$ ) after accounting for TMB. **CONCLUSIONS:** These data provide evidence for biologic depression risk in patients with lung cancer who have high levels of TMB. The underlying mechanism of the association is not clearly related to inflammation but warrants further analysis to broadly elucidate the mechanism of biologically derived depression in cancer.

### [Patterns of Symptom Management Medication Receipt at End-of-Life Among Medicare Beneficiaries With Lung Cancer.](#)

Saphire ML1, Prsic EH2, Canavan ME3, Wang SJ4, Presley CJ5, Davidoff AJ6. *J Pain Symptom Manage.* 2020 Apr;59(4):767-777.e1. doi: 10.1016/j.jpainsymman.2019.11.015. Epub 2019 Nov 26.

**CONTEXT:** Older adults with advanced lung cancer experience high symptom burden at end of life (EOL), yet hospice enrollment often happens late or not at all. Receipt of medications to manage symptoms in the outpatient setting, outside the Medicare hospice benefit, has not been described.

**OBJECTIVES:** We examined patterns of symptom management medication receipt at EOL for older adults who died of lung cancer. **METHODS:** This retrospective cohort used the Surveillance, Epidemiology, and End Results-Medicare database to identify decedents diagnosed with lung cancer at age 67 years and older between January 2008 and December 2013 who survived six months and greater after diagnosis. Using Medicare Part B and D claims, we identified monthly receipt of outpatient medications for symptomatic management of pain, emotional distress, fatigue, dyspnea, anorexia, and nausea/vomiting. Multivariable logistic regression estimated associations between medication receipt and patient demographic characteristics, comorbidity, and concurrent therapy. **RESULTS:** Of the 16,246 included patients, large proportions received medications for dyspnea (70.7%), pain (62.5%), and emotional distress (49.4%), with lower prevalence for other symptoms. Medication receipt increased from

six months to one month before death. Women and dual Medicaid enrolled were more likely to receive medications for pain, emotional distress, dyspnea, and nausea/vomiting. Receipt of symptom management medications decreased with increasing age and racial/ethnic minorities. **CONCLUSION:** Symptom management medication receipt was common and increasing toward EOL. Lower use by males, older adults, and nonwhites may reflect poor access or poor patient-provider communication. Further research is needed to understand these patterns and assess adequacy of symptom management in the outpatient setting.

**Association between early informed diagnosis and survival time in patients with lung cancer.**

Su T1,2, He C1, Li X3,4, Xiao L1, He J1, Bai Y2, Tang Y1,2. *Psychooncology*. 2020 Apr 7. doi: 10.1002/pon.5360. [Epub ahead of print]

**OBJECTIVE:** As a malignant tumor with high mortality, lung cancer (LC) often causes great trauma to patients, and a series of negative emotions and a heavy psychological burden accompanies poor prognosis. Whether or not to inform the patients of their condition has always been a controversial topic in the medical community. This retrospective cohort study investigated the association between early informed diagnosis and survival time in patients with LC. **METHODS:** A total of 29 825 patients with LC were enrolled between October 2002 and December 2016. The potential factors influencing LC survival were registered, including knowing their cancer diagnosis status, age, gender, pathological type, clinical stage, surgical history, hospital grade, and patient occupation. All participants were followed up every 6 months until June 2017. **RESULTS:** In June 2017, 23.1% of the participants still survived. Their median survival time (MST) was 11.20 months (95% confidence interval [CI], 10.98-11.43). Generally, patients that knew their cancer diagnosis had longer MST than those who did not (18.33 months vs 8.77 months,  $P < .001$ ). By stratified analysis, patients that knew their cancer diagnosis had longer survival time in each subgroup ( $P < .001$ , all subgroups). Cox regression analysis showed that knowing their cancer diagnosis was an independent influencing factor for survival in patients with LC (hazard ratio, 0.826; 95% CI, 0.802-0.851;  $P < .001$ ). **CONCLUSIONS:** Knowing their cancer diagnosis contributed to longer survival time in patients with LC, providing clear evidence that medical staff and patients' families should fully disclose cancer diagnoses to patients.

**Sleep quality, anxiety and depression in advanced lung cancer: patients and caregivers.**

He Y1,2, Sun LY3, Peng KW1, Luo MJ1, Deng L4, Tang T4, You CX5. *BMJ Support Palliat Care*. 2020 Apr 6. pii: bmjpspcare-2018-001684. doi: 10.1136/bmjpspcare-2018-001684. [Epub ahead of print]

**OBJECTIVE:** To investigate the clinical implications of sleep quality, anxiety and depression in patients with advanced lung cancer (LC) and their family caregivers (FCs). **METHODS:** A total of 98 patients with advanced LC and their FCs ( $n=98$ ) were recruited from the Oncology Department in Nanfang Hospital. The Pittsburgh Sleep Quality Index (PSQI), consisting of seven components that evaluate subjective sleep quality, sleep latency, duration of sleep, sleep efficiency, sleep disturbances, sleep medication usage and daytime dysfunction, was used to assess sleep quality. Using the tool of Zung Self-rating Anxiety Scale (SAS) and Zung Self-rating Depression Scale (SDS), we tested the patients' status of anxiety and depression, respectively. **RESULTS:** The prevalences of poor sleep quality, anxiety and depression in patients were 56.1%, 48.9% and 56.1%, respectively, while those in FCs were 16.3%, 32.6% and 25.5%, respectively. Patients had higher PSQI, SAS and SDS scores than did FCs ( $p < 0.05$ ). Significant correlations were found between the patients' and FCs' scores of PSQI/SAS/SDS ( $p < 0.05$ ). Multivariate Cox regression analyses indicated that sleep disturbances in patients (HR 0.413, 95% CI 0.21 to 0.80,  $p=0.01$ ) and the global PSQI score of FCs (HR 0.31, 95% CI 0.14 to 0.71,  $p=0.00$ ) were independent risk factors for patients' first-line progression-free survival (PFS). Moreover, patients' sleep latency (HR 2.329, 95% CI 1.36 to 3.96,  $p=0.00$ ) and epidermal growth factor receptor mutations (HR 1.953, 95% CI 1.12 to 3.38,  $p=0.01$ ) were significant prognostic factors for their overall survival (OS).



**CONCLUSIONS:** We demonstrated that presence of sleep disturbances in patients with advanced LC and the global PSQI Score of their FCs may be risk predictors for patients' poor first-line PFS. Patients' sleep latency was a potential risk factor for their OS.

[Physical activity for people with lung cancer.](#) Edbrooke L1, Granger CL2, Denehy L3. Aust J Gen Pract. 2020 Apr;49(4):175-181. doi: 10.31128/AJGP-09-19-5060.

**BACKGROUND:** International guidelines recommend exercise for all people with cancer. Effective supportive care interventions are required for people diagnosed with lung cancer to reduce morbidity associated with the disease process, frequently occurring comorbidities and treatment-related side effects.

**OBJECTIVE:** This article summarises the evidence regarding the safety, effectiveness and patient experiences of exercise and physical activity interventions for people with lung cancer. **DISCUSSION:** Exercise interventions for people with lung cancer are safe and effective at improving physical fitness, muscle strength and patient-reported outcomes including cancer-related fatigue, dyspnoea and health-related quality of life. Increasing evidence supports the use of exercise prior to treatment (prehabilitation) to improve outcomes following surgery. Individuals with lung cancer should be encouraged to be as physically active as possible. Throughout the patient's cancer journey, consideration and prescription of individualised exercise is an important component of care. General practitioners are well placed to coordinate this care, often in conjunction with exercise physiologists or physiotherapists.

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## COMPLEMENTARY & ALTERNATIVE THERAPY

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[An aqueous extract of a Bifidobacterium species induces apoptosis and inhibits invasiveness of non-small cell lung cancer cells.](#) An J1, Kim HS2, Yang KM2. J Microbiol Biotechnol. 2020 Apr 2. doi: 10.4014/jmb.1912.12054. [Epub ahead of print]

Chemotherapy regimens for non-small cell lung cancer (NSCLC) have various adverse effects on the human body. For this reason, probiotics have received attention regarding their potential value as a safe and natural complementary strategy for cancer prevention. This study analyzed the anticancer effects of aqueous extracts of probiotic bacteria *Bifidobacterium bifidum* (BB), *Bifidobacterium longum* (BL), *Bifidobacterium lactis* (BLA), *Bifidobacterium infantis* 1 (BI1), and *Bifidobacterium infantis* 2 (BI2) on NSCLC cell lines. When the aqueous extracts of probiotic *Bifidobacterium* species were applied to the NSCLC cell lines A549, H1299, and HCC827, cell death increased considerably; in particular, the aqueous extracts from BB and BLA markedly reduced cell proliferation. p38 phosphorylation induced by BB aqueous extract increased the expression of cleaved caspase 3 and cleaved poly (ADP-ribose) polymerase (PARP), consequently inducing the apoptosis of A549 and H1299 cells. When the p38 inhibitor SB203580 was applied, phosphorylation of p38 decreased, and the expression of cleaved caspase 3 and cleaved PARP was also inhibited, resulting in a reduction of cell death. In addition, BB aqueous extracts reduced the secretion of MMP-9, leading to inhibition of cancer cell invasion. By contrast, after transfection of short hairpin RNA shMMP-9 (for a knockdown of MMP-9) into cancer cells, BB aqueous extracts treatment failed to suppress the cancer cell invasiveness. According to our results about their anticancer effects on NSCLC, probiotics consisting of *Bifidobacterium* species may be useful as adjunctive anticancer treatment in the future.

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## MISCELLANEOUS WORKS

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[Metabolomics Profiles of Smokers from Two Ethnic Groups with Differing Lung Cancer Risk.](#) Dator R, Villalta PW, Thomson N, Jensen J, Hatsukami DK, Stepanov I, Warth B, Balbo S. Chem Res Toxicol. 2020 Apr 15. doi: 10.1021/acs.chemrestox.0c00064. [Epub ahead of print]

African American (AA) smokers are at a higher risk of developing lung cancer compared to Whites. The variations in the metabolism of nicotine and tobacco-derived carcinogens in these groups were reported previously with the levels of nicotine metabolites and carcinogen-derived metabolites measured using targeted approaches. While useful, these targeted strategies are not able to detect global metabolic changes for use in predicting the detrimental effects of tobacco use and ultimately lung cancer susceptibility among smokers. To address this limitation, we have performed global untargeted metabolomics profiling in urine of AA and White smokers to characterize the pattern of metabolites, identify differentially regulated pathways, and correlate these profiles with the observed variations in lung cancer risk between these two populations. Urine samples from AA (n=30) and White (n=30) smokers were used for metabolomics analysis acquired in both positive and negative electrospray ionization modes. LC-MS data were uploaded onto the cloud-based XCMS Online (<http://xcmsonline.scripps.edu>) platform for retention time correction, alignment, feature detection, annotation, statistical analysis, data visualization, and automated systems biology pathway analysis. The latter identified global differences in the metabolic pathways in the two groups including the metabolism of carbohydrates, amino acids, nucleotides, fatty acids, and nicotine. Significant differences in the nicotine degradation pathway (cotinine glucuronidation) in the two groups were observed and confirmed using a targeted LC-MS/MS approach. These results are consistent with previous studies demonstrating AA smokers with lower glucuronidation capacity compared to Whites. Furthermore, the D-glucuronate degradation pathway was found to be significantly different between the two populations, with lower amounts of the putative metabolites detected in AA compared to Whites. We hypothesize that the differential regulation of the D-glucuronate degradation pathway is a consequence of the variations in the glucuronidation capacity observed in the two groups. Other pathways including the metabolism of amino acids, nucleic acids, and fatty acids were also identified, however, the biological relevance and implications of these differences across ethnic groups need further investigation. Overall, the applied metabolomics approach revealed global differences in the metabolic networks and endogenous metabolites in AA and Whites, which could be used and validated as new potential panel of biomarkers that could be used to predict lung cancer susceptibility among smokers in population-based studies.

#### **[How we treat patients with lung cancer during the SARS-CoV-2 pandemic: primum non nocere.](#)**

Banna G1, Curioni-Fontecedro A2, Friedlaender A3, Addeo A4. *ESMO Open*. 2020 Apr;5(2). pii: e000765. doi: 10.1136/esmopen-2020-000765.

New cases of the novel coronavirus, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continue to rise worldwide. A few reports have showed that mortality due to SARS-CoV-2 is higher in elderly patients and other active comorbidities including cancer. To date, no effective treatment has been identified and management for critically ill patients relies on management in intensive care units. Patients with lung cancer are at risk of pulmonary complications from COVID-19.

Furthermore, the use of chemotherapy might have a negative impact in patient's outcome. Therefore, the risk/benefit ratio of systemic anticancer treatment (SACT) has to be considered. For each patient, several factors including age and comorbidities, as well as the number of hospital visits for treatment, can influence this risk. Each hospital around the world has issued some internal policy guidelines for oncologists, aiming to limit risks during this difficult time. We hereby propose a tool to support oncologists and physicians in treatment decision for patients with lung cancer. There are several variables to consider, including the extent of the epidemic, the local healthcare structure capacity, the risk of infection to the individual, the status of cancer, patients' comorbidities, age and details of the treatment. Given this heterogeneity, we have based our suggestions bearing in mind some general factors. There is not easy, universal solution to oncological care during this crisis and, to complicate matters, the duration of this pandemic is hard to predict. It is important to weigh the impact of each of our decisions in these trying times rather than rely on routine automatism.

[Chronic obstructive pulmonary disease and lung cancer incidence in never smokers: a cohort study.](#)

Park HY#1, Kang D#2,3, Shin SH1, et al. *Thorax*. 2020 Apr 2. pii: thoraxjnl-2019-213732. doi: 10.1136/thoraxjnl-2019-213732. [Epub ahead of print]

There has been limited evidence for the association between chronic obstructive pulmonary disease (COPD) and the incidence of lung cancer among never smokers. We aimed to estimate the risk of lung cancer incidence in never smokers with COPD, and to compare it with the risk associated with smoking. This cohort study involved 338 548 subjects, 40 to 84 years of age with no history of lung cancer at baseline, enrolled in the National Health Insurance Service National Sample Cohort. During 2 355 005 person-years of follow-up (median follow-up 7.0 years), 1834 participants developed lung cancer. Compared with never smokers without COPD, the fully-adjusted hazard ratios (95% CI) for lung cancer in never smokers with COPD, ever smokers without COPD, and ever smokers with COPD were 2.67 (2.09 to 3.40), 1.97 (1.75 to 2.21), and 6.19 (5.04 to 7.61), respectively. In this large national cohort study, COPD was also a strong independent risk factor for lung cancer incidence in never smokers, implying that COPD patients are at high risk of lung cancer, irrespective of smoking status.

[Communicating radon risk via a smartphone app: a pilot intervention study.](#) Kim S1, Brewster MS2, Schwartz GG3. *BMC Public Health*. 2020 Apr 22;20(1):547. doi: 10.1186/s12889-020-08677-7.

**BACKGROUND:** Residential radon is a major preventable cause of lung cancer. However, prevention requires radon testing and it has proven very challenging to motivate individuals to test their homes for hazards like radon that are invisible and whose health effects occur after a long latency following exposure. Novel approaches to radon communication are urgently needed. **METHODS:** We created a novel radon-education app for smartphones and examined its effectiveness in increasing radon knowledge and radon testing. We studied radon knowledge and attitudes and behavior relevant to radon testing before and after app use. **RESULTS:** Ninety-seven undergraduates installed the app on their smartphones and used it for a month. App use resulted in higher scores in the domains of radon knowledge ( $p < .001$ ); self-efficacy ( $p < .001$ ), and response efficacy ( $p < .001$ ). Twenty-three participants (24%) used the app to obtain a free radon test kit. Self-efficacy ( $p < .05$ ) and response efficacy ( $p < .01$ ) were positive predictors of ordering a test kit. The test process completion rate (the fraction of participants who ordered test kits, used them to test their houses and sent the kits to the lab) was 9%. **CONCLUSIONS:** A smartphone app is a promising venue for communicating radon risk and for stimulating radon testing. Future interventions designed to increase actual test kit use are required to maximize the benefit of the app.