Caring Ambassadors Lung Cancer Program
Literature Review, February 2019

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

A two-circular RNA signature as a noninvasive diagnostic biomarker for lung adenocarcinoma.
Liu XX1, Yang YE2, Liu X1, Zhang MY1, Li R1, Yin YH1, Qu YQ3. J Transl Med. 2019 Feb 18;17(1):50. doi: 10.1186/s12967-019-1800-z.

BACKGROUND:b Recently, circular RNAs (circRNAs) have been reported to be microRNA sponges and play essential roles in cancer development. This study aimed to evaluate whether circulating circRNAs could be used as diagnostic biomarkers for lung adenocarcinoma (LUAD). **METHODS:** The Gene Expression Omnibus (GEO) dataset was used to investigate differentially expressed circRNAs (DEcircRNAs) in paired LUAD tissues and adjacent nontumor tissues. The expression levels of the host genes were analyzed in The Cancer Genome Atlas (TCGA)-LUAD dataset, and the prognostic value was assessed using the Kaplan-Meier plotter. Quantitative real-time PCR (qRT-PCR) was performed to validate the expression of candidate circRNAs in the LUAD plasma and cells. The CCK8 assay was used to measure the function of circRNAs in cell proliferation. Competing endogenous RNA (ceRNA) network, gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were performed to predict the possible mechanisms and functions of circRNAs in LUAD. **RESULTS:** Two upregulated and two downregulated circRNAs were identified as candidate circRNAs using bioinformatics analysis. qRT-PCR demonstrated that hsa_circ_0005962 was upregulated in LUAD plasma and cells, whereas hsa_circ_0086414 was downregulated. Receiver operating characteristic (ROC) curve analysis confirmed that a signature comprising the two circRNAs had good diagnostic potential, with an area under the ROC curve (AUC) of 0.81 (P < 0.0001). In addition, we observed that overexpression of plasma hsa_circ_0086414 was related to EGFR mutations (P = 0.001). Plasma hsa_circ_0005962 displayed significantly different expression before and after surgery in patients with LUAD (P < 0.0001). In vitro experiments suggested that hsa_circ_0005962 promoted LUAD cell proliferation. For future studies, we predicted the circRNA-miRNA-mRNA network for hsa_circ_0005962. Bioinformatics analysis revealed that hsa_circ_0005962 might be involved in LUAD development. **CONCLUSION:** A circRNA signature was identified as a potential noninvasive biomarker for LUAD diagnosis.

Molecular Testing for EGFR Mutations and ALK Rearrangements in the Cytological Specimens From the Patients With Non-Small Cell Lung Cancer. Wang X1, Chen S, Emerson RE, Wu HH, et al. Appl Immunohistochem Mol Morphol. 2019 Feb;27(2):119-124. doi: 10.1097/PAI.0000000000000701.
OBJECTIVE: The aim of this study was to investigate epidermal growth factor receptor (EGFR) gene mutations and anaplastic lymphoma kinase (ALK) gene rearrangements using cytological specimens from the patients with a diagnosis of primary or metastatic lung non-small cell carcinoma. **MATERIALS AND METHODS:** A total 307 cases were submitted for EGFR mutational analysis and 265 cases for ALK analysis. The cytological specimen sources included lung, lymph node, liver, bone, adrenal gland, mesentery mass, and body fluids/bronchial brushing. EGFR mutations in the exons 18 to 21 were analyzed with Qiagen EGFR Pyro Kits. Fluorescence in situ hybridization (FISH) studies for ALK rearrangement inv(2)(p21; p23) were performed on the paraffin-embedded cell block sections utilizing dual-color Vysis LSI ALK Break Apart Probe Kit. **RESULTS:** Among 307 fine needle aspirate cases for EGFR analysis, 302 cases (269 from cell blocks, 33 from direct smears) had sufficient material for EGFR test. Five cases failed due to inadequate cellularity. Twenty six of 302 (8.6%) cases were positive for EGFR mutations. A total of 265 cases submitted for ALK analysis included 240 cases of fine needle aspirate, 25 cases of pleural fluid/pericardial fluid/bronchial washings. Eight cases failed because of low cellularity, whereas 257 of 265 cases had sufficient material for ALK FISH study. Nine of 257 cases (3.5%) revealed ALK rearrangement by FISH. **CONCLUSIONS:** The current study demonstrates that cytological specimens can yield sufficient material for EGFR mutations and ALK rearrangement test. Our study reveals that 8.6% of EGFR mutation rate and 3.5% of ALK rearrangement rate in the cytology specimens from the patients with primary or metastatic lung non-small cell carcinoma.

Poor Uptake of Lung Cancer Screening: Opportunities for Improvement. Triplette M1, Thayer JH2, Pipavath SN3, Crothers K4. J Am Coll Radiol. 2019 Feb 15. pii: S1546-1440(18)31583-7. doi: 10.1016/j.jacr.2018.12.018. [Epub ahead of print]
Lung cancer screening with low-dose chest CT has been demonstrated to reduce lung cancer mortality among a subset of high-risk current and former smokers. Despite randomized trial evidence and widespread guideline recommendations, uptake of lung cancer screening among currently eligible individuals remains poor. Recent studies estimate that less than 5% of all eligible individuals have undergone screening. Moreover, inappropriate screening of ineligible individuals seems to be common, and among those who have been screened, follow-up may also be poor. In this review, the authors examine recent studies demonstrating the current state of suboptimal implementation of lung cancer screening. The authors also introduce both patient- and provider-facing evidence-based interventions that may improve implementation of screening. These include tailored navigation interventions to overcome patient barriers throughout the screening care continuum and interventions to improve the identification of eligible individuals for providers. Further evidence on best practices around the implementation of lung cancer screening is essential to ensure that recent evidence can be translated into practice to improve the early detection of lung cancer for high-risk individuals.

Racial Differences in Smoking-related Disease Risk Perceptions Among Adults Completing Lung Cancer Screening: Follow-up Results from the ACRIN/NLST Ancillary Study. Perez GK1,2, Gareen IF3,4, Sicks J4, Lathan C5,6, Carr A7, Kumar P8, Ponzani C5, Hyland K7,9, Park ER7,5. J Racial Ethn Health Disparities. 2019 Feb 8. doi: 10.1007/s40615-019-00566-z. [Epub ahead of print]
Previous work suggests that, compared to white adults, black adults have lower perceived risk for smoking-related diseases (SRDs), which may influence cessation behavior and health outcomes; however, racial differences in SRD risk perceptions among high-risk patients (i.e., a group that exhibits elevated

risk for SRDs) following lung screening remain unknown. This paper thus examined differences in risk perceptions for lung cancer and other SRDs among black and white National Lung Screening Trial (NLST) participants. We administered a 10-item measure of perceived lifetime risk of lung cancer and other SRD (Smoking Risk Perceptions Scale; SRPS) to NLST participants at 1 year following lung screening to (1) establish the internal consistency of the SRPS for both black and white participants, (2) compare smoking-related disease risk perceptions between black and white participants, and (3) identify predictors of risk perceptions for black and white participants using multivariable linear regression models. We determined the SRPS items loaded onto two factors (personal and comparative risks; Cronbach's alpha = 0.93 and 0.95 for 1743 white and 194 black participants, respectively), thus demonstrating high internal consistency for both black and white adults. Compared to white participants, black adults demonstrated lower SRD risk perceptions (SRPS range = 10-50, mean difference = 2.55, SE = 0.50, p < 0.001), even after adjusting for smoking status and sociodemographics. Younger age, female gender, higher education, white race, and current smoking status were independently associated with high risk perceptions. Sociodemographic factors associated with lower risk perceptions resemble factors related to continued smoking. Findings suggest current and former black smokers are at risk of having lower risk perceptions for lung cancer and SRDs than white adults following lung cancer screening; these differences may explain observed racial differences in cessation outcomes. Although similar factors influence black and white adults' beliefs, risk perceptions may differentially impact smoking behavior among these groups. Behavior change models that guide tobacco treatment approaches, particularly for high-risk black smokers, should consider the influence of cultural factors on risk perceptions and cessation efforts.

Combining smoking cessation interventions with LDCT lung cancer screening: A systematic review. Iaccarino JM1, Duran C2, Slatore CG3, Wiener RS4, Kathuria H2. Prev Med. 2019 Feb 10;121:24-32. doi: 10.1016/j.ypmed.2019.02.016. [Epub ahead of print]
Providing smoking cessation treatment with annual low dose CT (LDCT) screening offers an opportunity to reduce smoking-related morbidity and mortality. However, the optimal approach for delivering cessation interventions in the LDCT screening context is unknown. We searched for randomized controlled trials and observational studies with a control group testing a smoking cessation intervention among adults undergoing LDCT screening through May 1, 2018 using MEDLINE, the Cochrane Library, Web of Science, EMBASE, PsycINFO, and ClinicalTrials.gov. Two reviewers independently reviewed each study to assess eligibility and extracted information using pre-specified protocols for included studies. Given significant differences in the interventions in each study, meta-analyses for the included studies could not be performed. Of 2513 identified studies, 9 met inclusion criteria. Five of the included studies were randomized controlled trials while 4 were observational studies with a control group. Studies were of varying quality, but overall were of poor to fair quality with significant potential for bias and limited generalizability. Based on the available studies, there was insufficient data to suggest a particular approach to smoking cessation counseling in the LDCT screening setting. While no studies compared combined pharmacotherapy and counseling to counseling alone or compared the various pharmacologic agents, we identified several studies underway investigating new approaches during LDCT screening. The optimal strategy for smoking cessation in patients undergoing LDCT screening remains unclear. Future studies should focus on evaluating effectiveness and implementation of combined counseling and pharmacotherapy to optimize smoking cessation during LDCT screening.

NSCLC - SURGERY

Clinical outcome of patients with recurrent non-small cell lung cancer after trimodality therapy.
Suzawa K1, Soh J1, Takahashi Y1, Sato H1, Shien K1, Yamamoto H1, Kanazawa S2, Kiura K3, Miyoshi S1, Toyooka S4. Surg Today. 2019 Feb 8. doi: 10.1007/s00595-019-1774-8. [Epub ahead of print]
PURPOSES: The purpose of this study was to review the clinical course of patients with recurrence after induction chemoradiotherapy followed by surgery (trimodality therapy) for locally advanced non-small cell lung cancer (LA-NSCLC) and to identify the factors associated with favorable clinical outcome after recurrence. **METHODS:** We analyzed the records of 140 patients with LA-NSCLC who were treated with trimodality therapy between 1999 and 2014. **RESULTS:** Recurrence developed after trimodality therapy in 48 patients. A yp-N positive status was associated with a high risk of recurrence (HR, 2.05; P = 0.048). Of the 45 of these patients able to be assessed retrospectively, 18 had oligometastatic recurrence and 20 underwent local treatment with curative intent. Local treatment was most frequently given to patients with oligometastatic recurrence (P < 0.001). The median post-recurrence survival (PRS) was 41.4 months, and the 2-year PRS rate was 62%. Patients who received local treatment showed better PRS (P = 0.009). The presence of liver metastasis (P = 0.008), bone metastasis (P = 0.041), or dissemination (P < 0.0001) were associated with worse PRS. **CONCLUSION:** The survival of patients who received aggressive local treatment for postoperative recurrence after trimodality therapy for LA-NSCLC was better than that of patients who did not.

Systemic immune-inflammation index (SII) is useful to predict survival outcomes in patients with surgically resected non-small cell lung cancer. Guo W1, Cai S2, Zhang F1, et al. Thorac Cancer. 2019 Feb 7. doi: 10.1111/1759-7714.12995. [Epub ahead of print]
BACKGROUND: The systemic immune-inflammation index (SII) is correlated with patient survival in various types of solid tumors. However, only a few studies have focused on the prognostic value of the SII in patients with surgically resected non-small cell lung cancer (NSCLC). **METHODS:** This study was a single center retrospective analysis of 569 NSCLC patients who underwent curative lobectomy at the Department of Thoracic Surgery, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College between 2006 and 2012. A receiver operating characteristic curve was plotted to compare the discriminatory ability of the SII for overall survival (OS). A Cox proportional hazards regression model was used to perform univariate and multivariate analyses. **RESULTS:** The SII, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) all correlated with OS in NSCLC patients, and the SII was an independent prognostic factor for OS (hazard ratio 1.256, 95% confidence interval 1.018-1.551; P = 0.034). The area under the receiver operating characteristic curve of the SII (0.547) was larger than the NLR (0.541) and PLR (0.531). Furthermore, the SII retained prognostic significance in the lung adenocarcinoma subgroup. **CONCLUSION:** The SII is a promising prognostic predictor for patients with surgically resected NSCLC and retained prognostic significance in the lung adenocarcinoma subgroup. The prognostic value of the SII is superior to the NLR and PLR.

Surgical wound-site inflammation: video-assisted thoracic surgery versus thoracotomy. Menna C1, De Falco E2, Teodonio L1, et al. Interact Cardiovasc Thorac Surg. 2019 Feb 1;28(2):240-246. doi: 10.1093/icvts/ivy231.
OBJECTIVES: Mechanical trauma occurring during pulmonary resection through both video-assisted thoracic surgery (VATS) or thoracotomy causes profound alterations in cytokines and the cellular network. The aim of this study was to analyse biological changes occurring in both the microenvironment

(wound site) and macroenvironment (systemic circulation) following pulmonary lobectomy via the VATS or thoracotomic approach. **METHODS:** From October 2016 to July 2017, 30 patients with clinical Stage I lung cancer were recruited. In 12 cases (the VATS group), surgery was performed through a video-assisted thoracoscopic approach and in 15 cases (the thoracotomy group) through a muscle-sparing minithoracotomy. Following the skin incision, the wound was irrigated with a saline solution (20 ml) and then collected. After the pulmonary resection, the surgical incision was re-irrigated. The number of polymorphonuclears, granulocytes and lymphocytes in the fluids was determined by the fluorescence activated cell sorting (FACS) analysis. Cytokine profiles of interleukin (IL)-6, tumour necrosis factor (TNF)-α, IL-1 and IL-8 from sera and fluids were detected by the enzyme linked immunosorbent assay (ELISA) assay. Functional results were evaluated through spirometry, and pain was assessed using the visual analogue scale. **RESULTS:** In the postoperative fluids of the VATS group, fewer polymorpho-nuclears were seen compared to the thoracotomy group (P = 0.001), as well as a decreased percentage of granulocytes (P = 0.01) and a parallel increased lymphocytes fraction (P = 0.001). Only the systemic IL-1β levels were significantly lower in postoperative sera of the VATS group (P = 0.038). No differences were observed regarding other cytokines. **CONCLUSIONS:** The local microenvironment during VATS differs from that of thoracotomy by not producing the same inflammatory phenotype. The clinical efficacy of a less invasive surgical approach is confirmed by a reduced inflammation of the systemic and local districts.

[Keys to successful induction chemoradiotherapy followed by surgery for stage III/N2 non-small cell lung cancer.](#) Sata Y1, Nakajima T1, Yamamoto T1, et al. Surg Today. 2019 Feb 18. doi: 10.1007/s00595-019-1766-8. [Epub ahead of print]
Surgical intervention after induction chemoradiation is designed as curative treatment for resectable stage III/N2 non-small cell lung cancer. However, there is no definitive evidence to support this approach, possibly because successful treatment requires certain "arts", such as proper patient selection, an appropriate induction regimen, and choice of the best surgical procedure. We review the previous reports and discuss our own experience to explore the appropriate strategy for patients with resectable stage III/N2 disease, and to identify the factors associated with successful surgical intervention. Among the studies reviewed, the complete resection rate among intention-to-treat cases was correlated well with the 5-year survival rate, whereas the pneumonectomy rate was correlated inversely with the 5-year survival rate. The clinical response rate and downstaging after induction treatment were not associated with survival. Based on these findings, we conclude that complete resection with the avoidance of pneumonectomy is important when selecting candidates for multimodal treatment including radical surgery.

[Clinical outcome of patients with recurrent non-small cell lung cancer after trimodality therapy.](#)
Suzawa K1, Soh J1, Takahashi Y1, Sato H1, Shien K1, Yamamoto H1, Kanazawa S2, Kiura K3, Miyoshi S1, Toyooka S4. Surg Today. 2019 Feb 8. doi: 10.1007/s00595-019-1774-8. [Epub ahead of print]
PURPOSES: The purpose of this study was to review the clinical course of patients with recurrence after induction chemoradiotherapy followed by surgery (trimodality therapy) for locally advanced non-small cell lung cancer (LA-NSCLC) and to identify the factors associated with favorable clinical outcome after recurrence. **METHODS:** We analyzed the records of 140 patients with LA-NSCLC who were treated with trimodality therapy between 1999 and 2014. **RESULTS:** Recurrence developed after trimodality therapy in 48 patients. A yp-N positive status was associated with a high risk of recurrence (HR, 2.05; P = 0.048). Of the 45 of these patients able to be assessed retrospectively, 18 had oligometastatic recurrence and 20 underwent local treatment with curative intent. Local treatment was most frequently given to patients with oligometastatic recurrence (P < 0.001). The median post-recurrence survival (PRS) was 41.4 months, and the 2-year PRS rate was 62%. Patients who received local treatment showed better

PRS (P = 0.009). The presence of liver metastasis (P = 0.008), bone metastasis (P = 0.041), or dissemination (P < 0.0001) were associated with worse PRS. **CONCLUSION:** The survival of patients who received aggressive local treatment for postoperative recurrence after trimodality therapy for LA-NSCLC was better than that of patients who did not.

[**Updates on Minimally Invasive Surgery in Non-Small Cell Lung Cancer.**](#) Ikeda N1. Curr Treat Options Oncol. 2019 Feb 11;20(2):16. doi: 10.1007/s11864-019-0614-9.
Video-assisted thoracic surgery (VATS) has become widely used since the 1990s and has become a standard treatment approach mainly for early-stage non-small cell lung cancer. The few randomized controlled trials providing evidence of the effectiveness of VATS lobectomy at present are supported by a large number of propensity-matched studies, several high-quality meta-analyses, and outcome studies. These studies provide comprehensive data demonstrating the lower morbidity, shorter chest tube duration, and shorter hospital stay of VATS than thoracotomy during the postoperative course. Moreover, VATS shows equivalent oncological outcome as thoracotomy and therefore should be performed for lobectomy as much as possible. Importantly, VATS has recently been applied to advanced cases and previously contraindicated complex procedures such as bronchoplasty and chest wall resection. Attention has also been paid to reduced port surgery performed by frontier surgeons. Thus, the indications of VATS have seen a significant expansion. This major development logically negates any hesitation to change to the VATS technique as any doubt will likely constrain its wider applications. Preparation of scientific learning environments is necessary and should be actively pursued to adopt new skills instead of debating between the choice of "VATS or open."

[**Is video-assisted thoracoscopy a sufficient approach for mediastinal lymph node dissection to treat lung cancer after neoadjuvant therapy?**](#) Tian Z1, Sui X1, Yang F1, Wang J1. Thorac Cancer. 2019 Feb 12. doi: 10.1111/1759-7714.12999. [Epub ahead of print]
BACKGROUND: The role of video-assisted thoracoscopic surgery (VATS) in mediastinal lymph node dissection (MLND) for non-small cell lung cancer (NSCLC) following neoadjuvant therapy remains controversial. The aim of this study was to demonstrate the sufficiency of VATS by evaluating perioperative and long-term outcomes. **METHODS:** Patients with locally advanced NSCLC and treated with radical surgery after neoadjuvant therapy were identified in our database. The thoroughness of MLND was compared by approach. Multivariable logistic regression analysis was used to evaluate predictors of sufficient MLND. Propensity score matching was performed. Kaplan-Meier and Cox proportional hazard analyses were used to assess long-term survival. **RESULTS:** Of the 127 enrolled patients, 56 underwent attempted VATS and 71 underwent thoracotomy. Multivariable logistic regression analysis revealed that approach was not a predictor of sufficient MLND (odds ratio 0.81, 95% confidence interval [CI] 0.364-1.803; P = 0.606). After matching, 28 pairs of patients were selected from the two groups. There was no significant difference between the numbers of dissected lymph nodes (15 vs. 20; P = 0.191) and nodal stations (7 vs. 7; P = 0.315). Recurrence-free (log-rank P = 0.613) and overall survival (log-rank P = 0.379) was similar in both groups. Multivariable Cox proportional hazards model analysis indicated that VATS was not an independent predictor of recurrence-free (hazard ratio 0.955, 95% CI 0.415-2.198; P = 0.913) or overall survival (hazard ratio 0.841, 95% CI 0.338-2.093; P = 0.709). **CONCLUSION:** Compared to thoracotomy, VATS is a sufficient approach for MLND to treat locally advanced NSCLC following neoadjuvant therapy without compromising long-term survival.

[**Quantitative computed tomography for predicting cardiopulmonary complications after lobectomy for lung cancer in patients with chronic obstructive pulmonary disease.**](#) Yasuura Y1, Maniwa T2, Mori K3, et al. Gen Thorac Cardiovasc Surg. 2019 Feb 22. doi: 10.1007/s11748-019-01080-z. [Epub ahead of print]

OBJECTIVES: In lung cancer resection, chronic obstructive pulmonary disease is a risk factor for post-operative complications. Few studies on post-operative complications of lung cancer resection have considered radiographic emphysematous change as an index. Here, we have examined the relationship between the regional ratio of the emphysematous area in pre-operative computed tomography images and cardiopulmonary complications in patients with chronic obstructive pulmonary disease who underwent lung cancer resection. **METHODS:** We retrospectively evaluated 159 patients with chronic obstructive pulmonary disease who underwent lobectomy for lung cancer at Shizuoka Cancer Center Hospital, Shizuoka, Japan, between 2002 and 2011. Pre-operative factors, including the proportion of the emphysematous area measured by computed tomography as a percentage of the low attenuation area (LAA%), as well as intraoperative factors were analyzed. Cardiopulmonary complications, including pyothorax, pneumonia and atelectasis, acute pulmonary injury, indwelling chest tube, long duration of oxygen supply, and arrhythmia, were evaluated. **RESULTS:** Cardiopulmonary complications were observed among 61 patients (38%). Univariate analysis revealed that patient age, percentage of forced expiratory volume in 1 s, LAA%, and volume of blood loss were significantly associated with cardiopulmonary complications. Multivariate analysis indicated patient age and LAA% as being significant independent predictors of cardiopulmonary complications. **CONCLUSIONS:** The regional ratio of the emphysematous area is useful for predicting cardiopulmonary complications in patients with chronic obstructive pulmonary disease who undergo lobectomy for lung cancer. In such patients who are also ≥ 70 years of age and exhibit LAA% $\geq 1.0\%$, careful intra- and post-operative management is warranted.

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

First-line afatinib vs gefitinib for patients with EGFR mutation-positive NSCLC (LUX-Lung 7): impact of afatinib dose adjustment and analysis of mode of initial progression for patients who continued treatment beyond progression. Schuler M1, Tan EH2, O'Byrne K3, et al. Cancer Res Clin Oncol. 2019 Feb 19. doi: 10.1007/s00432-019-02862-x. [Epub ahead of print]
PURPOSE: In the randomized phase IIb LUX-Lung 7 trial, afatinib significantly improved progression-free survival (PFS) and time-to-treatment failure vs gefitinib in patients with treatment-naïve epidermal growth factor receptor mutation-positive non-small cell lung cancer. We report post hoc analyses of tolerability-guided dose adjustment for afatinib and summarize the clinical characteristics of patients who continued afatinib/gefitinib beyond initial radiological progression in LUX-Lung 7. **METHODS:** Patients received afatinib 40 mg/day or gefitinib 250 mg/day until investigator-assessed progression or beyond if beneficial. In case of selected treatment-related adverse events (TRAEs), the afatinib dose could be reduced by 10-mg decrements to minimum 20 mg (only dose interruptions were permitted with gefitinib). **RESULTS:** All randomized patients were treated (afatinib, n = 160; gefitinib, n = 159). Sixty-three patients had afatinib dose reduction (< 40 mg/day; 47 within first 6 months). Dose reduction decreased TRAE incidence/severity (before vs after; all grade/grade 3: 100.0%/63.5% vs 90.5%/23.8%). There was no evidence of significant difference in PFS for patients who received < 40 mg/day vs ≥ 40 mg/day for the first 6 months [median: 12.8 vs 11.0 months; hazard ratio 1.34 (95% confidence interval 0.90-2.00)]. Twenty-four and 26 patients continued afatinib and gefitinib, respectively, beyond progression in target lesions; median time from nadir of target lesion diameters to initial progression was 6.7 months and 5.6 months. Of these patients, ~ 70% had objective response or non-complete response/non-progressive disease in non-target lesions at initial progression. **CONCLUSIONS:** Protocol-defined dose adjustment of afatinib may allow patients to remain on treatment longer, maximizing clinical benefit even in the presence of radiological progression.

[**Mixed response to osimertinib and the beneficial effects of additional local therapy.**](#)
Shinno Y1, Goto Y1, Sato J1, et al. Thorac Cancer. 2019 Feb 8. doi: 10.1111/1759-7714.12991. [Epub ahead of print]
BACKGROUND: Although non-small cell lung cancers (NSCLCs) harboring EGFR mutations initially respond well to EGFR-tyrosine kinase inhibitors (TKIs), they typically progress after approximately one year. The EGFR T790M mutation is the most common resistance mechanism. NSCLCs with T790M respond well to osimertinib; however, the heterogeneity of NSCLCs may limit the efficacy. Some patients exhibit a mixed response (MR), in which some lesions shrink and others progress, but little is known of the incidence and characteristics of such a response. We sought to determine the frequency and clinical course in MR patients. **METHODS:** We retrospectively reviewed the records of patients who had received osimertinib for NSCLC with EGFR T790M. **RESULTS:** Between April and December 2016, 48 patients were administered osimertinib. Seven patients (15%) exhibited one of two MR types: (i) progressive lesions that did not include the re-biopsy site (5 patients), and (ii) progressive lesions that included the re-biopsy site (2 patients). The most frequent progressive sites were liver and lung metastases (4 patients). Three patients continued osimertinib following an MR, one of whom had received local therapy for liver metastasis and achieved disease control on osimertinib for an additional four months. **CONCLUSION:** An MR was detected in 15% of NSCLC patients with T790M. This finding suggests that several different resistance mechanisms are active within a single patient who develops resistance to EGFR-TKIs. Osimertinib is basically effective for tumors that acquire resistance to EGFR-TKIs as a result of T790M mutation. Therefore, additional local therapy may be beneficial for patients who develop an MR to osimertinib.

[**Development of a PD-L1 Complementary Diagnostic Immunohistochemistry Assay (SP142) for Atezolizumab.**](#) Vennapusa B1, Baker B1, Kowanetz M2, et al. Appl Immunohistochem Mol Morphol. 2019 Feb;27(2):92-100. doi: 10.1097/PAI.0000000000000594.
Cancer immunotherapies, such as atezolizumab, are proving to be a valuable therapeutic strategy across indications, including non-small cell lung cancer (NSCLC) and urothelial cancer (UC). Here, we describe a diagnostic assay that measures programmed-death ligand 1 (PD-L1) expression, via immunohistochemistry, to identify patients who will derive the most benefit from treatment with atezolizumab, a humanized monoclonal anti-PD-L1 antibody. We describe the performance of the VENTANA PD-L1 (SP142) Assay in terms of specificity, sensitivity, and the ability to stain both tumor cells (TC) and tumor-infiltrating immune cells (IC), in NSCLC and UC tissues. The reader precision, repeatability and intermediate precision, interlaboratory reproducibility, and the effectiveness of pathologist training on the assessment of PD-L1 staining on both TC and IC were evaluated. We detail the analytical validation of the VENTANA PD-L1 (SP142) Assay for PD-L1 expression in NSCLC and UC tissues and show that the assay reliably evaluated staining on both TC and IC across multiple expression levels/clinical cut-offs. The reader precision showed high overall agreement when compared with consensus scores. In addition, pathologists met the predefined training criteria (≥85.0% overall percent agreement) for the assessment of PD-L1 expression in NSCLC and UC tissues with an average overall percent agreement ≥95.0%. The assay evaluates PD-L1 staining on both cell types and is robust and precise. In addition, it can help to identify those patients who may benefit the most from treatment with atezolizumab, although treatment benefit has been demonstrated in an all-comer NSCLC and UC patient population.

[**First-line afatinib vs gefitinib for patients with EGFR mutation-positive NSCLC (LUX-Lung 7): impact of afatinib dose adjustment and analysis of mode of initial progression for patients who continued treatment beyond progression.**](#) Schuler M1, Tan EH2, O'Byrne K3, et al. J Cancer Res Clin Oncol. 2019 Feb 19. doi: 10.1007/s00432-019-02862-x. [Epub ahead of print]

PURPOSE: In the randomized phase IIb LUX-Lung 7 trial, afatinib significantly improved progression-free survival (PFS) and time-to-treatment failure vs gefitinib in patients with treatment-naïve epidermal growth factor receptor mutation-positive non-small cell lung cancer. We report post hoc analyses of tolerability-guided dose adjustment for afatinib and summarize the clinical characteristics of patients who continued afatinib/gefitinib beyond initial radiological progression in LUX-Lung 7. **METHODS:** Patients received afatinib 40 mg/day or gefitinib 250 mg/day until investigator-assessed progression or beyond if beneficial. In case of selected treatment-related adverse events (TRAEs), the afatinib dose could be reduced by 10-mg decrements to minimum 20 mg (only dose interruptions were permitted with gefitinib). **RESULTS:** All randomized patients were treated (afatinib, n = 160; gefitinib, n = 159). Sixty-three patients had afatinib dose reduction (< 40 mg/day; 47 within first 6 months). Dose reduction decreased TRAE incidence/severity (before vs after; all grade/grade 3: 100.0%/63.5% vs 90.5%/23.8%). There was no evidence of significant difference in PFS for patients who received < 40 mg/day vs ≥ 40 mg/day for the first 6 months [median: 12.8 vs 11.0 months; hazard ratio 1.34 (95% confidence interval 0.90-2.00)]. Twenty-four and 26 patients continued afatinib and gefitinib, respectively, beyond progression in target lesions; median time from nadir of target lesion diameters to initial progression was 6.7 months and 5.6 months. Of these patients, ~ 70% had objective response or non-complete response/non-progressive disease in non-target lesions at initial progression. **CONCLUSIONS:** Protocol-defined dose adjustment of afatinib may allow patients to remain on treatment longer, maximizing clinical benefit even in the presence of radiological progression.

[Outcome of non-small cell lung cancer patients with brain metastases treated with checkpoint inhibitors.](#) Hendriks LEL1, Henon C2, Auclin E3, et al. J Thorac Oncol. 2019 Feb 16. pii: S1556-0864(19)30117-0. doi: 10.1016/j.jtho.2019.02.009. [Epub ahead of print]
INTRODUCTION: although frequent in non-small cell lung cancer (NSCLC), brain metastases (BM) patients are often excluded from immune checkpoint inhibitor (ICI) trials. We evaluated BM outcome in a less selected NSCLC cohort. **METHODS:** data from consecutive advanced ICI treated NSCLC patients were collected. 'Active' BM: new and/or growing lesions without any subsequent local treatment before ICI start. Objective response rate (ORR), progression free survival (PFS) and overall survival (OS) were evaluated. Multivariate analyses were performed using Cox proportional hazards model and logistic regression. **RESULTS:** 1025 patients were included; median follow-up from ICI start: 15.8 months. 255 (24.9%) had BM: 39.2% active, 14.3% symptomatic and 27.4% receiving steroids. Disease-specific Graded Prognostic Assessment (ds-GPA) was known for 94.5% (0-1: 35.7%, 1.5-2.5: 58.5%, 3: 5.8%). ORR was similar: 20.6% (BM) versus 22.7% (no BM) (p=0.484). Intracranial ORR (active BM with follow-up brain imaging, N=73): 27.3%. Median (95% CI) PFS: 1.7 (1.5-2.1) and 2.1 (1.9-2.5) months, respectively (p=0.009). 12.7% of BM patients had a dissociated cranial-extracranial response, 2 (0.8%) had brain pseudoprogression. Brain progression occurred more in active versus stable BM (54.2% vs 30%, p < 0.001). Median (95% CI) OS: 8.6 (6.8-12.0) (BM) and 11.4 (8.6-13.8) months (no BM), respectively (p=0.035). In the BM subgroup multivariate analysis, corticosteroid use (HR 2.37) was associated with poorer OS, while stable BM (HR 0.62) and higher ds-GPA classification (HR 0.48-0.52) were associated with improved OS. **CONCLUSION:** BM are in multivariate analysis not associated with a poorer survival in ICI treated NSCLC patients. Stable BM patients without baseline corticosteroids and a good ds-GPA classification have the best prognosis.

[PD-L1 expression, tumor mutational burden and cancer gene mutations are stronger predictors of benefit from immune checkpoint blockade than HLA class I genotype in non-small cell lung cancer.](#) Negrao MV1, Lam VK1, Reuben A1, et al. J Thorac Oncol. 2019 Feb 16. pii: S1556-0864(19)30116-9. doi: 10.1016/j.jtho.2019.02.008. [Epub ahead of print]

INTRODUCTION: Immune checkpoint blockade (ICB) has revolutionized the treatment of non-small cell lung cancer (NSCLC), but only ~15% of patients achieve durable benefit. Understanding resistance mechanisms to ICB is pivotal in developing more effective treatment strategies. Recent studies showed human leukocyte antigen (HLA) class I heterozygosity might be important in mediating benefit from ICB. We aimed to investigate the impact of HLA class I genotype on outcomes of NSCLC patients treated with ICB. **METHODS:** We collected HLA typing, genomic and clinical data from patients with advanced NSCLC treated with ICB at MD Anderson Cancer Center (MDACC cohort). We compared HLA class I heterozygous and homozygous patients for progression-free survival (PFS) and overall survival (OS). HLA I supertype/alleles were also analyzed. To validate our findings, we also analyzed two previously published independent cohorts of NSCLC (CheckMate-012 (CM012) and Chowell cohorts). **RESULTS:** No significant correlations were observed for HLA class I zygosity and PFS or OS in the MDACC (N=200), CM012 (N=75) or Chowell (n=371) cohorts. No HLA class I supertype/allele was consistently shown to be correlated with PFS or OS. Predictors of worse outcome across the 3 cohorts included: presence of targetable driver mutation, STK11 mutation, negative PD-L1 expression, and low tumor mutational burden. **CONCLUSIONS:** HLA class I genotype is not correlated with survival in advanced NSCLC treated with ICB. This suggests that the impact of HLA class I diversity may be disease specific, and that tumor genomic and immune markers are more impactful in predicting benefit from ICB in NSCLC.

[**The Role of Angiogenesis Inhibitors in the Era of Immune Checkpoint Inhibitors and Targeted Therapy in Metastatic Non-Small Cell Lung Cancer.**](#) Perdrizet K1, Leighl NB2. Curr Treat Options Oncol. 2019 Feb 18;20(3):21. doi: 10.1007/s11864-019-0617-6.
The treatment of advanced non-small cell lung cancer (NSCLC) has evolved to include targeted therapy, immunotherapy as well as chemotherapy for selected patients in the first-line setting. Angiogenesis inhibitors have been used in combination with chemotherapy in the first-line and maintenance settings providing improved progression-free survival (PFS) and objective response rate (ORR), as well as overall survival (OS) in selected studies. Biologic rationale exists for combining anti-angiogenic agents with immunotherapy and targeted kinase inhibitors (TKIs). A recent study has demonstrated improved survival when anti-PD-L1 therapy was added to chemotherapy plus bevacizumab. Subgroup analysis of patients with mutations in the epidermal growth factor receptor (EGFR) gene and rearrangements in the anaplastic lymphoma kinase (ALK) gene also demonstrated benefit with combined anti-PD-L1, bevacizumab, and platinum chemotherapy. Further investigation into combination therapy is warranted in the EGFR- and ALK-positive population given this signal. Anti-angiogenics combined with EGFR-targeted treatment in the wild-type population have shown modest PFS benefit with no OS benefit, and their routine use has not been adopted. The combination of EGFR inhibitors plus vascular endothelial growth factor (VEGF) inhibitors in the EGFR mutation-positive population has demonstrated substantial improvements in response and PFS; however, given the higher toxicity and lack of survival benefit to date, combination therapy in this group should be used with caution. At the present time, use of bevacizumab can be recommended with atezolizumab and chemotherapy for the first-line treatment of non-squamous NSCLC patients. Data with other checkpoint inhibitors and anti-angiogenics are too early to make firm recommendations regarding their use.

[**Re-challenge of afatinib after 1st generation EGFR-TKI failure in patients with previously treated non-small cell lung cancer harboring EGFR mutation.**](#) Yamaguchi O1, Kaira K2, Mouri A1, et al. Cancer Chemother Pharmacol. 2019 May;83(5):817-825. doi: 10.1007/s00280-019-03790-w. Epub 2019 Feb 13.
BACKGROUND: Re-challenge of erlotinib after gefitinib failure is reported to yield some benefit in patients with non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR)

mutation. However, little is known about the re-challenge of afatinib after 1st generate on EGFR tyrosine kinase inhibitor (TKI) failure. **METHODS:** From May 2015 to August 2018, 62 patients with advanced NSCLC harboring sensitive EGFR mutation received afatinib after gefitinib and/or erlotinib failure at our institution was included in our retrospective study. **RESULTS:** The overall response rate (ORR) and disease control rate (DCR) of afatinib as re-challenge were 17.0% and 79.2%, respectively. The median time on treatment of 1st generation EGFR-TKI (1st TKI) was 14 months. By multivariate analysis, smoking, performance status (PS), and time on treatment of 1st TKI with more than 10 months were confirmed to be independent prognostic factors predicting a worse progression-free survival (PFS), and significant prognostic markers for overall survival (OS) were PS and time on treatment of 1st TKI with more than 10 months, especially in patients with exon 19 deletion. **CONCLUSIONS:** Re-challenge of afatinib was identified as one of the therapeutic options after 1st TKI failure in the patients with advanced NSCLC harboring EGFR mutation when the time of treatment by prior 1st TKI is more than 10 months.

Persistent mutant oncogene specific T cells in two patients benefitting from anti-PD-1. Smith KN1,2, Llosa NJ1,2, Cottrell TR1,2,3, et al. J Immunother Cancer. 2019 Feb 11;7(1):40. doi: 10.1186/s40425-018-0492-x.

BACKGROUND: Several predictive biomarkers are currently approved or are under investigation for the selection of patients for checkpoint blockade. Tumor PD-L1 expression is used for stratification of non-small cell lung (NSCLC) patients, with tumor mutational burden (TMB) also being explored with promising results, and mismatch-repair deficiency is approved for tumor site-agnostic disease. While tumors with high PD-L1 expression, high TMB, or mismatch repair deficiency respond well to checkpoint blockade, tumors with lower PD-L1 expression, lower mutational burdens, or mismatch repair proficiency respond much less frequently. **CASE PRESENTATION:** We studied two patients with unexpected responses to checkpoint blockade monotherapy: a patient with PD-L1-negative and low mutational burden NSCLC and one with mismatch repair proficient colorectal cancer (CRC), both of whom lack the biomarkers associated with response to checkpoint blockade, yet achieved durable clinical benefit. Both maintained T-cell responses in peripheral blood to oncogenic driver mutations - BRAF-N581I in the NSCLC and AKT1-E17K in the CRC - years after treatment initiation. Mutation-specific T cells were also found in the primary tumor and underwent dynamic perturbations in the periphery upon treatment. **CONCLUSIONS:** These findings suggest that T cell responses to oncogenic driver mutations may be more prevalent than previously appreciated and could be harnessed in immunotherapeutic treatment, particularly for patients who lack the traditional biomarkers associated with response. Comprehensive studies are warranted to further delineate additional predictive biomarkers and populations of patients who may benefit from checkpoint blockade.

Afatinib-loaded immunoliposomes functionalized with cetuximab: A novel strategy targeting the epidermal growth factor receptor for treatment of non-small-cell lung cancer.
Lu X1, Liu S2, Han M1, et al. Int J Pharm. 2019 Feb 8;560:126-135. doi: 10.1016/j.ijpharm.2019.02.001. [Epub ahead of print]
Afatinib, a selective and irreversible inhibitor of tyrosine kinase, was approved for the treatment of advanced non-small-cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) overexpression in 2013. Cetuximab (CTX), an anti-EGFR monoclonal antibody, is co-administered with afatinib to improve efficacy. Unfortunately, dose-related adverse reactions caused by combination therapy have affected patient compliance, and have resulted in treatment discontinuation in severe cases. In the present study, afatinib was encapsulated in "liposomes" (LPs) to achieve longer circulation in the blood and an enhanced permeability-and-retention effect in tumors. Concomitantly, CTX was designed to bind to drug-loaded LPs to form "immuno-LPs" for tumor-cell selectivity and therapeutic activity. In vitro, the cellular internalization rate of immuno-LPs was significantly higher than that of LPs (p < 0.05). In vivo, a

markedly increased area under the curve and prolonged terminal half-life were detected in rats injected with the two LP formulations, indicating that LP encapsulation protected afatinib from binding to hemoglobin to control the risk of idiosyncratic drug reactions. Compared with free afatinib and LPs, immuno-LPs exhibited strongly enhanced drug delivery and antitumor efficacy in an NSCLC xenograft model, with stronger tumor selectivity and potentially fewer side-effects. Hence, EGFR-targeting immuno-LPs appear to be promising for NSCLC treatment.

[**Characteristics and outcomes of patients with metastatic KRAS mutant lung adenocarcinomas: The Lung Cancer Mutation Consortium experience.**](#) El Osta B1, Behera M1, Kim S2, et al. J Thorac Oncol. 2019 Feb 5. pii: S1556-0864(19)30097-8. doi: 10.1016/j.jtho.2019.01.020. [Epub ahead of print]
BACKGROUND: Mutations in the KRAS gene are the most common driver oncogenes present in lung adenocarcinomas. We analyzed the largest multi-institutional database available containing patients with metastatic KRAS mutant lung adenocarcinomas. **METHODS:** The Lung Cancer Mutation Consortium (LCMC) is a multi-institutional collaboration to study the genomic characteristics of lung adenocarcinomas, treat them with genomically directed therapeutic approaches, and assess their outcomes. Since its inception in 2009, the LCMC has enrolled over 1900 patients and has performed pretreatment, multiplexed, molecular characterization along with collecting clinical data. We evaluated the characteristics of patients with KRAS mutation in the LCMC and the association with overall survival (OS). **RESULTS:** Data from 1655 patients with metastatic lung adenocarcinomas were analyzed. 450 (27%) patients had a KRAS mutation, 58% female, 93% smokers, and median age of 65 years. Main KRAS subtypes were: G12C 39%; G12D and G12V at 18% each. Among patients with KRAS mutation, G12D had a higher proportion of never smokers (22%, P<0.001). Patients with KRAS mutant tumors had a trend toward shorter median survival compared to all others in the series (1.96 vs. 2.22; P=0.08) and lower 2-year survival rate (49% (95% CI: 44-54%) and 55% (95% CI: 52-58%), respectively. **CONCLUSIONS:** In the LCMC study, 27% of lung adenocarcinomas patients harbored a KRAS mutation and up to third of them had another oncogenic driver. Patients with both KRAS and STK11 mutations had a significantly inferior clinical outcome.

NSCLC - RADIOTHERAPY

[**Phase Ib evaluation of a self-adjuvanted protamine formulated mRNA-based active cancer immunotherapy, BI1361849 (CV9202), combined with local radiation treatment in patients with stage IV non-small cell lung cancer.**](#) Papachristofilou A1, Hipp MM2, Klinkhardt U2, et al. J Immunother Cancer. 2019 Feb 8;7(1):38. doi: 10.1186/s40425-019-0520-5.
BACKGROUND: Preclinical studies demonstrate synergism between cancer immunotherapy and local radiation, enhancing anti-tumor effects and promoting immune responses. BI1361849 (CV9202) is an active cancer immunotherapeutic comprising protamine-formulated, sequence-optimized mRNA encoding six non-small cell lung cancer (NSCLC)-associated antigens (NY-ESO-1, MAGE-C1, MAGE-C2, survivin, 5T4, and MUC-1), intended to induce targeted immune responses. **METHODS:** We describe a phase Ib clinical trial evaluating treatment with BI1361849 combined with local radiation in 26 stage IV NSCLC patients with partial response (PR)/stable disease (SD) after standard first-line therapy. Patients were stratified into three strata (1: non-squamous NSCLC, no epidermal growth factor receptor (EGFR) mutation, PR/SD after ≥4 cycles of platinum- and pemetrexed-based treatment [n = 16]; 2: squamous NSCLC, PR/SD after ≥4 cycles of platinum-based and non-platinum compound treatment [n = 8]; 3: non-squamous NSCLC, EGFR mutation, PR/SD after ≥3 and ≤ 6 months EGFR-tyrosine kinase inhibitor (TKI) treatment [n = 2]). Patients received intradermal BI1361849, local radiation (4 × 5 Gy), then BI1361849 until disease progression. Strata 1 and 3 also had maintenance pemetrexed or continued EGFR-TKI therapy, respectively. The primary endpoint was evaluation of safety; secondary objectives

included assessment of clinical efficacy (every 6 weeks during treatment) and of immune response (on Days 1 [baseline], 19 and 61). **RESULTS:** Study treatment was well tolerated; injection site reactions and flu-like symptoms were the most common BI1361849-related adverse events. Three patients had grade 3 BI1361849-related adverse events (fatigue, pyrexia); there was one grade 3 radiation-related event (dysphagia). In comparison to baseline, immunomonitoring revealed increased BI1361849 antigen-specific immune responses in the majority of patients (84%), whereby antigen-specific antibody levels were increased in 80% and functional T cells in 40% of patients, and involvement of multiple antigen specificities was evident in 52% of patients. One patient had a partial response in combination with pemetrexed maintenance, and 46.2% achieved stable disease as best overall response. Best overall response was SD in 57.7% for target lesions. **CONCLUSION:** The results support further investigation of mRNA-based immunotherapy in NSCLC including combinations with immune checkpoint inhibitors.

[**Clinical Outcomes of Patients With Recurrent Lung Cancer Reirradiated With Proton Therapy on the Proton Collaborative Group and University of Florida Proton Therapy Institute Prospective Registry Studies.**](#) Badiyan SN1, Rutenberg MS2, Hoppe BS2, et al. Pract Radiat Oncol. 2019 Feb 23. pii: S1879-8500(19)30056-6. doi: 10.1016/j.prro.2019.02.008. [Epub ahead of print]
PURPOSE: We sought to assess clinical outcomes and toxicities of patients with recurrent lung cancer reirradiated with proton beam therapy (PBT) who were enrolled in 2 prospective registry trials. **METHODS AND MATERIALS:** Seventy-nine consecutive patients were reirradiated with PBT at 8 institutions. Conventionally fractionated radiation therapy was used to treat the previous lung cancer in 68% of patients (median equivalent dose in 2 Gy fractions [EQD2], 60.2 Gy) and hypofractionated/ stereotactic body radiation therapy in 32% (median EQD2, 83.3 Gy). Nine patients (11%) received ≥2 courses of thoracic irradiation before PBT. Eastern Cooperative Oncology Group (ECOG) performance status was 2 to 3 in 13%. Median time from prior radiation therapy to PBT was 19.9 months. PBT was delivered with conventional fractionation in 58% (median EQD2, 60 Gy), hyperfractionation in 3% (median EQD2, 62.7 Gy), and hypofractionation in 39% (median EQD2, 60.4 Gy). Twenty-four patients (30%) received chemotherapy concurrently with PBT. **RESULTS:** All patients completed PBT as planned. At a median follow-up of 10.7 months after PBT, median overall survival (OS) and progression-free survival (PFS) were 15.2 months and 10.5 months, respectively. Acute and late grade 3 toxicities occurred in 6% and 1%, respectively. Three patients died after PBT from possible radiation toxicity. On multivariate analysis, ECOG performance status ≤1 was associated with OS (hazard ratio, 0.35; 95% confidence interval, 0.15-0.80; P = .014) and PFS (hazard ratio, 0.32; 95% confidence interval, 0.14-0.73; P = .007). **CONCLUSIONS:** This is the largest series to date of PBT reirradiation for recurrent lung cancer and indicates that reirradiation with PBT is well tolerated with acceptable toxicity and encouraging efficacy. ECOG performance status was associated with OS and PFS.

SMALL CELL LUNG CANCER - SCLC

[**Immunotherapy in extensive small cell lung cancer.**](#) Verma V#1,2, Sharma G#3, Singh A#1. Exp Hematol Oncol. 2019 Feb 4;8:5. doi: 10.1186/s40164-019-0129-x. eCollection 2019.
Small cell lung cancer which constitutes about 15% of lung cancers is pathobiologically and clinically distinct from non small cell cancer. Histologically it is characterized by small cells with scant cytoplasm, absent or inconspicuous nucleoli, extensive necrosis, and expresses neuroendocrine markers. It is on a spectrum of neuroendocrine cancer that extend from typical carcinoids to large cell to small cell cancer. Clinically it behaves in a more malignant fashion with a rapid doubling time, early metastasis. They respond rapidly to cytotoxic treatment however tend to develop resistance soon. Immunotherapy with checkpoint inhibitors take advantage of PD 1 ligand-receptor axis between the tumor and T cells or CTLA4 on T cells which when engaged lead to inhibition of T cells. This inhibition helps tumors to evade

immune surveillance. Checkpoint inhibitors break this axis by either binding to PD 1 ligands or PD 1 to CTLA4, thereby preventing tumors to evade the immune systems. This has led to remarkable responses in tumors. The immune related adverse effects can be severe however are experienced at much lower rates as compared to cytotoxic chemotherapy. Recently, CheckMate 032 has shown impressive response rates with Nivolumab and Nivolumab/Ipilimumab in relapsed small cell cancer. IMpower 133, a phase 3 trial showed that addition of Atezolizumab to Carbo/Etoposide led to a significant survival benefit in treatment naive extensive small cell cancer. This review will summarize recent developments and ongoing studies of immune therapy in extensive small cell cancer in addition to a brief summary of immune therapy landscape of Non small cell lung cancer. Investigational approaches to immune therapy have also been delineated.

[Comparison of Diagnosis-Specific Survival Scores for Patients with Small-Cell Lung Cancer Irradiated for Brain Metastases.](#) Rades D1, Hansen HC2, Janssen S3,4, Schild SE5. Cancers (Basel). 2019 Feb 16;11(2). pii: E233. doi: 10.3390/cancers11020233.
Diagnosis-specific survival scores including a new score developed in 157 patients with brain metastases from small-cell lung cancer (SCLC) receiving whole-brain radiotherapy (WBRT) with 30 Gy in 10 fractions (WBRT-30-SCLC) were compared. Three prognostic groups were designed based on the 6-month survival probabilities of significant or almost significant factors, (age, performance score, number of brain metastases, extra-cerebral metastasis). Six-month survival rates were 6% (6⁻11 points), 44% (12⁻14 points) and 86% (16⁻19 points). The WBRT-30-SCLC was compared to three disease-specific scores for brain metastasis from SCLC, the original and updated diagnosis-specific graded prognostic assessment DS-GPA classifications and the Rades-SCLC. Positive predictive values (PPVs) used to correctly predict death ≤6 months were 94% (WBRT-30-SCLC), 88% (original DS-GPA), 88% (updated DS-GPA) and 100% (Rades-SCLC). PPVs to predict survival ≥6 months were 86%, 75%, 76% and 100%. For WBRT-30-SCLC and Rades-SCLC, differences between poor and intermediate prognoses groups and between intermediate and favorable prognoses groups were significant. For both DS-GPA classifications, only the difference between poor and intermediate prognoses groups was significant. Of these disease-specific tools, Rades-SCLC appeared to be the most accurate in identifying patients dying ≤6 months and patients surviving ≥6 months after irradiation, followed by the new WBRT-30-SCLC and the DS-GPA classifications.

[Salvage surgery for small cell lung cancer after chemoradiotherapy.](#) Nakanishi K1, Mizuno T1, Sakakura N1, Kuroda H1, Shimizu J2, Hida T2, Yatabe Y3, Sakao Y1. Jpn J Clin Oncol. 2019 Feb 8. doi: 10.1093/jjco/hyz010. [Epub ahead of print]
There are few reports on the use of salvage surgery for small cell lung cancer (SCLC). Five patients who underwent resection of post-chemoradiotherapy residual lesion/local reprogression of SCLC between 2005 and 2017 were included in the study. We retrospectively reviewed their surgical outcomes and prognosis to assess the feasibility and potential efficacy of salvage surgery. Indications for salvage surgery were local reprogression (four patients) and residual lesion (one patient) with ycN0 disease. Complete pathological resection was achieved in four patients; however, malignant pleural effusion was diagnosed in one patient after the surgery. Morbidity and mortality rates were 0%. Estimated 5-year survival rate was 67%. Recurrence and death after surgery occurred only in the patient with malignant pleural effusion. We demonstrate the feasibility of salvage surgery in SCLC. In carefully-selected patients, especially those without lymph node involvement, salvage surgery may provide effective local control and favorable survival outcomes.

[Surgical resection of small cell lung carcinoma: prognostic factors and the tumor micro-environment.](#) Zhao X1, Kallakury B2, Chahine JJ2, Hartmann D2, et al. J Thorac Oncol. 2019 Feb 5. pii: S1556-0864(19)30096-6. doi: 10.1016/j.jtho.2019.01.019. [Epub ahead of print]

BACKGROUND: Surgery in small cell lung cancer (SCLC) is limited to very early stages, but several reports suggest a potential broader role. Little is known of the influence of microenvironment on the biology of SCLC. **METHODS:** We assessed the clinical prognostic factors in a large series of resected SCLC patients. The prognostic value of Programmed cell Death Ligand-1 (PD-L1) expression in tumor cells and tumor infiltrating lymphocytes (TILs), and the percentage of CD3, CD20, CD45 and CD68 positive cells, were also investigated. **RESULTS:** 205 SCLC cases were resected between 2005 and 2015 and the median follow-up was 29 months (range: 2-135 months). Median survival of all patients was 69 months, and 5-year survival rates were 63.8%, 65.5%, 34.9%, and 0% for pathological stages I, II, III, and IV, respectively. By multivariate analysis complete resection, cigarette index (CI), lymph node metastatic rate (LNR), percentage of CD3 positive cells and PD-L1 expression in tumor cells and TILs were independent prognostic factors. High PD-L1 expression was present in 3.2% and 33.5% of all tumor samples in tumor cells and TILs, respectively. High PD-L1 expression in tumor cells or TILs correlated with shorter survival, whereas high expression of CD3, CD20 and CD45 correlated with better survival. **CONCLUSIONS:** Resected stage II SCLC patients have similar survival as stage I, suggesting that surgery could be extended to patients with hilar lymph node involvement. Survival was better in tumors with a higher percentage of T cells and B cells, whereas PD-L1 expression in tumor cells and TILs correlated with worse survival, which suggests a potential role of immunotherapy in resected SCLC.

[Impact of thoracic radiation therapy after chemotherapy on survival in extensive-stage small cell lung cancer: A propensity score-matched analysis.](#) Deng L1, Zhou Z1, Xiao Z1, et al. Thorac Cancer. 2019 Feb 18. doi: 10.1111/1759-7714.13001. [Epub ahead of print]

BACKGROUND: The role of thoracic radiation therapy (TRT) after chemotherapy (CHT) in extensive-stage small cell lung cancer (ES-SCLC) has not been well defined. We investigated whether intensity-modulated radiotherapy (IMRT) improves outcomes in ES-SCLC after CHT compared to CHT alone. **METHODS:** A total of 292 patients who reached a complete response (CR), partial response (PR), or stable disease (SD) after CHT were assigned into groups: CHT + TRT and CHT alone. Propensity score matching was used to balance patient groups (n = 72 each). **RESULTS:** The five-year overall survival (OS: 12.3% vs. 3.6%; P < 0.001) and progression-free survival (PFS: 3.2% vs. 1.7%; P = 0.006) rates were significantly higher in the CHT + TRT group. This data was confirmed in the matched samples (5-year OS: 10.5% vs. 1.6%, P < 0.001; PFS: 4.3% vs. 0.0%, P = 0.023). The overall (P = 0.002) and locoregional (P < 0.001) recurrence rates in the CHT + TRT group were significantly lower than in the CHT group. Univariate analysis showed that response evaluation after CHT and TRT were significant prognostic factors of OS. Multivariate analyses revealed that N Stage 0-1 (P = 0.02), > 6 cycles of CHT (P = 0.042), CR + PR after CHT (P < 0.001), and TRT (P < 0.001) were independently associated with longer OS compared to CHT alone. **CONCLUSION:** TRT using IMRT is strongly correlated with improved OS and PFS in ES-SCLC patients reaching CR, PR or SD after CHT. A multicenter, randomized phase III clinical trial is needed to confirm these findings.

PALLIATIVE AND SUPPORTIVE CARE

[Combined aerobic exercise and high-intensity respiratory muscle training in patients surgically treated for non-small cell lung cancer: a pilot randomized clinical trial.](#) Messaggi-Sartor M1,2, Marco E3,2,4, Martínez-Téllez E5, et al. Eur J Phys Rehabil Med. 2019 Feb;55(1):113-122. doi: 10.23736/S1973-9087.18.05156-0. Epub 2018 Jul 6.

BACKGROUND: Lung resection surgery further decreases exercise capacity and negatively affects respiratory muscle function in patients with non-small cell lung cancer (NSCLC). The best design for exercise interventions in these patients has not been determined yet. **AIM:**To assess the impact of aerobic exercise and high-intensity respiratory muscle training on patient outcomes following lung cancer resection surgery. **DESIGN:**Prospective, single-blind, pilot randomized controlled trial. **SETTING:** Outpatient cardiopulmonary rehabilitation unit of two university hospitals. **POPULATION:** Thirty-seven patients with NSCLC after tumor resection. **METHODS:** Patients were randomly assigned to exercise training or usual post-operative care. The training program consisted of aerobic exercises and high-intensity respiratory muscle training (24 supervised sessions, 3 per week, 8 weeks). Primary outcome was exercise capacity assessed with peak oxygen uptake (VO2peak) during cardiopulmonary exercise test. Secondary outcomes included changes in respiratory muscle strength, levels of serum insulin growth factor I (IGF-I) and IGF binding protein 3 (IGFBP-3), and quality of life assessed with the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) questionnaire. **RESULTS:** The 8-week training program was associated with significant improvement in VO2peak (2.13 mL/Kg/min [95%CI 0.06 to 4.20]), maximal inspiratory and expiratory pressures (18.96 cmH2O [95% CI 2.7 to 24.1] and 18.58 cmH2O [95% CI 4.0 to 33.1], respectively) and IGFBP-3 (0.61 µg/mL [%95 CI 0.1 to 1.12]). No significant differences were observed in the EORTC QLQ-C30. **CONCLUSIONS:** An 8-week exercise program consisting of aerobic exercise and high-intensity respiratory muscle training improved exercise capacity, respiratory muscle strength, and serum IGFBP-3 levels in NSCLC patients after lung resection. There was no impact on the other outcomes assessed. **CLINICAL REHABILITATION IMPACT:** A combination of aerobic exercise and respiratory muscle training could be included in the rehabilitation program of deconditioned patients with NSCLC after lung resection surgery.

[Comprehensive validation of the functional assessment of anorexia/cachexia therapy (FAACT) anorexia/cachexia subscale (A/CS) in lung cancer patients with involuntary weight loss.](#) Gelhorn HL1, Gries KS2, Speck RM2, Duus EM3, Bourne RK3, Aggarwal D3, Cella D4. Qual Life Res. 2019 Feb 22. doi: 10.1007/s11136-019-02135-7. [Epub ahead of print]

PURPOSE: Comprehensive (qualitative and quantitative) assessments of the 12-item functional assessment of anorexia/cachexia therapy (FAACT) anorexia/cachexia subscale (A/CS) and relevant subscales were undertaken for use in constructing potential endpoints in clinical trials of non-small cell lung cancer (NSCLC) with involuntary weight loss. **METHODS:** Eleven participants (≥ 18 years) from six clinical sites with a diagnosis of stage III unresectable or stage IV NSCLC and involuntary weight loss (either ≥ 5% body weight loss within six months prior to screening or screening BMI < 20 kg/m2) were interviewed to evaluate the content validity of the A/CS domain. A psychometric evaluation was conducted on the A/CS domain, and symptoms and concerns subscales, using data from previously completed phase III clinical trials (ROMANA1 [N = 474] and ROMANA2 [N = 488]). **RESULTS:** Anorexia-related symptoms were highly relevant to participants and had important impacts on their lives including energy levels, and physical, social, and psychological functioning. The majority of participants endorsed the A/CS domain items and found them to be easily understood, relevant, and comprehensive. Confirmatory factor analyses established that the A/CS symptoms and concerns subscales provided an acceptable fit as single factor models in ROMANA1 and ROMANA2. Reliability, validity, and responsiveness were established for the 12item A/CS domain, 5item anorexia symptoms subscale, and 4-item anorexia concerns subscale. **CONCLUSIONS:** These scales have good content validity, favorable psychometric properties, and can be used for characterizing the effect of treatment on anorexia symptoms and/or anorexia-related concerns in patients with NSCLC.

[Survivor guilt: The secret burden of lung cancer survivorship.](#) Perloff T1, King JC1, Rigney M2, Ostroff JS3, Johnson Shen M4. J Psychosoc Oncol. 2019 Feb 23:1-13. doi: 10.1080/07347332.2019.1569191. [Epub ahead of print]
OBJECTIVES: Historically, long-term survival following diagnosis of lung cancer has been a rare occurrence. An overall poor prognosis and the low likelihood of long-term survival are thought to precipitate survivors experiencing what is referred to as survivor guilt. This study explored the prevalence and nature of survivor guilt among lung cancer survivors. **METHODS:** Lung cancer survivors (n = 108) completed an online survey through a national organization's online community platform. This survey included a commonly used measure of survivor guilt targeting lung cancer and a single item that asked about whether they had experienced survivor guilt associated with lung cancer. Additionally, survivors were asked to provide open-ended descriptions of survivor guilt. In-depth thematic analysis was used to analyze these in-depth responses from those with the highest guilt scores on the survey measure (top quartile). **RESULTS:** Survey responses revealed a majority of study respondents endorsed survivor guilt with 55% reporting an experience of survivor guilt associated with lung cancer. In addition, 63.9% of respondents scored above the mean on the survivor guilt scale. Qualitative analysis revealed five recurring themes among respondents with the highest survivor guilt scores (top quartile): 1) mentioning the death of others, 2) questioning "why not me?" 3) the role of the passage of time on emotions experienced, 4) the role of demographic and clinical characteristics' on survivor guilt, and 5) strategies for coping with survivor guilt. **CONCLUSIONS:** This study identifies survivor guilt in lung cancer survivors and raises clinical awareness that managing survivor guilt is a psychosocial challenge for lung cancer survivors. Results highlight the need for addressing this critical issue.

[Assessing the Psychosocial Needs of Newly Diagnosed Patients with Non-Small Cell Lung Cancer: Identifying Factors Associated with Distress.](#) Leung B1, Laskin J1,2, Wu J2,3, Bates A2,4, Ho C1,2. Psychooncology. 2019 Feb 13. doi: 10.1002/pon.5025. [Epub ahead of print]
BACKGROUND: The Psychosocial Screen for Cancer (PSSCAN-R) questionnaire is a validated screening tool used to identify the psychosocial needs of patients with cancer. It assesses patients' perceived social supports and psychosocial needs, and the presence of symptoms of depression and anxiety. The study goals were to assess the prevalence and factors associated with distress in patients with newly diagnosed NSCLC. **METHODS:** All patients with NSCLC referred to BC Cancer centres from 2011-2015, who completed a prospective PSSCAN-R questionnaire at the time of their first visit, were included in the study. Demographics and baseline disease characteristics were collected retrospectively. The Chi-squared test, Fisher's exact test and logistical regression analysis were used to compare factors associated with the presence of distress based on sex, age, stage of disease, and performance status (PS). **RESULTS:** 4281 NSCLC patients completed the PSSCAN-R questionnaire. Baseline characteristics: 70% were ≥65, 50% female, 52% metastatic disease, 47% ECOG ≥2. Patients who were female, <65, have metastatic disease and poor PS were more likely to report subclinical or clinical symptoms of anxiety. Symptoms of depression were associated with younger, female, poor PS patients and social isolation. **CONCLUSION:** Newly diagnosed patients with NSCLC are likely to report clinical symptoms of anxiety and depression, and have a high number of concerns in multiple psychosocial domains. Resource development for lung cancer patients should be based on their care needs with careful consideration of patients' age, gender, stage, and social situation to optimally support their psychosocial needs during treatment and follow up.

[Exercise training for advanced lung cancer.](#) Peddle-McIntyre CJ1, Singh F, Thomas R, Newton RU, Galvão DA, Cavalheri V. Cochrane Database Syst Rev. 2019 Feb 11;2:CD012685. doi: 10.1002/14651858.CD012685.pub2. [Epub ahead of print]

BACKGROUND: Patients with advanced lung cancer have a high symptom burden, which is often complicated by coexisting conditions. These issues, combined with the indirect effects of cancer treatment, can cumulatively lead patients to continued deconditioning and low exercise capacity. This is a concern as exercise capacity is considered a measure of whole body health, and is critical in a patient's ability to participate in life activities and tolerate difficult treatments. There is evidence that exercise training improves exercise capacity and other outcomes, such as muscle force and health-related quality of life (HRQoL), in cancer survivors. However, the effectiveness of exercise training on these outcomes in people with advanced lung cancer is currently unclear. **OBJECTIVES:** The primary aim of this review was to investigate the effects of exercise training on exercise capacity in adults with advanced lung cancer. Exercise capacity was defined as the six-minute walk distance (6MWD; in meters) measured during a six-minute walk test (6MWT; i.e. how far an individual can walk in six minutes on a flat course), or the peak oxygen uptake (i.e. VO_2peak) measured during a maximal incremental cardiopulmonary exercise test (CPET).The secondary aims were to determine the effects of exercise training on the force-generating capacity of peripheral muscles, disease-specific global HRQoL, physical functioning component of HRQoL, dyspnoea, fatigue, feelings of anxiety and depression, lung function, level of physical activity, adverse events, performance status, body weight and overall survival in adults with advanced lung cancer. **SEARCH METHODS:** We searched CENTRAL, MEDLINE (via PubMed), Embase (via Ovid), CINAHL, SPORTDiscus, PEDro, and SciELO on 7 July 2018. **SELECTION CRITERIA:** We included randomised controlled trials (RCTs) which compared exercise training versus no exercise training in adults with advanced lung cancer. **DATA COLLECTION AND ANALYSIS:** Two review authors independently screened the studies and selected those for inclusion. We performed meta-analyses for the following outcomes: exercise capacity, disease-specific global HRQoL, physical functioning HRQoL, dyspnoea, fatigue, feelings of anxiety and depression, and lung function (forced expiratory volume in one second (FEV1)). Two studies reported force-generating capacity of peripheral muscles, and we presented the results narratively. Limited data were available for level of physical activity, adverse events, performance status, body weight and overall survival. **MAIN RESULTS:** We identified six RCTs, involving 221 participants. The mean age of participants ranged from 59 to 70 years; the sample size ranged from 20 to 111 participants. Overall, we found that the risk of bias in the included studies was high, and the quality of evidence for all outcomes was low.Pooled data from four studies demonstrated that, on completion of the intervention period, exercise capacity (6MWD) was significantly higher in the intervention group than the control group (mean difference (MD) 63.33 m; 95% confidence interval (CI) 3.70 to 122.96). On completion of the intervention period, disease-specific global HRQoL was significantly better in the intervention group compared to the control group (standardised mean difference (SMD) 0.51; 95% CI 0.08 to 0.93). There was no significant difference between the intervention and control groups in physical functioning HRQoL (SMD 0.11; 95% CI -0.36 to 0.58), dyspnoea (SMD -0.27; 95% CI -0.64 to 0.10), fatigue (SMD 0.03; 95% CI -0.51 to 0.58), feelings of anxiety (MD -1.21 units on Hospital Anxiety and Depression Scale; 95% CI -5.88 to 3.45) and depression (SMD -1.26; 95% CI -4.68 to 2.17), and FEV1 (SMD 0.43; 95% CI -0.11 to 0.97). **AUTHORS' CONCLUSIONS:** Exercise training may improve or avoid the decline in exercise capacity and disease-specific global HRQoL for adults with advanced lung cancer. We found no significant effects of exercise training on dyspnoea, fatigue, feelings of anxiety and depression, or lung function. The findings of this review should be viewed with caution because of the heterogeneity between studies, the small sample sizes, and the high risk of bias of included studies. Larger, high-quality RCTs are needed to confirm and expand knowledge on the effects of exercise training in this population.

COMPLEMENTARY & ALTERNATIVE THERAPY

[Yifei Tongluo, a Chinese Herbal Formula, Suppresses Tumor Growth and Metastasis and Exerts Immunomodulatory Effect in Lewis Lung Carcinoma Mice.](#) Qi Q1, Hou Y2, Li A3, Sun Y4, Li S5, Zhao Z6,7,8. Molecules. 2019 Feb 18;24(4). pii: E731. doi: 10.3390/molecules24040731.

This study was aimed to investigate the anti-tumor, anti-metastasis and immunomodulatory effects of Yifei Tongluo (YFTL), a Chinese herbal formula, in Lewis lung carcinoma mice and to explore the underlying mechanisms. LLC cells were inoculated subcutaneously in C57BL/6 mice to establish the Lewis lung carcinoma model. We observed that YFTL effectively inhibited tumor growth and prolonged the overall survival of tumor-bearing mice. Additionally, YFTL treatment resulted in a significantly decreased number of surface lung metastatic lesions compared with the model control group. Meanwhile, TUNEL staining confirmed that the tumors from YFTL-treated mice exhibited a markedly higher apoptotic index. The results suggest that Akt and mitogen-activated protein kinase (MAPKs) pathways may be involved in YFTL-induced apoptosis. The results show that YFTL also inhibited the vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMP)-2, MMP-9, N-cadherin, and Vimentin expression, but increased E-cadherin expression. Mechanistic studies indicated that YFTL could suppress the angiogenesis and the epithelial-mesenchymal transition (EMT) of the tumor through Akt/ERK1/2 and TGFβ1/Smad2 pathways. In addition, YFTL also showed immunomodulatory activities in improving the immunosuppressive state of tumor-bearing mice. Therefore, our findings could support the development of YFTL as a potential antineoplastic agent and a potentially useful anti-metastatic agent for lung carcinoma therapy.

MISCELLANEOUS WORKS

[Using a Dedicated Interventional Pulmonology Practice Decreases Wait Time Before Treatment Initiation for New Lung Cancer Diagnoses.](#) Benn BS1, Parikh M2, Tsau PH3, Seeley E4, Krishna G4,5. Lung. 2019 Feb 19. doi: 10.1007/s00408-019-00207-6. [Epub ahead of print]

PURPOSE: While there is significant mortality and morbidity with lung cancer, early stage diagnoses carry a better prognosis. As lung cancer screening programs increase with more pulmonary nodules detected, expediting definitive treatment initiation for newly diagnosed patients is imperative. The objective of our analysis was to determine if the use of a dedicated interventional pulmonology practice decreases time delay from new diagnosis of lung cancer or metastatic disease to the chest to treatment initiation. **METHODS:** Retrospective chart analysis was done of 87 consecutive patients with a new diagnosis of primary lung cancer or metastatic cancer to the chest from our interventional pulmonology procedures. Demographic information and time intervals from abnormal imaging to procedure and to treatment initiation were recorded. **RESULTS:** Patients were older (mean age 69) and former or current smokers (72%). A median of 27 days (1-127 days) passed from our diagnostic biopsy to treatment initiation. A median of 53 total days (2-449 days) passed from abnormal imaging to definitive treatment. Endobronchial ultrasound-guided transbronchial needle aspiration was the most commonly used diagnostic procedure (59%), with non-small cell lung cancer the majority diagnosis (64%). For surgical patients, all biopsy-negative lymph nodes from our procedures were cancer-free at surgical excision. **CONCLUSIONS:** Compared to prior reports from international and United States cohorts, obtaining a tissue biopsy diagnosis through a gatekeeper interventional pulmonology practice decreases median delay from abnormal imaging to treatment initiation. This finding has the potential to positively impact patient outcomes and requires further evaluation.

[Effects of a Web-based Health Education Program on Quality of Life and Symptom Distress of Initially Diagnosed Advanced Non-Small Cell Lung Cancer Patients: A Randomized Controlled](#)

Trial. Huang CC1, Kuo HP2,3, Lin YE1,4, Chen SC5,6,7. J Cancer Educ. 2019 Feb;34(1):41-49. doi: 10.1007/s13187-017-1263-y.

Advanced non-small cell lung cancer (NSCLC) patients treated with chemotherapy experience functional decline and decreased quality of life. The purpose of this study was to evaluate the effects of a web-based health education program on global quality of life, quality of life-related functional dimensions, and symptom distress of initially diagnosed advanced non-small cell lung cancer patients. This study used a randomized, pre- and post-repeated measures design. A total of 55 participants were randomly assigned to an experimental group (n = 27) and a control group (n = 28). The experimental group participated in a web-based health education program, and the control group received usual care. Patients were assessed at 4 time points: baseline assessment (T0), and then 1, 2, and 3 months (T1, T2, and T3) after participating in the web-based health education program or receiving usual care. Patients in the experimental group had significantly greater global quality of life and emotional function, and significantly less top ten significant symptom distresses compared to those in the control group. There were no differences between the groups and within groups with respect to physical function, role function, cognitive function, and social function. The web-based health education can improve global quality of life, emotional function, and top ten significant symptom distresses in patients receiving chemotherapy during the first 3 months after initial diagnosis of advanced NSCLC. Web-based health education can improve quality of life and lessen distress of initially diagnosed NSCLC patients treated with chemotherapy.

Using a Dedicated Interventional Pulmonology Practice Decreases Wait Time Before Treatment Initiation for New Lung Cancer Diagnoses. Benn BS1, Parikh M2, Tsau PH3, Seeley E4, Krishna G4,5. Lung. 2019 Feb 19. doi: 10.1007/s00408-019-00207-6. [Epub ahead of print]

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Association Between Rurality and Lung Cancer Treatment Characteristics and Timeliness. Fairfield KM1,2, Black AW1, Lucas FL1,2, et al. J Rural Health. 2019 Feb 19. doi: 10.1111/jrh.12355. [Epub ahead of print]

BACKGROUND: Lung cancer is the leading cause of cancer-related mortality in the United States, and rural states bear a greater burden of disease. **METHODS:** We analyzed tumor registry data to examine relationships between rurality and lung cancer stage at diagnosis and treatment. Cases were from the Maine Cancer Registry from 2012 to 2015, and rurality was defined using rural-urban commuting areas.

Multivariable models were used to examine the relationships between rurality and treatment, adjusting for age, sex, poverty, education, insurance status, and cancer stage. **RESULTS:** We identified 5,338 adults with incident lung cancer; 3,429 (64.2%) were diagnosed at a late stage (III or IV). Rurality was not associated with stage at diagnosis. For patients with early-stage disease (I or II), rurality was not associated with receipt of treatment. However, for patients with late-stage disease, residents of large rural areas received more surgery (10%) compared with metropolitan (9%) or small/isolated rural areas (6%), P = .01. In multivariable analyses, patients in large rural areas received more chemotherapy (OR 1.48; 95% CI: 1.08-2.02) than those in metropolitan areas. Patients with early-stage disease residing in small/isolated rural areas had delays in treatment (median time to first treatment = 43 days, interquartile range [IQR] 22-68) compared with large rural (34 days, IQR 17-55) and metropolitan areas (35 days, IQR 17-60), P = .0009. **CONCLUSION:** Rurality is associated with differences in receipt of specific lung cancer treatments and in timeliness of treatment.

[Lung cancer stigma and depression: Validation of the Lung Cancer Stigma Inventory.](#)
Ostroff JS1, Riley KE1, Shen MJ2, Atkinson TM1, Williamson TJ1, Hamann HA3. Psychooncology. 2019 Feb 19. doi: 10.1002/pon.5033. [Epub ahead of print]
OBJECTIVE: In an effort to provide further evidence for the validity of the Lung Cancer Stigma Inventory (LCSI), this paper examined group differences in lung cancer stigma for patients who report clinically significant depressive symptoms and established a suggested scoring benchmark to identify patients with clinically meaningful levels of lung cancer stigma. **METHODS:** Patients (n=231) who were diagnosed with lung cancer and treated within the past 12 months at one of two NCI-designated Cancer Centers located in the northeast and southern parts of the United States completed a single battery of questionnaires examining lung cancer stigma and depressed mood. Group differences, bivariate correlations and receiver operating characteristics (ROC) analyses were conducted. **RESULTS:** Slightly more than a third of patients (35.9%) reported an elevated level of depression. There was a significant correlation (r = 0.44) between lung cancer stigma and depressive mood. The ROC curve analysis indicated an AUC of 0.71. A LCSI cutoff score of 37.5 yielded the optimal ratio of sensitivity (0.93) to specificity (0.70) for identifying patients with clinically meaningful lung cancer stigma. **CONCLUSIONS:** Consistent with prior work, lung cancer stigma, as measured by the LCSI, was found to be moderately associated with depressed mood. Clinical investigators may use an LCSI total score above 37.5 (i.e., greater than or equal to 38 on the LCSI scale of integer scores) as a clinical threshold for identifying patients who may be experiencing clinically meaningful stigma and may benefit from stigma-reducing interventions.

[Factors Affecting Racial Disparities in End-of-Life Care Costs Among Lung Cancer Patients: A SEER-Medicare-based Study.](#) Karanth S1, Rajan SS1, Revere FL1, Sharma G2. Am J Clin Oncol. 2019 Feb;42(2):143-153. doi: 10.1097/COC.0000000000000485.
OBJECTIVES: Racial disparities exist in end-of-life lung cancer care, which could potentially lead to considerable racial differences in end-of-life care costs. This study for the first time estimates the racial differences in end-of-life care costs among lung cancer patients, and identifies and quantifies factors that contribute the most to these differences using a statistical decomposition method. **METHODS:** This is a retrospective analysis of patients 66 years and older, diagnosed with stage I-IV lung cancer, who died on or before December 31, 2013, using the Surveillance Epidemiology and End Result-Medicare data from 1991 to 2013. Ordinary least square regression of logarithmically transformed cost was used to estimate racial differences in end-of-life care costs among lung cancer patients. Blinder-Oaxaca decomposition was used to identify and quantify factors that contributed the most to these differences. **RESULTS:** Non-Hispanic blacks had 10% to 13% higher end-of-life care costs as compared with non-Hispanic whites. Geographic variations, baseline comorbidity indices and stage at diagnosis contributed the most to

explaining the racial differences in costs, with geographic variation explaining most of the differences. However, the observed factors could only explain 25% to 32% of the racial differences in end-of-life care costs. **CONCLUSIONS:** Geographic differences in access to timely and appropriate care, and provider practice patterns, should be examined to understand the reasons behind geographic variations in racial disparity. Provider-level educational interventions to reduce small area practice variations and differential management of patients by race, as well as racially sensitive patient-level educational and navigational interventions might be critical in improving quality of care and reducing costs during end-of-life.

[**Association Between Reductions of Number of Cigarettes Smoked per Day and Mortality Among Older Adults in the United States.**](#) Inoue-Choi M1, Hartge P1, Park Y2, Abnet CC1, Freedman ND1. Am J Epidemiol. 2019 Feb 1;188(2):363-371. doi: 10.1093/aje/kwy227.

Many smokers do not quit but instead reduce the number of cigarettes they smoke per day (CPD) over their lifetime. Yet the associations of such changes in CPD with health risks are unclear. We examined the association of changes in CPD with subsequent death in the period 2004-2011 among 253,947 participants of the National Institutes of Health-AARP Diet and Health Study. Using a questionnaire assessing responders' history of smoking cigarettes, we identified cigarette smokers who quit, decreased, maintained, or increased their CPD between ages 25-29 and 50-59 years. Hazard ratios and 95% confidence intervals were obtained from multivariable adjusted Cox proportional hazards regression models. Relative to never smokers, smokers who maintained a consistent CPD had 2.93 times (95% confidence interval (CI): 2.82, 3.05) higher all-cause mortality risk, and participants who increased their CPD had still higher risk (hazard ratio (HR) = 3.37, 95% CI: 3.23, 3.52). Death risk was lower among participants who decreased their CPD (HR = 2.38, 95% CI: 2.25, 2.52) or quit smoking (for quitting between ages 30 and 39 years, HR = 1.32, 95% CI: 1.25, 1.39). Similar patterns were observed for smoking-related causes of death, with particularly strong associations for lung cancer and respiratory disease. Reductions in CPD over the lifetime meaningfully decreased death risk; however, cessation provided a larger benefit than even large declines in CPD.

[**Non-Smoking-Associated Lung Cancer: A distinct Entity in Terms of Tumor Biology, Patient Characteristics and Impact of Hereditary Cancer Predisposition.**](#) Smolle E1, Pichler M2. Cancers (Basel). 2019 Feb 10;11(2). pii: E204. doi: 10.3390/cancers11020204.

Non-small cell lung cancer (NSCLC) in non-, and especially in never-smoking patients is considered a biologically unique type of lung cancer, since risk factors and tumorigenic conditions, other than tobacco smoke, come into play. In this review article, we comprehensively searched and summarized the current literature with the aim to outline what exactly triggers lung cancer in non-smokers. Changes in the tumor microenvironment, distinct driver genes and genetic pathway alterations that are specific for non-smoking patients, as well as lifestyle-related risk factors apart from tobacco smoke are critically discussed. The data we have reviewed highlights once again the importance of personalized cancer therapy, i.e., careful molecular and genetic assessment of the tumor to provide tailored treatment options with optimum chances of good response-especially for the subgroups of never-smokers.

[**Analysis of Time to Treatment Discontinuation of Targeted Therapy, Immunotherapy, and Chemotherapy in clinical trials of patients with non-small cell lung cancer.**](#) Blumenthal GM1, Gong Y1, Kehl K2, Mishra-Kalyani P1, et al. Ann Oncol. 2019 Feb 22. pii: mdz060. doi: 10.1093/annonc/mdz060. [Epub ahead of print]

BACKGROUND: Pragmatic Endpoints such as Time to Treatment Discontinuation (TTD), defined as the date of starting a medication to the date of treatment discontinuation or death has been proposed as a potential efficacy endpoint for Real World Evidence (RWE) Trials, where imaging evaluation is less structured and standardized. **PATIENTS AND METHODS:** We studied 18 randomized clinical trials of

patients with metastatic non-small cell lung cancer (mNSCLC), initiated after 2007 and submitted to US Food and Drug Administration. TTD was calculated as date of randomization to date of discontinuation or death and compared to progression-free survival (PFS) and overall survival (OS) across all patients, as well as in treatment-defined subgroups (EGFR mutation positive treated with Tyrosine Kinase Inhibitor (TKI), EGFR wild-type treated with TKI, ALK-positive treated with TKI, Immune Checkpoint Inhibitor (ICI), Chemotherapy doublet with maintenance, Chemotherapy monotherapy). **RESULTS:** Overall across 8947 patients, TTD was more closely associated with PFS ($r = 0.87$, 95% CI 0.86-0.87) than with OS (0.68, 95% CI 0.67-0.69). Early TTD (PFS - TTD $\geq$ 3 months) occurred in 7.7% of patients overall, and was more common with chemo monotherapy (15.0%) while late TTD (TTD - PFS $\geq$ 3 months) occurred in 6.0% of patients overall, and was more common in EGFR positive and ALK positive patients (12.4% and 22.9%). In oncogene-targeted subgroups (EGFR positive and ALK positive), median TTDs (13.4 and 14.1 months) exceeded median PFS (11.4 and 11.3 months). **CONCLUSIONS:** At the patient level, TTD is associated with PFS across therapeutic classes. Median TTD exceeds median PFS for biomarker-selected patients receiving oncogene-targeted therapies. TTD should be prospectively studied further as an endpoint for pragmatic randomized RWE trials only for continuously administered therapies.