Caring Ambassadors Lung Cancer Program
Literature Review, April 2018

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Circulating tumor DNA measurement provides reliable mutation detection in mice with human lung cancer xenografts. Wei L1, Xie L1,2, Wang X1, Ma H2, Lv L1, Liu L2, Song X3,4. Lab Invest. 2018 Mar 1. doi: 10.1038/s41374-018-0041-8. [Epub ahead of print]
Genotype-directed targeted therapy has become one of the standard treatment options for non-small cell lung cancer (NSCLC). There have been numerous limitations associated with mutation analysis of tissue samples. Consequently, mutational profile analysis of circulating cell-free DNA (cfDNA) by highly sensitive droplet digital PCR (ddPCR) assay has been developed. Possibly due to differences in cfDNA concentrations, previous studies have shown numerous discrepancies in mutation detection consistency between tissue and cfDNA. In order to rigorously analyze the amount of cfDNA needed, we constructed 72 athymic nude mice xenografted with NCI-H1975 (harboring a EGFR T790M mutation) or NCI-H460 (harboring a KRAS Q61H mutation) human NSCLC. We thoroughly investigated the relationship between plasma cfDNA using Q-PCR targeting human long interspersed nuclear element-1 (LINE-1) retrotransposon and the mouse ACTB gene, and the accuracy of mutation detection by ddPCR at different times post-graft. Our results show that the concentration and fragmentation of human (tumor) derived cfDNA (hctDNA) were positively correlated with tumor weight, but not with mouse-derived cfDNA (mcfDNA). Quantification of cfDNA by Q-PCR depends on the amplified target length. Mutation copies in plasma of per milliliter were positively linked to tumor weight, hctDNA level and hctDNA/mcfDNA ratio, respectively. Furthermore, tumor weight, hctDNA level and ratio of hctDNA/mcfDNA were significantly higher in cfDNA mutation-positive mice than in negative mice. Also, our data indicate that when plasma hctDNA level and hctDNA/mcfDNA ratio reach a certain level in xenografted mice, plasma cfDNA mutation can be detected. In summary, the present study suggests that determination of ctDNA levels may be essential for reliable mutation detection by analysis of cfDNA.

Inflammatory Gene Polymorphisms in Lung Cancer Susceptibility. Eaton KD1, Romine PE2, Goodman GE3, Thornquist MD4, Barnett MJ3, Petersdorf EW5. J Thorac Oncol. 2018 Mar 23. pii: S1556-0864(18)30090-X. doi: 10.1016/j.jtho.2018.01.022. [Epub ahead of print]

INTRODUCTION: Chronic inflammation has been implicated in carcinogenesis, with increasing evidence of its role in lung cancer. We aimed to evaluate the role of genetic polymorphisms in inflammation-related genes in the risk for development of lung cancer. **METHODS:** A nested case-control study design was used, and 625 cases and 625 well-matched controls were selected from participants in the β-Carotene and Retinol Efficacy Trial, which is a large, prospective lung cancer chemoprevention trial. The association between lung cancer incidence and survival and 23 polymorphisms descriptive of 11 inflammation-related genes (interferon gamma gene [IFNG], interleukin 10 gene [IL10], interleukin 1 alpha gene [IL1A], interleukin 1 beta gene [IL1B], interleukin 2 gene [IL2], interleukin 4 receptor gene [IL4R], interleukin 4 gene [IL4], interleukin 6 gene [IL6], prostaglandin-endoperoxide synthase 2 gene [PTGS2] (also known as COX2), transforming growth factor beta 1 gene [TGFB1], and tumor necrosis factor alpha gene [TNFA]) was evaluated. **RESULTS:** Of the 23 polymorphisms, two were associated with risk for lung cancer. Compared with individuals with the wild-type (CC) variant, individuals carrying the minor allele variants of the IL-1β-511C>T promoter polymorphism (rs16944) (CT and TT) had decreased odds of lung cancer (OR = 0.74, [95% confidence interval (CI): 0.58-0.94] and OR = 0.71 [95% CI: 0.50-1.01], respectively, p = 0.03). Similar results were observed for the IL-1β-1464 C>G promoter polymorphism (rs1143623), with presence of the minor variants CG and CC having decreased odds of lung cancer (OR = 0.75 [95% CI: 0.59-0.95] and OR = 0.69 [95% CI: 0.46-1.03], respectively, p = 0.03). Survival was not influenced by genotype. **CONCLUSIONS:** This study provides further evidence that IL1B promoter polymorphisms may modulate the risk for development of lung cancer.

Intrinsic and Extrinsic Regulation of PD-L2 Expression in Oncogene-Driven Non-Small Cell Lung Cancer. Shibahara D1, Tanaka K2, Iwama E2, Kubo N2, Ota K2, Azuma K3, Harada T4, Fujita J5, Nakanishi Y2, Okamoto I6. J Thorac Oncol. 2018 Mar 26. pii: S1556-0864(18)30215-6. doi: 10.1016/j.jtho.2018.03.012. [Epub ahead of print]

INTRODUCTION: The interaction of programmed cell death-ligand 2 (PD-L2) with programmed cell death-1 (PD-1) is implicated in tumor immune escape. The regulation of PD-L2 expression in tumor cells has remained unclear, however. We here examined intrinsic and extrinsic regulation of PD-L2 expression in non-small cell lung cancer (NSCLC). **METHODS:** PD-L2 expression was evaluated by reverse transcription and real-time polymerase chain reaction analysis and by flow cytometry. **RESULTS:** BEAS-2B cells stably expressing an activated mutant form of the epidermal growth factor receptor (EGFR) or the EML4-ALK fusion oncoprotein manifested increased expression of PD-L2 at both mRNA and protein levels. Furthermore, treatment of NSCLC cell lines that harbor such driver oncogenes with corresponding EGFR or ALK tyrosine kinase inhibitors or depletion of EGFR or ALK by siRNA transfection suppressed expression of PD-L2, demonstrating that activating EGFR mutations or EML4-ALK fusion intrinsically induce PD-L2 expression. We also found that interferon-γ extrinsically induced expression of PD-L2 via STAT1 signaling in NSCLC cells. Oncogene-driven expression of PD-L2 in NSCLC cells was inhibited by knockdown of the transcription factors STAT3 or c-FOS. Interferon-γ also activated STAT3 and c-FOS, suggesting that these proteins may also contribute to the extrinsic induction of PD-L2 expression. **CONCLUSIONS:** Expression of PD-L2 is induced intrinsically by activating EGFR mutations or EML4-ALK fusion as well as extrinsically by interferon-γ, with STAT3 and c-FOS possibly contributing to both intrinsic and extrinsic pathways. Our results thus provide insight into the complexity of tumor immune escape in NSCLC.

[**Circulating long noncoding RNA act as potential novel biomarkers for diagnosis and prognosis of non-small cell lung cancer.**](#) Xie Y1, Zhang Y2, Du L1, et al. Mol Oncol. 2018 Mar 5. doi: 10.1002/1878-0261.12188. [Epub ahead of print]
Lung cancer is the first leading cause of cancer deaths worldwide. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. Increasing evidence shows that long noncoding RNA (lncRNA) are capable of modulating tumor initiation, proliferation and metastasis. In the present study, we aimed to evaluate whether circulating lncRNA could be used as biomarkers for diagnosis and prognosis of NSCLC. Expression profiles of 14 lncRNA selected from other studies were validated in 20 pairs of tissues by quantitative real-time PCR, and the dysregulated lncRNA thus identified were further validated in serum samples from two independent cohorts along with three tumor makers (CEA, CYFRA21-1, and SCCA). Receiver-operating characteristic analysis was utilized to estimate the diagnostic efficiency of the candidate lncRNA and tumor markers. Importantly, we observed an association between lncRNA expression and overall survival (OS) rate of NSCLC. The expressions of SOX2 overlapping transcript (SOX2OT) and ANRIL were obviously upregulated in NSCLC tissues and serum samples compared with normal controls (P < 0.01). Based on the data from the training set, we next used a logistic regression model to construct an NSCLC diagnostic panel consisting of two lncRNA and three tumor markers. The area under the curve of this panel was 0.853 (95% confidence interval = 0.804-0.894, sensitivity = 77.1%, specificity = 79.2%), and this was distinctly superior to any biomarker alone (all at P < 0.05). Similar results were observed in the validation set. Intriguingly, Kaplan-Meier analysis demonstrated that low expressions of SOX2OT and ANRIL were both associated with higher OS rate (P = 0.008 and 0.017, respectively), and SOX2OT could be used as an independent prognostic factor (P = 0.036). Taken together, our study demonstrated that the newly developed diagnostic panel consisting of SOX2OT, ANRIL, CEA, CYFRA21-1, and SCCA could be valuable in NSCLC diagnosis. LncRNA SOX2OT and ANRIL might be ideal biomarkers for NSCLC prognosis.

[**Usefulness of Plasma Exosomal MicroRNA-451a as a Noninvasive Biomarker for Early Prediction of Recurrence and Prognosis of Non-Small Cell Lung Cancer.**](#) Kanaoka R, Iinuma H, Dejima H, Sakai T, Uehara H, Matsutani N, Kawamura M. Oncology. 2018 Mar 13. doi: 10.1159/000487006. [Epub ahead of print]
OBJECTIVES: The aim of this study was to clarify the usefulness of plasma exosomal microRNA-451a (miR-451a) as a novel biomarker for the early prediction of recurrence and prognosis in non-small cell lung cancer (NSCLC) patients after curative resection. **METHODS:** Before surgery, plasma samples were collected and exosomal microRNA (miRNA) levels were evaluated. We first profiled specific exosomal miRNAs related to recurrence in 6 NSCLC patients with stage IA cancer by miRNA microarray. We then validated the usefulness of selected miRNAs as biomarkers using the other 285 NSCLC patients. **RESULTS:** Plasma exosomal miR-451a showed the highest upregulation in the NSCLC patients with recurrence in the miRNA microarray analysis. A significant positive correlation was demonstrated between exosomal miR-451a levels and NSCLC tissue miR-451a levels. Exosomal miR-451a showed a significant association with lymph node metastasis, vascular invasion, and stage. In stage I, II, or III patients, the overall survival (OS) and disease-free survival (DFS) rates among the high-exosomal-miR-451a patients were significantly worse than those among the low-exosomal-miR-451a patients. In Cox multivariate analysis, exosomal miR-451a showed significance for OS and DFS. **CONCLUSION:** Plasma exosomal miR-451a might serve as a reliable biomarker for the prediction of recurrence and prognosis in NSCLC patients with stage I, II, or III cancer.

[**CXCL14 and NOS1 expression in specimens from patients with stage I-IIIA nonsmall cell lung cancer after curative resection.**](#) Ji X1, Shen Z, Zhao B, Yuan X, Zhu X. Medicine (Baltimore). 2018 Mar;97(10):e0101. doi: 10.1097/MD.0000000000010101.

Many studies show that CXC chemokine ligand 14 (CXCL14) is highly expressed in tumor-associated stromal cells, promoting tumor cell growth, and invasion. Because of its unclear receptors, CXCL14-initiated intracellular signal cascades remain largely unknown. However, CXCL14 can regulate nitric oxide synthase 1 (NOS1) as its intracellular molecular target. In this paper, we investigated the expression of CXCL14 and NOS1 in specimens from patients with stage I-IIIA nonsmall cell lung cancer (NSCLC) after curative resection, and evaluated the prognostic significance of this gene expression in stromal fibroblasts and cancer cells.Immunohistochemistry was used to detect the expression of CXCL14 and NOS1 in 106 formalin fixed, paraffin-embedded specimens from patients with stage I-IIIA NSCLC. The chi-square test was performed to examine the correlation of CXCL14 and NOS1 expression level with clinicopathological features. The effects of the expression of CXCL14 or NOS1 on progression-free survival (PFS) and overall survival (OS) were determined by Kaplan-Meier and Cox hazard proportional model.The percentages of high CXCL14 expression in stromal fibroblasts and that in cancer cells were 46.2% (49/106) and 23.6% (25/106), respectively. The positive expression rates of NOS1 in cancer cells were 42.5% (45/106). The result indicated that there was a significant positive correlation between CXCL14 expression level in stromal fibroblasts and that in cancer cells ($\chi=4.158$, P=.041). In addition, the expression of CXCL14 in stromal fibroblasts was significantly correlated with NOS1 expression in cancer cells ($\chi=16.156$, P<.001). The 5-year PFS rates with low and high CXCL14 expression in stromal fibroblasts were 66.7% and 14.3% ($\chi=44.008$, P<.001), respectively, and the 5-year OS rates with those were 87.1% and 43.5% ($\chi=21.531$, P<.001), respectively. The 5-year PFS rates with negative and positive expression of NOS1 in cancer cells were 62.3% and 15.6% ($\chi=33.756$, P<.001), respectively, and the 5-year OS rates with those were 86.4% and 40.1% ($\chi=24.430$, P<0.01), respectively.Both the high expression of CXCL14 in stromal fibroblasts and the positive expression of NOS1 in cancer cells are independent negative predictors of PFS and OS in patients with stage I-IIIA NSCLC after curative resection.

SCREENING, DIAGNOSIS AND STAGING

[**Rapid on-site evaluation using telecytology: A major cancer center experience.**](#) Lin O1, Rudomina D1, Feratovic R1, Sirintrapun SJ1. Diagn Cytopathol. 2018 Mar 25. doi: 10.1002/dc.23925. [Epub ahead of print]

BACKGROUND: Rapid on-site evaluation (ROSE) with cytology preparations plays a critical role in minimally invasive procedures. The time spent by a pathologist performing ROSE is unpredictable and could be used for more cost-effective activities. The solution encountered by several institutions to address this issue is the use of telecytology (TC). This study analyzes the experience of using telecytology for ROSE in a major cancer center over a period of over 2 years. **METHODS:** A retrospective analysis of all remote TC evaluations for adequacy on fine needle aspiration (FNA) and touch preparations (TP) of core biopsies (CB) performed at a major cancer center was performed. The preliminary adequacy assessment was then compared to the adequacy assessment at final diagnosis. **RESULTS:** A total of 12 949 adequacy assessments were analyzed. The most common sites biopsied in our institution were lymph node, lung, and liver. There were 7725 adequacy assessments for CB (59.7%), while adequacy assessment for FNA specimens represented 40.3% (n = 5224) of the total number of specimens evaluated by ROSE. Perfect concordance between initial adequacy assessment and the adequacy assessment at final cytologic diagnosis was 93% (12 049/12 949). The final diagnosis adequacy upgrade rate was 6.7% (n = 863), and the adequacy downgrade (a specimen considered adequate on-site that was determined to be nondiagnostic on final examination) was 0.3% (n = 37). **CONCLUSIONS:** TC can be easily implemented

with the current technologies available. It is cost-effective and allows for better patient care with a more efficient use of the pathologist's time and laboratory resources.

Benefits and Challenges of Lung Cancer Screening in Older Adults. Fabrikant MS1, Wisnivesky JP2, Marron T3, Taioli E4, Veluswamy RR5. Clin Ther. 2018 Mar 21. pii: S0149-2918(18)30095-X. doi: 10.1016/j.clinthera.2018.03.003. [Epub ahead of print]

PURPOSE: Lung cancer screening with low-dose computed tomography has been shown to significantly reduce lung cancer-related mortality in high-risk patients. However, patients diagnosed with lung cancer are typically older and often have multiple age- and smoking-related comorbidities. As a result, cancer screening in older adults remains a complex decision, requiring careful consideration of patients' risk characteristics and life expectancy to ensure that the benefits outweigh the risks of screening. In this review, we evaluate the evidence regarding lung cancer screening, with a focus on older patients.
METHODS: PubMed was searched to identify relevant studies evaluating the clinical outcomes of lung cancer screening. The key words used in our search included non-small cell lung cancer (NSCLC), screening, older, comorbidities, computed tomography, and survival. While we primarily looked for articles specific to older patients, we also focused on subgroup analysis in older patients in larger studies. Finally, we reviewed all relevant guidelines regarding lung cancer screening. **FINDINGS:** Guidelines recommend that lung cancer screening be considered in adults aged 55 to 80 years who are at high risk based on smoking history (ie, 30-pack-year smoking history; having smoked within the past 15 years). Patients who fit these criteria have been shown to have a 20% reduction in lung cancer-related mortality with the use of low-dose computed tomography versus chest radiography. High rates of false-positive results and potential overdiagnoses were also observed. Therefore, screening is generally not recommended in adults with severe comorbidities or short life expectancy, who may experience limited benefit and higher risks with screening. However, several studies have shown a benefit with continued lung cancer screening with appropriate selection of older individuals at the highest risk and with the lowest comorbidities. **IMPLICATIONS:** Older patients experience the highest risk for lung cancer incidence and mortality, and stand to be the most likely to benefit from lung cancer screening. However, careful consideration must be given to higher rates of false-positives and overdiagnosis in this population, as well as tolerability of surgery and competing risks for death from other causes. The appropriate selection of older individuals for lung cancer screening can be greatly optimized by using validated risk-based targeting.

The serum-based VeriStrat® test is associated with proinflammatory reactants and clinical outcome in non-small cell lung cancer patients. Fidler MJ1, Fhied CL2, Roder J3, Basu S4, Sayidine S2, Fughhi I1, Pool M2, Batus M1, Bonomi P1, Borgia JA5,6,7. BMC Cancer. 2018 Mar 20;18(1):310. doi: 10.1186/s12885-018-4193-0.

BACKGROUND: The VeriStrat test is a serum proteomic signature originally discovered in non-responders to second line gefitinib treatment and subsequently used to predict differential benefit from erlotinib versus chemotherapy in previously treated advanced non-small cell lung cancer (NSCLC). Multiple studies highlight the clinical utility of the VeriStrat test, however, the mechanistic connection between VeriStrat-poor classification and poor prognosis in untreated and previously treated patients is still an active area of research. The aim of this study was to correlate VeriStrat status with other circulating biomarkers in advanced NSCLC patients - each with respect to clinical outcomes.
METHODS: Serum samples were prospectively collected from 57 patients receiving salvage chemotherapy and 70 non-EGFR mutated patients receiving erlotinib. Patients were classified as either VeriStrat good or poor based on the VeriStrat test. Luminex immunoassays were used to measure circulating levels of 102 distinct biomarkers implicated in tumor aggressiveness and treatment resistance. A Cox PH model was used to evaluate associations between biomarker levels and clinical outcome,

whereas the association of VeriStrat classifications with biomarker levels was assessed via the Mann-Whitney Rank Sum test. **RESULTS:** VeriStrat was prognostic for outcome within the erlotinib treated patients (HR = 0.29, p < 0.0001) and predictive of differential treatment benefit between erlotinib and chemotherapy ((interaction HR = 0.25; interaction p = 0.0035). A total of 27 biomarkers out of 102 unique analytes were found to be significantly associated with OS (Cox PH p ≤ 0.05), whereas 16 biomarkers were found to be associated with PFS. Thrombospondin-2, C-reactive protein, TNF-receptor I, and placental growth factor were the analytes most highly associated with OS, all with Cox PH p-values ≤0.0001. VeriStrat status was found to be significantly associated with 23 circulating biomarkers (Mann-Whitney Rank Sum p ≤ 0.05), 6 of which had p < 0.001, including C-reactive protein, IL-6, serum amyloid A, CYFRA 21.1, IGF-II, osteopontin, and ferritin. **CONCLUSIONS:** Strong associations were observed between survival and VeriStrat classifications as well as select circulating biomarkers associated with fibrosis, inflammation, and acute phase reactants as part of this study. The associations between these biomarkers and VeriStrat classification might have therapeutic implications for poor prognosis NSCLC patients, particularly with new immunotherapeutic treatment options.

[Revisions to the TNM Staging of Lung Cancer: Rationale, Significance, and Clinical Application.](#)
Carter BW1, Lichtenberger JP 3rd1, Benveniste MK1, de Groot PM1, Wu CC1, Erasmus JJ1, Truong MT1. Radiographics. 2018 Mar-Apr;38(2):374-391. doi: 10.1148/rg.2018170081.
Lung cancer remains the leading cause of cancer-related mortality worldwide. To formulate effective treatment strategies and optimize patient outcomes, accurate staging is essential. Lung cancer staging has traditionally relied on a TNM staging system, for which the International Association for the Study of Lung Cancer (IASLC) has recently proposed changes. The revised classification for this eighth edition of the TNM staging system (TNM-8) is based on detailed analysis of a new large international database of lung cancer cases assembled by the IASLC for the purposes of this project. Fundamental changes incorporated into TNM-8 include (a) modifications to the T classification on the basis of 1-cm increments in tumor size; (b) grouping of lung cancers that result in partial or complete lung atelectasis or pneumonitis; (c) grouping of tumors with involvement of a main bronchus irrespective of distance from the carina; (d) reassignment of diaphragmatic invasion in terms of T classification; (e) elimination of mediastinal pleural invasion from the T classification; and (f) subdivision of the M classification into different descriptors on the basis of the number and site of extrathoracic metastases. In response to these revisions, established stage groups have been modified, and others have been created. In addition, recommendations for classifying patterns of disease that result in multiple sites of pulmonary involvement, including multiple primary lung cancers, lung cancers with separate tumor nodules, multiple ground-glass/lepidic lesions, and consolidation, as well as recommendations for lesion measurement, are addressed. Understanding the key revisions introduced in TNM-8 allows radiologists to accurately stage patients with lung cancer and optimize therapy. ©RSNA, 2018.

[Liquid Biopsy in Tumor Genetic Diagnosis.](#) Jung A1, Kirchner T. Dtsch Arztebl Int. 2018 Mar 9;115(10):169-174. doi: 10.3238/arztebl.2018.0169.
BACKGROUND: Liquid biopsy involves the analysis of cell-free nucleic acids, mainly circulating free DNA (cfDNA), in bodily fluids such as blood. The obtaining of specimens is easier for patients and less invasive than tissue biopsy, but the method has certain limitations. **METHODS:** This review is based on pertinent publications retrieved by a selective literature search. **RESULTS:** Because the concentration of cfDNA in plasma is less than 0.001%, special amplifying techniques must be used to enable a search for specific mutations. Liquid biopsy can be used in patients with non-small cell lung cancer (NSCLC) if no tissue is available for biopsy; when performed for this indication, it has 67% sensitivity and 94% specificity. If liquid biopsy does not reveal a mutation, this may be due either to the absence of the mutation in the tumor or to the inadequate sensitivity of the measuring technique. This uncertainty

associated with negative findings can be reduced by the simultaneous demonstration of reference mutations derived from a primary tumor tissue analysis. In comparison to tissue studies, the search for tumor-specific mutations by liquid biopsy is 70% sensitive and 69% specific; this corresponds to a positive predictive value of 86% and a negative predictive value of 46%. **CONCLUSION:** Liquid biopsy and tumor tissue analysis are complementary, rather than alternative, techniques for therapeutically relevant genetic investigation of tumors. Comparative studies are needed so that further indications can be determined for liquid biopsy in the diagnostic evaluation of cancer.

[**Detection of Subsolid Nodules in Lung Cancer Screening: Complementary Sensitivity of Visual Reading and Computer-Aided Diagnosis.**](#) Silva M, Schaefer-Prokop CM, Jacobs C, Capretti G, Ciompi F, van Ginneken B, Pastorino U, Sverzellati N. Invest Radiol. 2018 Mar 14. doi: 10.1097/RLI.0000000000000464. [Epub ahead of print]

OBJECTIVES: The aim of this study was to compare computer-aided diagnosis (CAD) and visual reading for the detection of subsolid nodules (SSNs) in volumetrl measuremic low-dose computed tomography (LDCT) for lung cancer screening. **MATERIALS AND METHODS:** Prospective visual detection (VD) and manuaent of SSN were performed in the 2303 baseline volumetric LDCTs of the Multicenter Italian Lung Detection trial. Baseline and 2- and 4-year LDCTs underwent retrospective CAD analysis, subsequently reviewed by 2 experienced thoracic radiologists. The reference standard was defined by the cumulative number of SSNs detected by any reading method between VD and CAD. The number of false-positive CAD marks per scan (FP/scan) was calculated. The positive predictive value of CAD was quantified per nodule (PPV) and per screenee (PPV). The sensitivity and negative predictive value were compared between CAD and VD. The longitudinal 3-time-point sensitivity of CAD was calculated in the subgroup of persistent SSNs seen by VD (ratio between the prevalent SSNs detected by CAD through 3 time points and the total number of persistent prevalent SSNs detected by VD) to test the sensitivity of iterated CAD analysis during a screening program. Semiautomatic characteristics (diameter, volume, and mass; both for whole nodule and solid component) were compared between SSN detected CAD-only or VD-only to investigate whether either reading method could suffer from specific sensitivity weakness related to SSN features. Semiautomatic and manual diameters were compared using Spearman ρ correlation and Bland-Altman plot. **RESULTS:** Computer-aided diagnosis and VD detected a total of 194 SSNs in 6.7% (155/2,303) of screenees at baseline LDCT. The CAD showed mean FP/scan of 0.26 (604/2,303); PPV 22.5% (175/779) for any SSN, with 54.4% (37/68) for PSN and 19.4% for NSN (138/711; P < 0.001); PPV 25.6% (137/536). The sensitivity of CAD was superior to that of VD (88.4% and 34.2%, P < 0.001), as well as negative predictive value (99.2% and 95.5%, P < 0.001). The longitudinal 3-time-point sensitivity of CAD was 87.5% (42/48). There was no influence of semiautomatic characteristics on the performance of either reading method. The diameter of the solid component in PSN was larger by CAD compared with manual measurement. At baseline, CAD detected 3 of 4 SSNs, which were first overlooked by VD and subsequently evolved to lung cancer. **CONCLUSIONS:** Computer-aided diagnosis and VD as concurrent reading methods showed complementary performance, with CAD having a higher sensitivity, especially for PSN, but requiring visual confirmation to reduce false-positive calls. Computer-aided diagnosis and VD should be jointly used for LDCT reading to reduce false-negatives of either lone method. The semiautomatic measurement of solid core showed systematic shift toward a larger diameter, potentially resulting in an up-shift within Lung CT Screening Reporting and Data System classification.

[Molecular Pathology of Lung Cancer Cytology Specimens: A Concise Review.](#) Jain D, Roy-Chowdhuri S1. Arch Pathol Lab Med. 2018 Mar 16. doi: 10.5858/arpa.2017-0444-RA. [Epub ahead of print]

There has been a paradigm shift in the understanding of molecular pathogenesis of lung cancer. A number of oncogenic drivers have been identified in non-small cell lung carcinoma, such as the epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) gene rearrangement. Because of the clinical presentation at an advanced stage of disease in non-small cell lung carcinoma patients, the use of minimally invasive techniques is preferred to obtain a tumor sample for diagnosis. These techniques include image-guided biopsies and fine-needle aspirations, and frequently the cytology specimen may be the only tissue sample available for the diagnosis and molecular testing for these patients. **OBJECTIVE:** To review the current literature and evaluate the role of cytology specimens in lung cancer mutation testing. We reviewed the types of specimens received in the laboratory, specimen processing, the effect of preanalytic factors on downstream molecular studies, and the commonly used molecular techniques for biomarker testing in lung cancer. **DATA SOURCES:** PubMed and Google search engines were used to review the published literature on the topic. **CONCLUSIONS:** Mutation testing is feasible on a variety of cytologic specimen types and preparations. However, a thorough understanding of the cytology workflow for the processing of samples and appropriate background knowledge of the molecular tests are necessary for triaging, and optimum use of these specimens is necessary to guide patient management.

[Translation of knowledge to practice - Improving awareness in NSCLC molecular testing.](#) Zer A1, Cutz JC2, Sekhon H3, et al. J Thorac Oncol. 2018 Mar 10. pii: S1556-0864(18)30187-4. doi: 10.1016/j.jtho.2018.03.005. [Epub ahead of print]

BACKGROUND: Molecular testing in advanced lung cancer is standard in guiding treatment selection. However, population-wide implementation of testing remains a challenge. We developed a knowledge translation intervention to improve understanding among diagnostic specialists about molecular testing and appropriate diagnostic sampling in lung cancer. **METHODS:** Specialty-specific education programs were developed from existing literature and input from Canadian leaders in lung pathology, respirology, interventional radiology, thoracic surgery, radiation and medical oncology. The programs, including key messages, review of current data, existing guidelines, group discussion and participant feedback, were administered at provincial and national specialty meetings. Participant knowledge was assessed before and after the intervention using anonymous questionnaires. Molecular testing rates (EGFR) in Ontario were also evaluated before and after the intervention period. **RESULTS:** Ten programs were administered to diagnostic specialists including respirologists, pathologists, thoracic surgeons, radiologists, radiation and medical oncologists, with completion of 255 pre- and 219 post-intervention surveys. At baseline, 30% were unsure of tissue handling methods for molecular testing, 20% chose an incorrect technique and half were unfamiliar with how to initiate testing. Post-intervention, specialist knowledge improved regarding tissue handling, appropriate fixation techniques, and uncertainty decreased from 30% to 2% (p<0.001). A 12% increase (relative 57%) in molecular testing requests (EGFR) in Ontario was observed over the intervention period (p=0.0032). **CONCLUSIONS:** Significant knowledge gaps exist among diagnostic specialists regarding molecular testing and targeted therapy in lung cancer. This initiative significantly improved understanding of the importance and methods of successful molecular testing, and correlated with increased testing rates.

Effectiveness of Implemented Interventions on Pathologic Nodal Staging of Non-Small Cell Lung Cancer. Ray MA1, Faris NR2, Smeltzer MP1, et al. Ann Thorac Surg. 2018 Mar 10. pii: S0003-4975(18)30333-3. doi: 10.1016/j.athoracsur.2018.02.021. [Epub ahead of print]
BACKGROUND: Accurate pathologic nodal staging improves early-stage non-small-cell lung cancer survival. In an ongoing implementation study, we measured the impact of a surgical lymph node specimen collection kit and a more thorough pathologic gross dissection method, on attainment of guideline-recommended pathologic nodal staging quality. **METHODS:** We prospectively collected data on curative-intent non-small cell lung cancer resections from 2009-2016 from 11 hospitals in 4 contiguous Dartmouth Hospital Referral Regions. We categorized patients into 4 groups based on exposure to the two interventions in our staggered implementation study design. We used Chi-squared tests to examine the differences in demographic and disease characteristics and surgical quality criteria across implementation groups. **RESULTS:** Of 2,469 patients, 1,615 (65%) received neither intervention; 167 (7%) received only the pathology intervention; 264 (11%) received only the surgery intervention; 423 (17%) had both. Rates of non-examination of lymph nodes reduced sequentially in the order of no intervention, novel dissection, kit, and combined interventions, including non-examination of: any lymph nodes, hilar/intrapulmonary and mediastinal nodes (p<0.001 for all comparisons). The rates of attainment of National Comprehensive Cancer Network, Commission on Cancer, American Joint Committee on Cancer, and American College of Surgeons Oncology Group guidelines increased significantly in the same sequential order (p<0.001 for all comparisons). **CONCLUSIONS:** The combined effect of two interventions to improve pathologic lymph node examination has a greater effect on attainment of a range of surgical quality criteria than either intervention alone.

Hybrid Capture-Based Comprehensive Genomic Profiling Identifies Lung Cancer Patients with Well-Characterized Sensitizing Epidermal Growth Factor Receptor Point Mutations That Were Not Detected by Standard of Care Testing. Suh JH1, Schrock AB2, Johnson A2, et al. Oncologist. 2018 Mar 14. pii: theoncologist.2017-0493. doi: 10.1634/theoncologist.2017-0493. [Epub ahead of print]
BACKGROUND: In our recent study, of cases positive for epidermal growth factor receptor (EGFR) exon 19 deletions using comprehensive genomic profiling (CGP), 17/77 (22%) patients with prior standard of care (SOC) EGFR testing results available were previously negative for exon 19 deletion. Our aim was to compare the detection rates of CGP versus SOC testing for well-characterized sensitizing EGFR point mutations (pm) in our 6,832-patient cohort. **MATERIALS AND METHODS:** DNA was extracted from 40 microns of formalin-fixed paraffin-embedded sections from 6,832 consecutive cases of non-small cell lung cancer (NSCLC) of various histologies (2012-2015). CGP was performed using a hybrid capture, adaptor ligation-based next-generation sequencing assay to a mean coverage depth of 576×. Genomic alterations (pm, small indels, copy number changes and rearrangements) involving EGFR were recorded for each case and compared with prior testing results if available. **RESULTS:** Overall, there were 482 instances of EGFR exon 21 L858R (359) and L861Q (20), exon 18 G719X (73) and exon 20 S768I (30) pm, of which 103 unique cases had prior EGFR testing results that were available for review. Of these 103 cases, CGP identified 22 patients (21%) with sensitizing EGFR pm that were not detected by SOC testing, including 9/75 (12%) patients with L858R, 4/7 (57%) patients with L861Q, 8/20 (40%) patients with G719X, and 4/7 (57%) patients with S768I pm (some patients had multiple EGFR pm). In cases with available clinical data, benefit from small molecule inhibitor therapy was observed. **CONCLUSION:** CGP, even when applied to low tumor purity clinical-grade specimens, can detect well-known EGFR pm in NSCLC patients that would otherwise not be detected by SOC testing. Taken together with EGFR exon 19 deletions, over 20% of patients who are positive for EGFR-activating mutations using CGP are previously negative by SOC EGFR mutation testing, suggesting that thousands of such patients per year in the U.S. alone could experience improved clinical outcomes when hybrid capture-based CGP is used to inform therapeutic decisions. **IMPLICATIONS FOR PRACTICE:** This

study points out that genomic profiling, as based on hybrid capture next-generation sequencing, can identify lung cancer patients with point mutation in epidermal growth factor receptor (EGFR) missed by standard molecular testing who can likely benefit from anti-EGFR targeted therapy. Beyond the specific findings regarding false-negative point mutation testing for EGFR, this study highlights the need for oncologists and pathologists to be cognizant of the performance characteristics of testing deployed and the importance of clinical intuition in questioning the results of laboratory testing.

Clinical Significance of Molecular Micrometastasis in the Sentinel Lymph Node of Early-stage Non-Small Cell Lung Cancer Patients. Lafuente-Sanchis A1, Estors-Guerrero M2, Zúñiga Á1, et al. Am J Clin Oncol. 2018 Mar 5. doi: 10.1097/COC.0000000000000432. [Epub ahead of print]
OBJECTIVES: Metastatic affectation of lymph node is the main prognostic factor in localized lung cancer. A pathologic study of the obtained samples, even after adequate lymphadenectomy, showed tumor relapses for 20% of stage I patients after oncological curative surgery. We evaluated the prognostic value of molecular micrometastasis in the sentinel lymph node of patients with early-stage lung cancer. **PATIENTS AND METHODS:** The sentinel node was marked immediately after performing thoracotomy by peritumorally injecting 0.25 mCi of nanocoloid of albumin (Nanocol1) labeled with Tc-99m in 0.3 mL. Guided by a Navigator1 gammagraphic sensor, we proceeded to its resection. The RNA of the tissue was extracted, and the presence of genes CEACAM5, BPIFA1, and CK7 in mRNA was studied. The significant association between the presence of micrometastasis, clinicopathologic characteristics, and patients' outcome was assessed. **RESULTS:** Eighty-nine stage I-II non-small cell lung cancer patients were included in the study. Of the 89 analyzed sentinel lymph nodes, 44 (49.4%) were positive for CK7, 24 (26.9%) for CEACAM5, and 17 (19.1%) for BPIFA1, whereas 10 (11.2%) were positive for the 3 analyzed genes. A survival analysis showed no significant relation between the presence of molecular micrometastasis in the sentinel node and patients' progression. **CONCLUSIONS:** The molecular analysis of the sentinel node in patients with early-stage lung cancer shows node affectation in cases staged as stage I/II by hematoxylin-eosin or an immunohistochemical analysis. However, this nodal affectation was not apparently related to patients' outcome.

Genomic Testing in Lung Cancer: Past, Present, and Future. Mascaux C1,1, Tsao MS1, Hirsch FR1. J Natl Compr Canc Netw. 2018 Mar;16(3):323-334. doi: 10.6004/jnccn.2017.7019.
Precision medicine commonly refers to the selection of the most effective cancer treatments based on the presence of specific biomarkers (eg, genomic abnormalities) in a patient's tumor. Therefore, genomic testing is used to identify patients whose tumors harbor the vulnerability that is sensitive to corresponding targeted therapies. This approach allows for the selection of patients who have the greatest chance of deriving benefit from the treatments, reduces toxicity, and significantly improves outcome; precision medicine is recommended for advanced non-small cell lung cancer. This article reviews the evolution of genomic testing in lung cancer, from its development, including first success and failures, to its current use in the care of patients with lung cancer, and addresses future considerations, such as the expected increase of targetable abnormalities, the need to follow the genomic profile over time, and tumor heterogeneity.

Programmed death ligand 1 testing in non-small cell lung carcinoma cytology cell block and aspirate smear preparations. Noll B1, Wang WL1, Gong Y1, Zhao J1, Kalhor N1, Prieto V1, Staerkel G1, Roy-Chowdhuri S1. Cancer Cytopathol. 2018 Mar 2. doi: 10.1002/cncy.21987. [Epub ahead of print]
BACKGROUND: Immune checkpoint inhibitors targeting the programmed cell death 1 (PD-1) receptor and its ligand, programmed death ligand 1 (PD-L1), have emerged as a therapeutic approach for patients with non-small cell lung carcinoma (NSCLC). PD-L1 expression, assessed by immunohistochemistry (IHC), is used to select patients for PD-1/PD-L1 inhibitor therapy. Most studies have been performed with

histology specimens, with limited data available on the performance in cytology specimens. This study evaluated PD-L1 in cytology specimens and compared the results with those from paired core-needle biopsy for concordance. **METHODS:** Forty-one NSCLC fine-needle aspiration cases that had paired core-needle biopsy specimens with PD-L1 IHC were selected. A Papanicolaou-stained direct smear and a cell block section from each case were stained with a Dako PD-L1 pharmDx antibody (clone 22C3). Only slides with 100 or more tumor cells (37 smears and 38 cell blocks) were evaluated. Tumor proportion scores (TPS) were assessed on the basis of the partial/complete membranous staining of tumor cells and were correlated with those of paired core-needle biopsy. **RESULTS:** All 9 smears that were negative for PD-L1 staining showed 100% concordance with the paired core-needle biopsy, whereas 28 smears with PD-L1 expression showed a similar TPS, except for 1 smear that was discordant. In contrast, 10 negative paired core-needle biopsy cases corresponded to 9 concordant negative cell blocks, whereas 1 cell block had a TPS of 1% to 5%. The remaining 28 cell blocks demonstrated PD-L1 expression, with 22 cases showing a TPS similar to that of the paired core-needle biopsy, whereas 6 cell blocks were discordant, likely because of intratumoral heterogeneity. **CONCLUSIONS:** The results show that NSCLC cytology samples evaluated for PD-L1 have high concordance with paired core-needle biopsy samples and can be used for assessing PD-L1 expression. Cancer Cytopathol 2018. © 2018 American Cancer Society.

[Improved EGFR mutation detection using combined exosomal RNA and circulating tumor DNA in NSCLC patient plasma.](#) Krug AK1, Enderle D1, Karlovich C2, et al. Ann Oncol. 2018 Mar 1;29(3):700-706. doi: 10.1093/annonc/mdx765.

BACKGROUND: A major limitation of circulating tumor DNA (ctDNA) for somatic mutation detection has been the low level of ctDNA found in a subset of cancer patients. We investigated whether using a combined isolation of exosomal RNA (exoRNA) and cell-free DNA (cfDNA) could improve blood-based liquid biopsy for EGFR mutation detection in non-small-cell lung cancer (NSCLC) patients.

PATIENTS AND METHODS: Matched pretreatment tumor and plasma were collected from 84 patients enrolled in TIGER-X (NCT01526928), a phase 1/2 study of rociletinib in mutant EGFR NSCLC patients. The combined isolated exoRNA and cfDNA (exoNA) was analyzed blinded for mutations using a targeted next-generation sequencing panel (EXO1000) and compared with existing data from the same samples using analysis of ctDNA by BEAMing. **RESULTS:** For exoNA, the sensitivity was 98% for detection of activating EGFR mutations and 90% for EGFR T790M. The corresponding sensitivities for ctDNA by BEAMing were 82% for activating mutations and 84% for T790M. In a subgroup of patients with intrathoracic metastatic disease (M0/M1a; n = 21), the sensitivity increased from 26% to 74% for activating mutations (P = 0.003) and from 19% to 31% for T790M (P = 0.5) when using exoNA for detection. **CONCLUSIONS:** Combining exoRNA and ctDNA increased the sensitivity for EGFR mutation detection in plasma, with the largest improvement seen in the subgroup of M0/M1a disease patients known to have low levels of ctDNA and poses challenges for mutation detection on ctDNA alone.

[Usefulness of Bronchoscopic Rebiopsy of Non-Small Cell Lung Cancer with Acquired Resistance to Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor.](#) Goag EK1, Lee JM1, Chung KS1, et al. J Cancer. 2018 Mar 2;9(6):1113-1120. doi: 10.7150/jca.21650. eCollection 2018.

BACKGROUND: Approximately 50% of non-small cell lung cancer (NSCLC) patients with acquired resistance to EGFR-TKI harbor the EGFR mutation T790M. The recent development and wide use of third-generation EGFR-TKIs targeting T790M-mutant NSCLCs have increased the importance of rebiopsy after EGFR-TKI failure. We aimed to investigate the advantages of flexible bronchoscopy as a rebiopsy method and the prevalence of and factors affecting the T790M mutation after EGFR-TKI failure. **METHODS:** We investigated 139 patients who had undergone bronchoscopic rebiopsy and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) between Sep 2014 and

Jul 2016. **RESULTS:** Among the 139 patients, bronchoscopic rebiopsy yielded successful pathological diagnoses in 102 (73.4%). Among them, 41 patients with EGFR-mutant lung adenocarcinoma and EGFR-TKI progression were selected for an investigation of T790M mutation prevalence at rebiopsy. The initial EGFR mutations were exon 19 del (56.1%), L858R or L861Q (34.1%), and others (9.8%). The most common rebiopsy method was transbronchial lung biopsy (41.5%), followed by EBUS-TBNA (26.8%) and endobronchial biopsy (19.5%). The median interval to T790M emergence was the longest among cases with exon 19 deletion (14.1 months), followed by exon 21 L858R or L861Q (11.3 months) and other rare EGFR mutations (2.9 months). The T790M mutation was identified in 18 (43.9%) patients, and exon 19 del was the most significant factor affecting T790M mutation development (hazard ratio: 6.875, P = 0.014). **CONCLUSIONS:** Bronchoscopy was more useful than other rebiopsy approaches. The T790M emergence rate was highest in cases with exon 19 deletion, likely as a consequence of long-term EGFR-TKI exposure.

Lung Cancer Screening in the Community Setting. Cattaneo SM 2nd1, Meisenberg BR2, Geronimo MCM3, Bhandari B3, Maxted JW3, Brady-Copertino CJ2. Ann Thorac Surg. 2018 Mar 1. pii: S0003-4975(18)30262-5. doi: 10.1016/j.athoracsur.2018.01.075. [Epub ahead of print]
BACKGROUND: Lung cancer has high incidence and high mortality burden particularly since it is typically diagnosed in later stages. The National Lung Screening Trial demonstrated a lung cancer specific mortality benefit in high risk current and former smokers with yearly low dose chest CT. Lung cancer screening is thus recommended but it is unclear if the results of the National Lung Screening Trial can be replicated in community settings. **METHODS:** A retrospective review was performed of the lung screening program over its first five years, 2012-2016. Patient demographics, initial screening results, follow up, and management results were analyzed in relation to the National Lung Screening Trial results. Annual adherence was defined as returning for imaging within one year + 90 days. **RESULTS:** 1241 persons underwent initial screening over the 5-year period. 78.6% of findings were benign and only annual repeat low dose chest CT was recommended. 29 cancers were identified in 26 participants (2%) of which 72% were stage I. Annual adherence rate to repeat imaging after low risk baseline scan was 37% and any follow up rate was 51% despite programmatic efforts to follow screening recommendations. When positive findings required more intensive evaluation, most commonly by repeat chest CT scan, adherence was 88%. 1.1% of all participants had invasive biopsies for benign results. Complications of biopsy were minimal. **CONCLUSIONS:** Our review demonstrates that a community-based program can approximate the results of the National Lung Screening Trial in detecting early lung cancers. Further study of the adherence phenomenon is essential.

Early Results From the Implementation of a Lung Cancer Screening Program: The Beaumont Health System Experience. Lanni TB Jr1, Stevens C2, Farah M3, Boyer A3, Davis J3, Welsh R4, Keena D5, Akhtar A6, Mezwa D3. Am J Clin Oncol. 2018 Mar;41(3):218-222. doi: 10.1097/COC.0000000000000254.
PURPOSE: In 2010, a new study published by the National Lung Screening Trial showed a 20% reduction in mortality for those patients screened with low-dose computed topography (CT) versus x-ray. Recently, the Centers of Medicare and Medicaid have agreed to cover this service for those patients who meet the screening criteria. We compare the outcomes and costs associated with developing and implementing a lung cancer screening program. **MATERIALS AND METHODS:** One thousand sixty-five patients were screened from January 2014 to December 2014. These patients were screened on a low-dose CT screening protocol throughout Beaumont Health System. The American College of Radiology Lung Imaging Reporting and Data System (Lung-RADS) were used to assign the score for each patient. Screening eligibility criteria were based on the National Comprehensive Cancer Network guidelines. Downstream activity and revenue was determined after initial low-dose CT screening. **RESULTS:** At 1

year, 20 patients (1.6%) were diagnosed with lung cancer and another 15 patients were diagnosed with another form of cancer after screening. The median age, packs per day, and pack years smoked for all patients was 63, 1.0, and 39.0 years, respectively. Lung-RADS scores for all patients was 18% (1), 24.1% (2), 6.3% (3), and 5.4% (4). The net revenue for all activity after screening was $3.2 million.
CONCLUSIONS: The establishment of a low-dose CT lung cancer screening program improved the ability to screen patients as demonstrated by the number of patients screened and those diagnosed with a malignancy. These findings were also consistent with the findings from the National Lung Screening Trial study.

[Analytical validation of a next generation sequencing liquid biopsy assay for high sensitivity broad molecular profiling.](#) Plagnol V1, Woodhouse S1, Howarth K1, et al. PLoS One. 2018 Mar 15;13(3):e0193802. doi: 10.1371/journal.pone.0193802. eCollection 2018.
Circulating tumor DNA (ctDNA) analysis is being incorporated into cancer care; notably in profiling patients to guide treatment decisions. Responses to targeted therapies have been observed in patients with actionable mutations detected in plasma DNA at variant allele fractions (VAFs) below 0.5%. Highly sensitive methods are therefore required for optimal clinical use. To enable objective assessment of assay performance, detailed analytical validation is required. We developed the InVisionFirst™ assay, an assay based on enhanced tagged amplicon sequencing (eTAm-Seq™) technology to profile 36 genes commonly mutated in non-small cell lung cancer (NSCLC) and other cancer types for actionable genomic alterations in cell-free DNA. The assay has been developed to detect point mutations, indels, amplifications and gene fusions that commonly occur in NSCLC. For analytical validation, two 10mL blood tubes were collected from NSCLC patients and healthy volunteer donors. In addition, contrived samples were used to represent a wide spectrum of genetic aberrations and VAFs. Samples were analyzed by multiple operators, at different times and using different reagent Lots. Results were compared with digital PCR (dPCR). The InVisionFirst assay demonstrated an excellent limit of detection, with 99.48% sensitivity for SNVs present at VAF range 0.25%-0.33%, 92.46% sensitivity for indels at 0.25% VAF and a high rate of detection at lower frequencies while retaining high specificity (99.9997% per base). The assay also detected ALK and ROS1 gene fusions, and DNA amplifications in ERBB2, FGFR1, MET and EGFR with high sensitivity and specificity. Comparison between the InVisionFirst assay and dPCR in a series of cancer patients showed high concordance. This analytical validation demonstrated that the InVisionFirst assay is highly sensitive, specific and robust, and meets analytical requirements for clinical applications.

[Comparison of the SuperARMS and Droplet Digital PCR for Detecting EGFR Mutation in ctDNA From NSCLC Patients.](#) Feng WN1, Gu WQ2, Zhao N2, Pan YM3, Luo W3, Zhang H1, Liang JM1, Yang J2, Deng YM4. Transl Oncol. 2018 Apr;11(2):542-545. doi: 10.1016/j.tranon.2018.02.007. Epub 2018 Mar 8.
BACKGROUND: Liquid biopsy is emerging as an important approach for tumor genotyping in non-small cell lung cancer, ddPCR and SuperARMS are both methods with high sensitivity and specificity for detecting EGFR mutation in plasma. We aimed to compare ddPCR and SuperARMS to detect plasma EGFR status in a cohort of advanced NSCLC patients. **METHOD:** A total of 79 tumor tissues and paired plasma samples were collected. The EGFR mutation status in tissue was tested by ADx-ARMS, matched plasma was detected by ddPCR and SuperARMS, respectively. **RESULTS:** The EGFR mutation rates were identified as 64.6% (tissue, ARMS), 55.7% (plasma, ddPCR), and 49.4% (plasma, Super ARMS), respectively. The sensitivity of ddPCR was similar with Super-ARMS in plasma EGFR detection (80.4% vs 76.5%), as well as the specificity (89.3% vs 100%). And the McNemar's test showed there was no significant difference (P = .125). The concordance rate between SuperARMS and ddPCR was 91.1%. A significant interaction was observed between cfDNA EGFR mutation status and EGFR-TKIs treatment tested by both methods. **CONCLUSION:** Super-ARMS and ddPCR share the similar accuracy for EGFR

mutation detection in plasma biopsy; both methods predicted well the efficacy of EGFR-TKIs by detecting plasma EGFR status.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[Differences in postoperative changes in pulmonary functions following segmentectomy compared with lobectomy.] Nomori H1, Shiraishi A2, Cong Y1, Sugimura H1, Mishima S1. Eur J Cardiothorac Surg. 2018 Mar 1;53(3):640-647. doi: 10.1093/ejcts/ezx357.
OBJECTIVES: To clarify differences in postoperative changes in systemic and regional pulmonary functions between segmentectomy and lobectomy in patients with lung cancer, we compared the 2 procedures using lung perfusion scintigraphy with a fusion image of single-photon emission computed tomography and computed tomography. **METHODS:** This study is a retrospective matched cohort study of consecutively acquired data. Pulmonary function tests and perfusion single-photon emission computed tomography/computed tomography were conducted before surgery and 6 months after surgery to measure changes in forced expiratory volume in 1 s of a whole lung, contralateral lung and a lobe. After exactly matching the site of the resected lobe between the 2 procedures, propensity scores for age, sex, smoking status and pulmonary function were used to match them. **RESULTS:** Of the 184 patients treated with segmentectomy and the 208 patients treated with lobectomy between 2013 and 2016, 103 patients were selected from each group after the matching. Whole lung function was significantly more preserved after segmentectomy than after lobectomy (P < 0.001). Segmentectomy preserved the function of the operated lobe with $48 \pm 21\%$ of the preoperative function. The function of the ipsilateral non-operated lobe increased after segmentectomy (P = 0.003) but not after lobectomy (P = 0.97). Contralateral lung function increased after both procedures (P < 0.001). **CONCLUSIONS:** Our data suggest that segmentectomy preserved whole lung function better than lobectomy, because it not only preserved the lobe but also increased the function of the ipsilateral non-operated lobe. Lobectomy did not result in an increase of ipsilateral non-operated lobe function. Contralateral lung function increased after both procedures. The postoperative increase in regional functions could be the result of compensatory lung growth.

[Long-Term Results for Clinical Stage IA Lung Cancer- Comparing Lobectomy and Sublobar Resection.] Subramanian M1, McMurry T2, Meyers BF1, Puri V1, Kozower BD3. Ann Thorac Surg. 2018 Mar 23. pii: S0003-4975(18)30387-4. doi: 10.1016/j.athoracsur.2018.02.049. [Epub ahead of print]
BACKGROUND: Lobectomy has been compared with sublobar resection for the treatment of stage IA non-small cell lung cancer (NSCLC). Accurate long-term data are lacking on the risk of recurrence in routine clinical practice. This study utilizes a unique and representative dataset to compare recurrence, overall survival (OS) and lymph node staging between lobectomy and sublobar resection. **METHODS:** The American College of Surgeons performed a Special Study of the National Cancer Data Base, reabstracting records to augment NSCLC data with enhanced information on preoperative comorbidity and cancer recurrence (2007-2012). For patients treated with lobectomy or sublobar resection (wedge/segmentectomy) for clinical stage IA NSCLC, propensity matching and competing risks models compared 5-year OS and risk of cancer recurrence. Secondary measures included lymph nodes collected, pathologic upstaging, and surgical margin status. **RESULTS:** 1687 stage IA patients were identified (1354 lobectomy and 333 sublobar resections). Propensity matching yielded 325 pairs. Lobectomy and sublobar resection groups had similar 5-year OS (61.8% vs. 55.6%, p=0.561). The sublobar group had a 39% increased risk of NSCLC recurrence (HR = 1.39, 95% CI 1.04-1.87). Median lymph node counts were higher for lobectomy patients [7 (3,10) vs. 1 (0,4) (P<0.001)]. **CONCLUSIONS:** In an enhanced

national dataset representative of outcomes for stage IA NSCLC, sublobar resection was associated with a 39% increased risk of cancer recurrence. The majority of patients treated with sublobar resection had an inadequate lymph node assessment. These real world results must be considered when existing clinical trial results comparing these treatments are extrapolated for clinical use.

[Should surgery be part of the multimodality treatment for stage IIIB non-small cell lung cancer?](#)
Collaud S1, Provost B1, Besse B2, Fabre D1, Le Chevalier T1,2, Mercier O1, Mussot S1, Fadel E1. J Surg Oncol. 2018 Mar 24. doi: 10.1002/jso.25042. [Epub ahead of print]

BACKGROUND: Traditionally, treatment for stage IIIB (T4N2M0 and T1-4N3M0) NSCLC consists in definitive chemoradiation. Surgery is used only anecdotally. Here, we studied outcome for patients treated with multimodality including surgery. **METHODS:** Patients who underwent surgery for stage IIIB between 2000 and 2015 were retrospectively reviewed and data analyzed. Patients were selected for surgery if they would tolerate multimodality treatment, the tumor was deemed upfront resectable, and N2-N3 involvement was limited to a non-bulky single site. Survival was calculated from the date of surgery until last follow-up. Univariate and multivariate analysis were performed to identify prognostic factors. **RESULTS:** During the study period, 5416 patients underwent resection for NSCLC in our center. Sixty patients (1%) had clinical stage IIIB. Thirty-two patients had T4N2 NSCLC involving the carina and/or superior vena cava (n = 25, 78%), left atrium (n = 5, 16%), or other (n = 2, 6%). Half of the 28 patients with N3-disease had supraclavicular node involvement. Pneumonectomy was performed in 27 patients (45%). Twenty-nine patients (48%) had induction therapy, with chemotherapy alone. Adjuvant therapy was administered to 52 patients (87%), mostly chemoradiation. Complete resection rate was 92%. Post-operative mortality was 3%. Three- and 5-year overall survivals were 51% and 39%, respectively. Multivariate analysis identified incomplete resection (P = 0.008) and absence of adjuvant treatment (P = 0.032) as poor survival prognostic factors. **CONCLUSIONS:** Surgery can be considered as a component of multimodality therapy in highly selected patients with stage IIIB NSCLC based on encouraging 5-year survival of 39%.

[Favourable outcomes in patients with early-stage non-small-cell lung cancer operated on by video-assisted thoracoscopic surgery: a propensity score-matched analysis.](#)
Dziedzic R1, Marjanski T1, Binczyk F2, Polanska J2, Sawicka W3, Rzyman W1. Eur J Cardiothorac Surg. 2018 Mar 14. doi: 10.1093/ejcts/ezy101. [Epub ahead of print]

OBJECTIVES: The video-assisted thoracoscopic surgery (VATS) approach has become a standard for the treatment of early-stage non-small-cell lung cancer (NSCLC). Recently published meta-analyses proved the benefit of VATS versus thoracotomy for overall survival (OS) and reduction of postoperative complications. The aim of this study was to compare early outcomes, long-term survival and rate of postoperative complications of the VATS approach versus thoracotomy. **METHODS:** In this retrospective cohort study, we analysed 982 individuals who underwent surgical resection for Stage I-IIA NSCLC between 2007 and 2015. Thirty- and 90-day mortality rates, length of hospital stay, rate of complications and OS were assessed. Propensity score matching was performed to compare 2 groups of patients. Two hundred and twenty-five individuals from the thoracotomy group and 225 patients from the VATS group were matched regarding pTNM, sex, the Charlson comorbidity index, type of resection and histological diagnosis. **RESULTS:** In the propensity score-matched patient group, the VATS approach was associated with a significant benefit regarding OS (P = 0.042). Although no significant difference was observed (P = 0.14) in the 3-year survival rate of patients who had a thoracotomy versus VATS, the 5-year survival rate among patients with VATS increased significantly (61% vs 78%, P = 0.0081). The adjusted VATS-related hazard ratio for pTNM, sex and age was 0.63 (95% confidence interval 0.40-0.98). The VATS surgical approach also reduced both the rate of postoperative atelectasis (4% for VATS vs 10% for open thoracotomy; P = 0.0052) and the need for blood transfusions (4% vs 12% respectively,

P = 0.0054) and significantly shortened the postoperative length of stay (mean 7.25 vs 9.34 days, P < 0.0001). No significant differences in the 30-day mortality (1% vs 1%, P = 0.66) and 90-day mortality (1% vs 1%, P = 0.48) rates were observed. **CONCLUSIONS:** Patients with early-stage NSCLC operated on with VATS had fewer complications, shorter postoperative length of stay and better OS compared to those who were operated on by thoracotomy.

[Robotic Versus Video-Assisted Thoracoscopic Lung Resection During Early Program Development.](url) Kaur MN1, Xie F2, Shiwcharan A3, Patterson L4, Shargall Y5, Finley C5, Schieman C6, Dalimonte T7, Fahim C8, Hanna WC9. Ann Thorac Surg. 2018 Apr;105(4):1050-1057. doi: 10.1016/j.athoracsur.2017.11.013. Epub 2018 Mar 2.
BACKGROUND: The objective of this study is to compare robotic portal (RP) to video-assisted thoracoscopic surgery (VATS) pulmonary resections for early stage non-small cell lung cancer with respect to health care resource utilization during the first year of a robotic surgery program in thoracic oncology. **METHODS:** Patients who underwent anatomic lung resections using RP (n = 42) or VATS (n = 96) for early stage non-small cell lung cancer between April 2014 and March 2015 at a single institution were identified. Patient-level case costing data for hospital and home care-associated resource variables were recorded. We adopted a health care payer perspective and 30-day posthospital discharge/death time horizon. Parametric or nonparametric tests were used as appropriate and incremental cost difference using 10,000 bootstrap samples using bias-corrected and accelerated method to generate 95% confidence intervals for total cost. **RESULTS:** Baseline demographic and clinical characteristics were comparable between the two groups. The median total hospital cost per patient was $15,247 (95% confidence interval: $15,643 to $18,945) in the RP cohort, compared with $12,131 (95% confidence interval: $13,218 to $15,879) in the VATS cohort (n = 96; p < 0.001). Longer operating times in the RP group were the main driver of higher hospital costs. Post-hoc analysis of mean operating room time for first 20 RP procedures versus remaining 22 RP procedures found a mean difference of 71 minutes (p = 0.004), resulting in an intraoperative cost difference of $883.38 (p = 0.036). **CONCLUSIONS:** A micro-costing analysis demonstrates that RP pulmonary resection for early stage non-small cell lung cancer utilizes more health care resource dollars when compared with VATS during early program development, but offers similar perioperative outcomes.

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

[Detection of EGFR, KRAS and BRAF mutations in metastatic cells from cerebrospinal fluid.](url)
Frankel D1, Nanni-Metellus I2, Robaglia-Schlupp A1, et al. Clin Chem Lab Med. 2018 Jan 8. pii: /j/cclm.ahead-of-print/cclm-2017-0527/cclm-2017-0527.xml. doi: 10.1515/cclm-2017-0527. [Epub ahead of print]
BACKGROUND: In lung adenocarcinoma, molecular profiling of actionable genes has become essential to set up targeted therapies. However, the feasibility and the relevance of molecular profiling from the cerebrospinal fluid (CSF) in the context of meningeal metastasis have been poorly assessed. **METHODS:** We selected patients with stage IV lung adenocarcinoma harbouring metastatic cells in the CSF after cytological analysis. Seven samples from six patients were eligible for molecular testing of epidermal growth factor receptor (EGFR), V-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue (KRAS), v-Raf murine sarcoma viral oncogene homologue B1 (BRAF) and human epidermal growth factor receptor 2 (HER2) mutations using quantitative polymerase chain reaction (PCR) high-resolution melting curve analysis and Sanger sequencing after DNA extraction from the cell pellets of the CSF. **RESULTS:** Five patients showed mutations in one or two actionable genes, two harboured an EGFR mutation (exons 19 and 21), one only a KRAS mutation, one both EGFR and KRAS mutations and one a BRAF mutation. In all cases, the results of mutation testing provided new major information for patient management, leading

to therapeutic adaptation. CSF molecular analysis identified mutations not detected in other neoplastic sites for two patients. In one case, the EGFR p.Thr790Met was identified. CSF was also the only sample available for genetic testing for almost all patients at the time of disease progression. **CONCLUSIONS:** When cancer cells are present in the CSF, the molecular profiling from the cell pellets is relevant, as it can detect supplemental or different mutations compared to a previous analysis of the primitive tumour or plasma cell-free DNA and allows the adaptation of the treatment strategy.

[Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study.](#) Garassino MC1, Cho BC2, Kim JH3, et al. Lancet Oncol. 2018 Apr;19(4):521-536. doi: 10.1016/S1470-2045(18)30144-X. Epub 2018 Mar 12. **BACKGROUND:** Immune checkpoint inhibitors are a new standard of care for patients with advanced non-small-cell lung cancer (NSCLC) without EGFR tyrosine kinase or anaplastic lymphoma kinase (ALK) genetic aberrations (EGFR-/ALK-), but clinical benefit in patients with EGFR mutations or ALK rearrangements (EGFR+/ALK+) has not been shown. We assessed the effect of durvalumab (anti-PD-L1) treatment in three cohorts of patients with NSCLC defined by EGFR/ALK status and tumour expression of PD-L1. **METHODS:** ATLANTIC is a phase 2, open-label, single-arm trial at 139 study centres in Asia, Europe, and North America. Eligible patients had advanced NSCLC with disease progression following at least two previous systemic regimens, including platinum-based chemotherapy (and tyrosine kinase inhibitor therapy if indicated); were aged 18 years or older; had a WHO performance status score of 0 or 1; and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Key exclusion criteria included mixed small-cell lung cancer and NSCLC histology; previous exposure to any anti-PD-1 or anti-PD-L1 antibody; and any previous grade 3 or worse immune-related adverse event while receiving any immunotherapy agent. Patients in cohort 1 had EGFR+/ALK+ NSCLC with at least 25%, or less than 25%, of tumour cells with PD-L1 expression. Patients in cohorts 2 and 3 had EGFR-/ALK- NSCLC; cohort 2 included patients with at least 25%, or less than 25%, of tumour cells with PD-L1 expression, and cohort 3 included patients with at least 90% of tumour cells with PD-L1 expression. Patients received durvalumab (10 mg/kg) every 2 weeks, via intravenous infusion, for up to 12 months. Retreatment was allowed for patients who benefited but then progressed after completing 12 months. The primary endpoint was the proportion of patients with increased tumour expression of PD-L1 (defined as ≥25% of tumour cells in cohorts 1 and 2, and ≥90% of tumour cells in cohort 3) who achieved an objective response, assessed in patients who were evaluable for response per independent central review according to RECIST version 1.1. Safety was assessed in all patients who received at least one dose of durvalumab and for whom any post-dose data were available. The trial is ongoing, but is no longer open to accrual, and is registered with ClinicalTrials.gov, number NCT02087423. **FINDINGS:** Between Feb 25, 2014, and Dec 28, 2015, 444 patients were enrolled and received durvalumab: 111 in cohort 1, 265 in cohort 2, and 68 in cohort 3. Among patients with at least 25% of tumour cells expressing PD-L1 who were evaluable for objective response per independent central review, an objective response was achieved in 9 (12·2%, 95% CI 5·7-21·8) of 74 patients in cohort 1 and 24 (16·4%, 10·8-23·5) of 146 patients in cohort 2. In cohort 3, 21 (30·9%, 20·2-43·3) of 68 patients achieved an objective response. Grade 3 or 4 treatment-related adverse events occurred in 40 (9%) of 444 patients overall: six (5%) of 111 patients in cohort 1, 22 (8%) of 265 in cohort 2, and 12 (18%) of 68 in cohort 3. The most common treatment-related grade 3 or 4 adverse events were pneumonitis (four patients [1%]), elevated gamma-glutamyltransferase (four [1%]), diarrhoea (three [1%]), infusion-related reaction (three [1%]), elevated aspartate aminotransferase (two [<1%]), elevated transaminases (two [<1%]), vomiting (two [<1%]), and fatigue (two [<1%]). Treatment-related serious adverse events occurred in 27 (6%) of 444 patients overall: five (5%) of 111 patients in cohort 1, 14 (5%) of 265 in cohort 2, and eight (12%) of 68 in cohort 3. The most common serious adverse events overall were pneumonitis (five patients [1%]), fatigue (three [1%]), and infusion-related reaction (three [1%]). Immune-mediated events were manageable with

standard treatment guidelines. **INTERPRETATION:** In patients with advanced and heavily pretreated NSCLC, the clinical activity and safety profile of durvalumab was consistent with that of other anti-PD-1 and anti-PD-L1 agents. Responses were recorded in all cohorts; the proportion of patients with EGFR-/ALK- NSCLC (cohorts 2 and 3) achieving a response was higher than the proportion with EGFR+/ALK+ NSCLC (cohort 1) achieving a response. The clinical activity of durvalumab in patients with EGFR+ NSCLC with ≥25% of tumour cells expressing PD-L1 was encouraging, and further investigation of durvalumab in patients with EGFR+/ALK+ NSCLC is warranted. **FUNDING:** AstraZeneca.

[Five-Year Follow-Up of Nivolumab in Previously Treated Advanced Non-Small-Cell Lung Cancer: Results From the CA209-003 Study.](#) Gettinger S1, Horn L1, Jackman D1, et al. J Clin Oncol. 2018 Mar 23:JCO2017770412. doi: 10.1200/JCO.2017.77.0412. [Epub ahead of print]

PURPOSE: In two phase III studies, nivolumab, a programmed death-1 (PD-1) inhibitor antibody, improved overall survival (OS) versus docetaxel in pretreated advanced non-small-cell lung cancer (NSCLC). We report 5-year follow-up results from an early phase I study of nivolumab in this patient population and describe characteristics of 5-year survivors. Patients and **METHODS:** Patients with pretreated, advanced NSCLC received nivolumab 1, 3, or 10 mg/kg every 2 weeks in 8-week cycles for up to 96 weeks. OS from the time of first dose was estimated by the Kaplan-Meier method. **RESULTS:** The estimated 5-year OS rate was 16% for all treated patients (N = 129); 5-year OS rates were similar for squamous (16%) and nonsquamous (15%) NSCLC. Of 16 5-year survivors, most (88%) were known current or former smokers. Of 10 5-year survivors with quantifiable PD-1 ligand 1 expression, 70% had ≥ 1% PD-1 ligand 1 expression at baseline. Twelve 5-year survivors (75%) achieved a partial response to nivolumab per Response Evaluation Criteria in Solid Tumors, version 1.0, and two each (12%) had stable disease and progressive disease as best response. Nine 5-year survivors (56%) completed the maximum 96 weeks of nivolumab; four (25%) discontinued owing to adverse events and three (19%) owing to disease progression. As of a November 2016 database lock, 12 5-year survivors (75%) received no subsequent therapy and were without evidence of progressive disease at last follow-up. **CONCLUSIONS:** Nivolumab treatment resulted in long-term OS and durable responses in a proportion of patients with pretreated advanced NSCLC. Long-term survivors had diverse baseline and on-treatment characteristics.

[Long-term safety and survival with gefitinib in select patients with advanced non-small cell lung cancer: Results from the US IRESSA Clinical Access Program (ICAP).](#)
Hirsch FR1, Sequist LV2, Gore I3, et al. Cancer. 2018 Mar 26. doi: 10.1002/cncr.31313. [Epub ahead of print]

BACKGROUND: This is the first report of long-term (>10 years) safety, tolerability, and survival data on patients with non-small cell lung cancer (NSCLC) who received treatment with gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. **METHODS:** Patients with advanced NSCLC (N = 191) who entered the IRESSA Clinical Access Program (ICAP) (June 2011 to January 2013) and had previously obtained a clinical benefit from gefitinib therapy (including patients who had received gefitinib since 2001) were analyzed for adverse events (AEs). A subset of patients (n = 79) underwent retrospective chart review to capture demographic, safety, and survival data. **RESULTS:** Seventy-five of 191 patients (39%) remained on long-term gefitinib therapy as of September 2016. Overall, serious AEs (SAEs) were reported in 64 patients (34%), the majority of which were attributed to underlying disease or comorbidities; only 3 patients (1.6%) had SAEs that were considered as possibly gefitinib-related. In the retrospective chart review cohort, 70% of patients were women; 58% were former smokers, and 30% were never-smokers; 56% were diagnosed with adenocarcinoma, and 13% were diagnosed with squamous carcinoma. Although EGFR mutational status was tested in only 17 patients (22%), it was assumed that most tumors were EGFR-mutation-positive. The median duration of gefitinib therapy was 11.1 years (7.8

years before and 3.5 years during ICAP), with 10-year and 15-year survival rates of 86% and 59%, respectively, from the initiation of therapy. **CONCLUSIONS:** A subset of long-term NSCLC survivors who were receiving gefitinib had an excellent long-term safety profile. Although it is assumed that most of these patients' tumors harbor EGFR mutations, molecular studies of available tumor specimens are planned to uncover the features that predict long-term survival. Cancer 2018. © 2018 American Cancer Society.

[**The use of alectinib in the first-line treatment of anaplastic lymphoma kinase-positive non-small-cell lung cancer.**](#) Gadgeel SM1. Future Oncol. 2018 Mar 14. doi: 10.2217/fon-2018-0027. [Epub ahead of print]
Anaplastic lymphoma kinase (ALK) gene rearrangements as driver genetic alterations occur in approximately 2-4% of non-small-cell lung cancer (NSCLC) patients. Alectinib, a next generation ALK inhibitor, recently demonstrated, in two separate Phase III trials, superior efficacy to crizotinib, the first ALK inhibitor to demonstrate clinical efficacy in ALK-positive NSCLC patients. Alectinib also demonstrated superior efficacy in the CNS. The data from these two Phase III studies suggest that the efficacy of starting with alectinib is superior to the overall clinical efficacy of starting with crizotinib followed by switching to alectinib at the time of disease progression. These results have changed the standard of care to alectinib as front-line therapy for advanced ALK-positive NSCLC patients. Areas covered: this paper reviews the available data on alectinib as front-line therapy in patients with ALK-positive NSCLC patients including its activity against brain metastases. In addition, the paper will review the data with other ALK inhibitors as front-line therapy.

[**Nivolumab in routine practice for older patients with advanced or metastatic non-small cell lung cancer.**](#) Sabatier R1, Nicolas E2, Paciencia M3, et al. J Geriatr Oncol. 2018 Mar 9. pii: S1879-4068(18)30090-0. doi: 10.1016/j.jgo.2018.02.011. [Epub ahead of print]
BACKGROUND: Nivolumab is approved worldwide as second-line treatment for metastatic non-small cell lung cancer (NSCLC). Despite the fact that most of these cancers are being diagnosed in the older patients, few of the patients were included in pivotal trials. We aimed to describe efficacy and safety in a "real-world" older population. **PATIENTS AND METHODS:** We retrospectively collected data from older patients (≥70 years old) with advanced or metastatic NSCLC treated with Nivolumab in our institution. We analyzed safety (CTCAE v4.0 criteria), efficacy (clinical benefit rate, progression-free survival, and overall survival), and correlated these features to geriatric parameters and PD-L1 expression. Along with this cohort, we assessed safety at a national level by retrieving all cases of Nivolumab (prescribed for NSCLC) induced adverse events analyzed by the French pharmacovigilance network during the inclusion period. **RESULTS:** From July 2015 to September 2016, 30 patients were enrolled with a median age of 75.2. Clinical benefit rate was 30.6%. Median progression-free survival and overall survival were 3.3 and 7.1 months, respectively. Fifteen patients (50%) presented an immune-related adverse event (IrAE) of any grade, including four high grade IrAEs. Two hundred and eighty IrAEs had been notified to the French pharmacovigilance network including 91 (35.2%) concerning older patients. Frequency and pattern of IrAEs were similar for older patients and younger subjects. **CONCLUSIONS:** Even though frequency and patterns of IrAEs are different from pivotal studies, these results don't seem specific to older patients. Further prospective investigations are needed to better characterize and predict the impact of Nivolumab on older patients with NSCLC.

A Prospective Observational Study Evaluating the Correlation of c-MET Expression and EGFR Gene Mutation with Response to Erlotinib as Second-Line Treatment for Patients with Advanced/Metastatic Non-Small-Cell Lung Cancer. Park CK1, Oh IJ1, Choi YD2, Jang TW3, Lee JE4, Ryu JS5, Lee SY6, Kim YC1. Oncology. 2018 Mar 2. doi: 10.1159/000486896. [Epub ahead of print]

OBJECTIVES: We aimed to evaluate the prevalence and predictive role of c-MET expression and EGFR mutation in the efficacy of erlotinib in non-small-cell lung cancer (NSCLC). **METHODS:** We prospectively recruited 196 patients with stage IV or recurrent NSCLC treated with erlotinib after failure of first-line chemotherapy. Immunohistochemistry was used to evaluate c-MET overexpression, silver in situ hybridization (SISH) to assess gene copy number, and real-time polymerase chain reaction to detect EGFR mutations, respectively, in tumor tissue. **RESULTS:** The major histologic type was adenocarcinoma (66.8%). c-MET was overexpressed in 55.8% (87/156) and dominant in females as well as non-squamous histology. Although c-MET gene amplification and high polysomy were observed in 2.0% (3/152) and 11.2% (17/152), they did not correlate with any characteristics. EGFR mutation was detected in 13.1% (20/153). The objective response rate of erlotinib was higher (61.1 vs. 3.7%, p < 0.001) and the median progression-free survival (PFS) was longer (10.2 vs. 1.9 months, p < 0.001) in EGFR-sensitizing mutations. However, c-MET positivity did not show a significant correlation with response to erlotinib or PFS. **CONCLUSION:** We reconfirmed EGFR mutation as a strong predictive marker of NSCLC. However, c-MET positivity was not associated with response or PFS, although c-MET overexpression correlated with some clinical characteristics.

CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two phase II trials. Goss G1, Tsai CM2, Shepherd FA3, et al. Ann Oncol. 2018 Mar 1;29(3):687-693. doi: 10.1093/annonc/mdx820.

BACKGROUND: Central nervous system (CNS) metastases are common in patients with non-small-cell lung cancer (NSCLC). Osimertinib has shown systemic efficacy in patients with CNS metastases, and early clinical evidence shows efficacy in the CNS. To evaluate osimertinib activity further, we present a pre-specified subgroup analysis of CNS response using pooled data from two phase II studies: AURA extension (NCT01802632) and AURA2 (NCT02094261). **PATIENTS AND METHODS:** Patients with T790M-positive advanced NSCLC, who had progressed following prior epidermal growth factor receptor-tyrosine kinase inhibitor treatment, received osimertinib 80 mg od (n = 411). Patients with stable, asymptomatic CNS metastases were eligible for enrolment; prior CNS treatment was allowed. Patients with ≥1 measurable CNS lesion (per RECIST 1.1) on baseline brain scan by blinded independent central neuroradiology review (BICR) were included in the evaluable for CNS response set (cEFR). The primary outcome for this CNS analysis was CNS objective response rate (ORR) by BICR; secondary outcomes included CNS duration of response, disease control rate (DCR) and progression-free survival (PFS). **RESULTS:** Of 128 patients with CNS metastases on baseline brain scans, 50 were included in the cEFR. Confirmed CNS ORR and DCR were 54% [27/50; 95% confidence interval (CI) 39-68] and 92% (46/50; 95% CI 81-98), respectively. CNS response was observed regardless of prior radiotherapy to the brain. Median CNS duration of response (22% maturity) was not reached (range, 1-15 months); at 9 months, 75% (95% CI 53-88) of patients were estimated to remain in response. Median follow-up for CNS PFS was 11 months; median CNS PFS was not reached (95% CI, 7, not calculable). The safety profile observed in the cEFR was consistent with the overall patient population. **CONCLUSIONS:** Osimertinib demonstrated clinically meaningful efficacy against CNS metastases, with a high DCR, encouraging ORR, and safety profile consistent with that reported previously.

Phase II study of bevacizumab, cisplatin, and docetaxel plus maintenance bevacizumab as first-line treatment for patients with advanced non-squamous non-small-cell lung cancer combined with exploratory analysis of circulating endothelial cells: Thoracic Oncology Research Group (TORG)1016. Ikeda S1, Kato T2,3, et al. BMC Cancer. 2018 Mar 2;18(1):241. doi: 10.1186/s12885-018-4150-y.

BACKGROUND: Preclinical studies have demonstrated that docetaxel and bevacizumab may act synergistically by decreasing endothelial cell proliferation and preventing circulating endothelial progenitor mobilization. The objective of this study was to assess the efficacy and safety of a combination therapy of bevacizumab, cisplatin, and docetaxel in chemotherapy-naive Japanese patients with advanced non-squamous non-small-cell lung cancer (NSCLC). **METHODS:** Eligible patients were chemotherapy-naive and had advanced/recurrent non-squamous NSCLC. The patients received 4 cycles of docetaxel (60 mg/m2), cisplatin (80 mg/m2), and bevacizumab (15 mg/kg) once every 3 weeks, followed by bevacizumab as maintenance therapy, every 3 weeks until disease progression or attainment of unacceptable toxicity level. The primary endpoint was objective response rate (ORR). The numbers of circulating endothelial cells (CEC) were also estimated on days 1 and 8 of the first cycle for the exploratory analysis of efficacy prediction. **RESULTS:** A total of 47 patients were enrolled from October 2010 to April 2012. Bevacizumab as maintenance therapy was administered to 41 patients (87.2%), and the median number of total treatment cycles was 9 (range: 1-36). ORR, median progression-free survival (PFS), and median overall survival of the patients were 74.5%, 9.0 months, and 27.5 months, respectively. The most common grade 3/4 adverse event was neutropenia (95.7%), followed by leukopenia (59.6%) and hypertension (46.8%). PFS was longer in patients with ≥10 count increase in CECs than that in patients with < 10 count increase in CECs (respective median PFS of 11.0 months versus 6.90 months) although the difference was not statistically significant (p = 0.074). **CONCLUSIONS:** A combination therapy of bevacizumab, cisplatin, and docetaxel, followed by bevacizumab as maintenance was highly effective in patients with non-squamous NSCLC despite the high incidence of grade 3/4 neutropenia. The increase in CEC count between days 1 and 8 may predict the efficacy of our bevacizumab-contained treatment regimen.

Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non-Small-Cell Lung Cancer. Haratani K1, Hayashi H1, Chiba Y2, et al. JAMA Oncol. 2018 Mar 1;4(3):374-378. doi: 10.1001/jamaoncol.2017.2925.

IMPORTANCE: Immune-related adverse events (irAEs) have been associated with the efficacy of PD-1 (programmed cell death protein 1) inhibitors in patients with melanoma, but whether such an association exists for non-small-cell lung cancer (NSCLC) has remained unknown. **OBJECTIVE:** To evaluate the relation of irAEs to nivolumab efficacy in NSCLC. **DESIGN, SETTING, AND PARTICIPANTS:** In this study based on landmark and multivariable analyses, a total of 134 patients with advanced or recurrent NSCLC who were treated with nivolumab in the second-line setting or later between December 2015 and August 2016 were identified from a review of medical records from multiple institutions, including a university hospital and community hospitals. Data were updated as of December 31, 2016. **EXPOSURES:** The absence or presence of any irAE before the landmark date. **MAIN OUTCOMES AND MEASURES:** Kaplan-Meier curves of progression-free survival (PFS) according to the development of irAEs in 6-week landmark analysis were evaluated with the log-rank test as a preplanned primary objective. Overall survival (OS) was similarly evaluated. Multivariable analysis of both PFS and OS was performed with Cox proportional hazard regression models. **RESULTS:** In a cohort of 134 patients (median [range] age, 68 [33-85] years; 90 men [67%], 44 women [33%]), irAEs were observed in 69 of the 134 study patients (51%), including 12 patients (9%) with such events of grade 3 or 4, and 24 patients (18%) requiring systemic corticosteroid therapy. In 6-week landmark analysis, median PFS was 9.2 months (95% CI, 4.4 to not reached [NR]) and 4.8 months (95% CI, 3.0 to 7.5) (P = .04) whereas

median OS was NR (95% CI, 12.3 to NR) and 11.1 months (95% CI, 9.6 to NR) (P = .01) for patients with or without irAEs, respectively. Multivariable analysis also revealed that irAEs were positively associated with survival outcome, with hazard ratios of 0.525 (95% CI, 0.287 to 0.937; P = .03) for PFS and 0.282 (95% CI, 0.101 to 0.667; P = .003) for OS. **CONCLUSIONS AND RELEVANCE:** Development of irAEs was associated with survival outcome of nivolumab treatment in patients with advanced or recurrent NSCLC. Further studies are needed to confirm our findings.

[Overall Survival Results of the Feasibility Study of Adjuvant Chemotherapy With Docetaxel Plus Cisplatin Followed by Long-term Single-agent Administration of S-1 in Patients With Completely Resected Non-Small Cell Lung Cancer: Thoracic Oncology Research Group (TORG) 0809.](#) Niho S1, Ikeda N2, Michimae H3, et al. Am J Clin Oncol. 2018 Mar 7. doi: 10.1097/COC.0000000000000438. [Epub ahead of print]
OBJECTIVES: The TORG0809 study was a multicenter feasibility study of long-term single-agent therapy with S-1 after docetaxel plus cisplatin therapy in patients with completely resected stage II or stage IIIA non-small cell lung cancer. We report the results of the final overall survival (OS) analysis. **PATIENTS AND METHODS:** A total of 129 eligible patients received 3 cycles of docetaxel (60 mg/m, day 1) plus cisplatin (80 mg/m, day 1), followed by S-1 at 40 mg/m twice daily for 14 consecutive days, for >6 months (maximum, 1 y). **RESULTS:** At the cutoff date of April 13, 2016, the median follow-up time was 6.0 years. Of the 129 patients, 43 had died, and 74 patients developed disease recurrence or died. The median OS had not been reached. The 5-year OS rate was 71% [95% confidence interval (CI), 62-78]. The 5-year OS rates in the patients with stage II and stage IIIA were 76% and 68%, respectively. The median recurrence-free survival (RFS) duration was 3.4 years (95% CI, 2.3-5.7). The 5-year RFS rate was 44% (95% CI, 36-53). The 5-year RFS rates in patients with stage II and stage IIIA disease were 57% and 38%, respectively. Disease recurrence occurred in 68 patients, and 62 of these patients received second-line chemotherapy. The most common sites of recurrence were the brain (n=22) and mediastinal lymph nodes (n=22). **CONCLUSION:** The survival data obtained from this study are promising and comparable to those reported from a previous study conducted in Japan.

[Stromal PDGFR-β Expression is Associated with Postoperative Survival of Non-Small Cell Lung Cancer Patients Receiving Preoperative Chemo- or Chemoradiotherapy Followed by Surgery.](#) Kanzaki R1, Ose N2, Kawamura T2, Funaki S2, Shintani Y2, Minami M2, Takakura N3, Okumura M2. World J Surg. 2018 Mar 6. doi: 10.1007/s00268-018-4560-7. [Epub ahead of print]
BACKGROUND: PDGFR-β is used as a stromal biomarker and is functional in mesenchymal cells of the tumor microenvironment. The significance of stromal PDGFR-β expression in non-small cell lung cancer (NSCLC) in patients undergoing preoperative chemo- or chemoradiotherapy had not been determined. **METHODS:** Patients with NSCLC undergoing preoperative chemo- or chemoradiotherapy between 1996 and 2014 were assessed for expression of stromal PDGFR-β by immunohistochemistry using resected specimens. Relationships between stromal PDGFR-β expression and survival after operation were analyzed. Forty-three patients who underwent surgery without preoperative treatment in 2005 were also analyzed as a chemo-naïve control group. **RESULTS:** The mean age of the 92 patients was 60.2 years. Seventy-eight (85%) were male, and 14 (15%) were female. Fifty-four patients (59%) underwent preoperative chemoradiotherapy, and 38 patients (41%) underwent preoperative chemotherapy. Regimens for preoperative chemotherapy were cisplatin (CDDP) based in 48 patients (52%) and carboplatin (CBDCA) based in 43 (42%). While stromal cells expressed PDGFR-β in 21 chemo-naïve patients (49%), stromal cells expressed PDGFR-β in 65 patients who underwent preoperative therapy (p = 0.02). The 5-year disease-free survival rate (DFS) of the PDGFR-β-positive group was significantly worse than that of the negative group (27 vs. 48%, p = 0.04). The 5-year disease-specific survival rate (DSS) in the stromal PDGFR-β-positive group was also significantly worse than in

the negative group (43 vs. 70%, p = 0.01). On the other hand, stromal PDGFR-β expression did not influence survival in chemo-naïve patients. **CONCLUSIONS:** Stromal PDGFR-β expression is negatively associated with DFS and DSS in patients with NSCLC undergoing preoperative chemo- or chemoradiotherapy.

[Phase 1/2 Study of the Safety and Tolerability of Nivolumab Plus Crizotinib for the First-line Treatment of ALK Translocation-Positive Advanced Non-Small Cell Lung Cancer (CheckMate 370).](#) Spigel DR1, Reynolds C2, Waterhouse D3, et al. J Thorac Oncol. 2018 Mar 5. pii: S1556-0864(18)30176-X. doi: 10.1016/j.jtho.2018.02.022. [Epub ahead of print]
INTRODUCTION: Crizotinib, an anaplastic lymphoma kinase inhibitor, is a first-line treatment for ALK translocation-positive advanced non-small cell lung cancer (NSCLC); however, patients eventually progress. Immunotherapies, including the programmed death-1 inhibitor nivolumab, have resulted in durable responses and long-term overall survival in patients with NSCLC. We hypothesized that combining targeted therapy with immunotherapy could result in more patients with responses and/or more durable responses. Herein we report data from a study assessing nivolumab plus crizotinib in patients with previously untreated advanced ALK translocation-positive NSCLC. **PATIENTS AND METHODS:** Group E in CheckMate 370 was a single-arm cohort designed to evaluate the safety of first-line nivolumab (240 mg every 2 weeks) plus crizotinib (250 mg twice daily) in patients with ALK translocation-positive NSCLC. The primary endpoint of safety would be met if ≤20% of patients discontinued treatment due to treatment-related adverse events by week 17. Objective response rate was a secondary endpoint. A planned safety review occurred in November 2016; the data cutoff was May 26, 2017. **RESULTS:** Of the first 13 patients treated with nivolumab plus crizotinib, five (38%) developed severe hepatic toxicities leading to the discontinuation of the combination. Of these, two patients died and the presence of severe hepatic toxicities may have contributed to death. Enrollment was closed and combination treatment discontinued due to observed grade ≥3 hepatic toxicities. Five patients (38%) had a partial response. **CONCLUSIONS:** These findings do not support further evaluation of nivolumab 240 mg every 2 weeks plus crizotinib 250 mg twice daily.

partial response. **CONCLUSIONS:** These findings do not support further evaluation of nivolumab 240 mg every 2 weeks plus crizotinib 250 mg twice daily.

NSCLC - RADIOTHERAPY

[Volumetric modulated arc therapy treatment planning of thoracic vertebral metastases using stereotactic body radiotherapy.](#) Mallory M1, Pokhrel D2, Badkul R1, Jiang H1, Lominska C1, Wang F1. J Appl Clin Med Phys. 2018 Jan 19. doi: 10.1002/acm2.12252. [Epub ahead of print]
PURPOSE/OBJECTIVES: To retrospectively evaluate the plan quality, treatment efficiency, and accuracy of volumetric modulated arc therapy (VMAT) plans for thoracic spine metastases using stereotactic body radiotherapy (SBRT). **MATERIALS/METHODS:** Seven patients with thoracic vertebral metastases treated with noncoplanar hybrid arcs (NCHA) (1 to 2 3D-conformal partial arcs +7 to 9 IMRT beams) were re-optimized with VMAT plans using three coplanar arcs. Tumors were located between T2 and T7 and PTVs ranged between 24.3 and 240.1 cc (median 48.1 cc). All prescriptions were 30 Gy in 5 fractions with 6 MV beams treated using the Novalis Tx linac equipped with high definition multileaf collimators (HDMLC). MR images were fused with planning CTs for target and OAR contouring. Plans were compared for target coverage using conformality index (CI), homogeneity index (HI), D90, D98, D2, and Dmedian. Normal tissue sparing was evaluated by comparing doses to the spinal cord (Dmax, D0.35, and D1.2 cc), esophagus (Dmax and D5 cc), heart (Dmax, D15 cc), and lung (V5 and V10). Data analysis was performed with a two-sided t-test for each set of parameters. Dose delivery efficiency and accuracy of each VMAT plan was assessed via quality assurance (QA) using a MapCHECK device. The Beam-on time (BOT) was recorded, and a gamma index was used to compare dose agreement between the planned and measured doses. **RESULTS:** VMAT plans resulted in improved CI (1.02 vs. 1.36, P = 0.05), HI (0.14 vs. 0.27, P = 0.01), D98 (28.4 vs. 26.8 Gy, P = 0.03), D2 (32.9 vs. 36.0 Gy, P = 0.02), and Dmedian (31.4 vs. 33.7 Gy, P = 0.01). D90 was improved but not statistically significant (30.4 vs. 31.0 Gy, P = 0.38). VMAT plans showed statistically significant improvements in normal tissue sparing: Esophagus Dmax (22.5 vs. 27.0 Gy, P = 0.03), Esophagus 5 cc (17.6 vs. 21.5 Gy, P = 0.02), and Heart Dmax (13.1 vs. 15.8 Gy, P = 0.03). Improvements were also observed in spinal cord and lung sparing as well but were not statistically significant. The BOT showed significant reduction for VMAT, 4.7 ± 0.6 min vs. 7.1 ± 1 min for NCHA (not accounting for couch kicks). VMAT plans demonstrated an accurate dose delivery of $95.5 \pm 1.0\%$ for clinical gamma passing rate of 3%/3 mm criteria, which was similar to NCHA plans. **CONCLUSIONS:** VMAT plans have shown improved dose distributions and normal tissue sparing compared to NCHA plans. Significant reductions in treatment time could potentially minimize patient discomfort and intrafraction movement errors. VMAT planning for SBRT is an attractive option for the treatment of metastases to thoracic vertebrae, and further investigation using alternative fractionation schedules is warranted.

[Stereotactic body radiation therapy (SBRT) in the management of non-small-cell lung cancer: Clinical impact and patient perspectives.](#) Donovan EK1,2, Swaminath A1,2. Lung Cancer (Auckl). 2018 Mar 16;9:13-23. doi: 10.2147/LCTT.S129833. eCollection 2018.
Stereotactic body radiation therapy (SBRT) has emerged as a new technology in radiotherapy delivery, allowing for potentially curative treatment in many patients previously felt not to be candidates for radical surgical resection of stage I non-small-cell lung cancer (NSCLC). Several studies have demonstrated very high local control rates using SBRT, and more recent data have suggested overall survival may approach that of surgery in operable patients. However, SBRT is not without unique toxicities, and the balance of toxicity, and effect on patient-reported quality of life need to be considered with respect to oncologic outcomes. We therefore aim to review SBRT in the context of important patient-related factors, including quality of life in several domains (and in comparison to other therapies such as conventional radiation,

surgery, or no treatment). We will also describe scenarios in which SBRT may be reasonably offered (i.e. elderly patients and those with severe COPD), and where it may need to be approached with some caution due to increased risks of toxicity (i.e. tumor location, patients with interstitial lung disease). In total, we hope to characterize the physical, emotional, and functional consequences of SBRT, in relation to other management strategies, in order to aid the clinician in deciding whether SBRT is the optimal treatment choice for each patient with early NSCLC.

Changes in Treatment Patterns and Overall Survival in Patients With Early-Stage Non-Small Cell Lung Cancer in the United States After the Incorporation of Stereotactic Ablative Radiation Therapy: A Population-based Analysis.

Haque W1, Szeja S2, Tann A2, Kalra S3, Teh BS4. Am J Clin Oncol. 2018 Mar;41(3):259-266. doi: 10.1097/COC.0000000000000265.

PURPOSE: Technologic developments have made radiation therapy (RT) more effective and have introduced new treatment options, such as stereotactic ablative radiation therapy (SABR). This study sought to determine changes in practice patterns for treatment of stage IA non-small cell lung cancer (NSCLC) after the introduction of SABR into the United States. This population-based study also examined changes in survival during this time period for all patients and specifically for patients treated with RT, surgery, or observation. **METHODS:** We included patients in the Surveillance, Epidemiology, and End Results database diagnosed with stage IA NSCLC diagnosed between 2004 and 2012. Changes in treatment patterns were assessed. Outcomes were compared across 2 time periods: 2004 to 2008 (pre-SABR) and 2009 to 2012 (post-SABR). Kaplan-Meier and Cox regression were performed to compare overall survival (OS) for patients treated with surgery, RT, or observation. **RESULTS:** A total of 32,249 patients met the specified criteria. Comparing patients diagnosed in 2004 to those diagnosed in 2012, RT use increased from 13% to 29% (P<0.001), surgery use decreased from 76% to 61% (P<0.001), and patients observed decreased from 11% to 10% (P=0.3). There was no significant OS improvement in all patients or those patients who were observed; there were significant improvements in OS for patients treated with RT (hazard ratio=0.768; 95% confidence interval, 0.711-0.829) and those patients treated with surgery (hazard ratio=0.9; 95% confidence interval, 0.855-0.962). **CONCLUSIONS:** There has been an increase in RT utilization and decrease in surgical utilization after the incorporation of SABR by radiation oncologists within the United States. In addition, there has been an improvement in OS for patients treated with definitive RT for early-stage NSCLC between 2004 and 2012 that may be associated with increased utilization of SABR.

A model combining age, equivalent uniform dose and IL-8 may predict radiation esophagitis in patients with non-small cell lung cancer.

Wang S1, Campbell J2, Stenmark MH3, Stanton P2, Zhao J2, Matuszak MM3, Ten Haken RK3, Kong FM4. Radiother Oncol. 2018 Mar;126(3):506-510. doi: 10.1016/j.radonc.2017.12.026.

BACKGROUND AND PURPOSE: To study whether cytokine markers may improve predictive accuracy of radiation esophagitis (RE) in non-small cell lung cancer (NSCLC) patients. **MATERIALS AND METHODS:** A total of 129 patients with stage I-III NSCLC treated with radiotherapy (RT) from prospective studies were included. Thirty inflammatory cytokines were measured in platelet-poor plasma samples. Logistic regression was performed to evaluate the risk factors of RE. Stepwise Akaike information criterion (AIC) and likelihood ratio test were used to assess model predictions. **RESULTS:** Forty-nine of 129 patients (38.0%) developed grade ≥2 RE. Univariate analysis showed that age, stage, concurrent chemotherapy, and eight dosimetric parameters were significantly associated with grade ≥2 RE (p < 0.05). IL-4, IL-5, IL-8, IL-13, IL-15, IL-1α, TGFα and eotaxin were also associated with grade ≥2 RE (p < 0.1). Age, esophagus generalized equivalent uniform dose (EUD), and baseline IL-8 were independently associated grade ≥2 RE. The combination of these three factors had significantly higher predictive power than any single factor alone. Addition of IL-8 to toxicity model significantly improves

RE predictive accuracy (p = 0.019). **CONCLUSIONS:** Combining baseline level of IL-8, age and esophagus EUD may predict RE more accurately. Refinement of this model with larger sample sizes and validation from multicenter database are warranted.

Radiomics analysis at PET/CT contributes to prognosis of recurrence and survival in lung cancer treated with stereotactic body radiotherapy. Oikonomou A1, Khalvati F2, Tyrrell PN3, et al. Sci Rep. 2018 Mar 5;8(1):4003. doi: 10.1038/s41598-018-22357-y.

We sought to quantify contribution of radiomics and SUVmax at PET/CT to predict clinical outcome in lung cancer patients treated with stereotactic body radiotherapy (SBRT). 150 patients with 172 lung cancers, who underwent SBRT were retrospectively included. Radiomics were applied on PET/CT. Principal components (PC) for 42 CT and PET-derived features were examined to determine which ones accounted for most of variability. Survival analysis quantified ability of radiomics and SUVmax to predict outcome. PCs including homogeneity, size, maximum intensity, mean and median gray level, standard deviation, entropy, kurtosis, skewness, morphology and asymmetry were included in prediction models for regional control (RC) [PC4-HR:0.38, p = 0.02], distant control (DC) [PC4-HR:0.51, p = 0.02 and PC1-HR:1.12, p = 0.01], recurrence free probability (RFP) [PC1-HR:1.08, p = 0.04], disease specific survival (DSS) [PC2-HR:1.34, p = 0.03 and PC3-HR:0.64, p = 0.02] and overall survival (OS) [PC4-HR:0.45, p = 0.004 and PC3-HR:0.74, p = 0.02]. In combined analysis with SUVmax, PC1 lost predictive ability over SUVmax for RFP [HR:1.1, p = 0.04] and DC [HR:1.13, p = 0.002], while PC4 remained predictive of DC independent of SUVmax [HR:0.5, p = 0.02]. Radiomics remained the only predictors of OS, DSS and RC. Neither SUVmax nor radiomics predicted recurrence free survival. Radiomics on PET/CT provided complementary information for prediction of control and survival in SBRT-treated lung cancer patients.

A Methodology to Investigate the Impact of Image Distortions on the Radiation Dose When Using Magnetic Resonance Images for Planning. Yan Y1, Yang J2, Beddar S3, et al. Phys Med Biol. 2018 Mar 12. doi: 10.1088/1361-6560/aab5c3. [Epub ahead of print]

We developed a novel technique to study the impact of geometric distortion of magnetic resonance imaging (MRI) on intensity-modulated radiation therapy treatment planning.  The measured 3D datasets of residual geometric distortion (a 1.5-T MRI component of an MRI linear accelerator system) was fitted with a second-order polynomial model to map the spatial dependence of geometric distortions. Then the geometric distortion model was applied to computed tomography (CT) image and structure data to simulate the distortion of MRI data and structures. Fourteen CT-based treatment plans were selected from patients treated for gastrointestinal, genitourinary, thoracic, head and neck, or spinal tumors. Plans based on the distorted CT and structure data were generated (as the distorted plans). Dose deviations of the distorted plans were calculated and compared with the original plans to study the dosimetric impact of MRI distortion.  The MRI geometric distortion led to notable dose deviations in 5 of the 14 patients, causing loss of target coverage of up to 3.68% and dose deviations to organs at risk in three patients, increasing the mean dose to the chest wall by up to 6.19 Gy in a gastrointestinal patient, and increases the maximum dose to the lung by 5.17 Gy in a thoracic patient. &#13.

Stereotactic ablative radiation therapy in lung cancer: an emerging standard. Mutsaers A1, Chen H, Louie AV. Curr Opin Pulm Med. 2018 Mar 7. doi: 10.1097/MCP.0000000000000482. [Epub ahead of print]

PURPOSE OF REVIEW: Significant advances have been made in the field of stereotactic ablative radiotherapy (SABR) for the treatment of pulmonary neoplasms in recent years. This review aims to summarize recent salient evidence on SABR for early-stage nonsmall cell lung cancer (ES-NSCLC).

RECENT FINDINGS: In medically inoperable patients, SABR remains the standard of care. The optimal SABR dosing regimen is being studied. Comparisons with non-SABR radiotherapy regimens with lower doses per fraction revealed benefit of SABR. In operable patients, no prospective clinical trial comparing SABR and surgery has been completed, although multiple trials are currently underway to address this question. SABR is generally cost-effective and safe in most patients, with preserved patient-reported quality of life. However, increased toxicity with SABR is noted in patients with disease close to, or invading the proximal tracheobronchial tree. Significant SABR-related toxicity and mortality is also reported in patients with coexisting interstitial lung disease. Considerations on pathologic confirmation, surveillance and multiple primaries are also addressed. **SUMMARY:** SABR is an effective and safe treatment for inoperable ES-NSCLC. Ongoing trials and comparative effectiveness research will help to clarify SABR's role in various lung cancer indications going forward.

SMALL CELL LUNG CANCER - SCLC

[Randomized Phase III Trial of Irinotecan Plus Cisplatin Versus Etoposide Plus Cisplatin in Chemotherapy-Naïve Korean Patients with Extensive-Disease Small Cell Lung Cancer.](#) Kim DW1, Kim HG2, Kim JH3, et al. Cancer Res Treat. 2018 Mar 12. doi: 10.4143/crt.2018.019. [Epub ahead of print]

PURPOSE: This randomized phase III study was designed to compare the efficacy and safety of irinotecan plus cisplatin (IP) over etoposide plus cisplatin (EP) in Korean patients with extensive-disease small-cell lung cancer (SCLC). **MATERIALS AND METHODS:** Patients were randomly assigned to receive IP, composed of irinotecan 65 mg/m2 intravenously on days 1 and 8 + cisplatin 70 mg/m2 intravenously on day1 every 3 weeks, or EP, composed of etoposide 100 mg/m2 intravenously on days 1, 2, 3+cisplatin 70 mg/m2 intravenously on day 1, every 3 weeks for a maximum of six cycles, until disease progression, or until unacceptable toxicity occurred. The primary endpoint was overall survival. **RESULTS:** A total of 362 patients were randomized to IP (n=173) and EP (n=189) arms. There were no significant differences between IP and EP arms for the median overall survival (10.9 vs. 10.3 months, p=0.120) and the median progression-free survival (6.5 vs. 5.8 months, p=0.1125). However, there was a significant difference in response rate (62.4 vs. 48.2%, p=0.0064). The pre-planned subgroup analyses showed that IP was associated with longer overall survival in male (11.3 vs. 10.1 months, p=0.0361), <65 years old (12.7 vs. 11.3 months, p=0.0240), and ECOG performance status 0/1 (12.4 vs. 10.9 months, p=0.0407) patient groups. The severity of treatment-related adverse events such as grade 3/4 anemia, nausea and diarrhea was more frequent in patients treated with IP. **CONCLUSION:** The IP chemotherapy did not significantly improve the survival compared with EP chemotherapy in Korean patients with extensive-disease SCLC. (ClinicalTrials.gov Identifier: NCT00349492).

[The effect of post-progression survival on overall survival among patients with sensitive relapse of small cell lung cancer.](#) Miura Y1,2, Imai H3, Sakurai R2,4, Kaira K5, Sunaga N2, Minato K1, Saito R4, Hisada T2. Med Oncol. 2018 Mar 5;35(4):45. doi: 10.1007/s12032-018-1107-6.

Recent studies have suggested that, among patients with advanced lung cancer, subsequent treatment after failure of first-line or second-line chemotherapy has a greater effect on overall survival (OS) than tumor shrinkage or progression-free survival (PFS). However, no studies have examined this issue among patients with sensitive relapse of small cell lung cancer (SCLC). We retrospectively evaluate 77 patients with sensitive relapse of SCLC who received second-line chemotherapy after first-line platinum doublet chemotherapy between January 1999 and November 2013. The analyses included patient characteristics, treatment parameters, tumor shrinkage, PFS, post-progression survival (PPS), and OS. Spearman rank correlation analysis and linear regression analysis revealed that PPS was strongly correlated with OS ($r = 0.91$, $p < 0.01$, $R2 = 0.96$), PFS was moderately correlated with OS ($r = 0.58$, $p < 0.01$, $R2 = 0.28$), and

tumor shrinkage was weakly correlated with OS ($r = 0.34$, $p < 0.01$, $R2 = 0.12$). A multivariate Cox proportional hazards model with a stepwise regression procedure revealed that PPS was significantly associated with age at the start of second-line chemotherapy, best response to second-line and third-line chemotherapy, and the number of regimens after progression beyond second-line chemotherapy ($p < 0.05$). These findings suggest that PPS has a stronger effect than PFS on OS among patients with sensitive relapse of SCLC. Thus, response to second-line chemotherapy and subsequent treatment for disease progression after second-line chemotherapy may be important factors that influence OS.

Targeting CREB pathway suppresses Small Cell lung Cancer. Xia Y1, Zhan C2, Feng M2, Leblanc M3, Ke E4, Yeddula N5, Verma IM6. Mol Cancer Res. 2018 Mar 9. pii: molcanres.0576.2017. doi: 10.1158/1541-7786.MCR-17-0576. [Epub ahead of print]
Small cell lung cancer (SCLC) is the most deadly subtype of lung cancer due to its dismal prognosis. We have developed a lentiviral vector-mediated SCLC mouse model and have explored the role of both the NF-κB and CREB families of transcription factors in this model. Surprisingly, induction of NF-κB activity, which promotes tumor progression in many cancer types including non-small cell lung carcinoma (NSCLC), is dispensable in SCLC. Instead, suppression of NF-κB activity in SCLC tumors moderately accelerated tumor development. Examination of gene expression signatures of both mouse and human SCLC tumors revealed overall low NF-κB but high CREB activity. Blocking CREB activation by a dominant-negative form of PKA (dnPKA) completely abolished the development of SCLC. Similarly, expression of dnPKA or treatment with PKA inhibitor H89 greatly reduced the growth of SCLC tumors in syngeneic transplantation models. Altogether, our results strongly suggest that targeting CREB is a promising therapeutic strategy against SCLC. **IMPLICATIONS:** Activity of the transcription factor CREB is elevated in SCLC tumors, which helps to maintain its neuroendocrine signature and cell proliferation. Our results highlight the importance of targeting the CREB pathway to develop new therapeutics to combat SCLC.

Adjuvant chemotherapy following surgical resection improves survival in patients with early-stage small cell lung cancer. Yao Y1, Zhou Y1, Yang Z1, Huang H1, Shen H1. Oncol Res. 2018 Mar 9. doi: 10.3727/096504018X15202953107093. [Epub ahead of print]
The purpose of this study was to determine the effects of resection coupled with standard chemotherapy on survival prognosis of patients with early-stage small cell lung carcinoma (SCLC). Patients (n=110) with mediastinal lymph node-negative SCLC were enrolled in this study. The baseline clinical data of patients with surgery was retrospectively reviewed. Overall and progression-free survival were measured by Kaplan-Meier and log-rank test analyses. Ninety-eight patients received mediastinoscopy biopsy and pulmonary lobectomy or sublobar resection, and 67 patients underwent adjuvant chemotherapy after pulmonary lobectomy. Adjuvant chemotherapy after surgical intervention was associated with longer OS (median OS 42.14 months (m) vs. 33.53 m, p =0.01) and PFS (median PFS 25.20 m vs. 13.48 m, p =0.000) compared to resection alone for all patients. Adjuvant chemotherapy was associated with improvement of survival for N1 patients with stage II (median OS 36.42 m vs. 26.68 m, p =0.021). The median PFS was 19.02 months (16.08, 21.96) and 13.25 months (10.19, 16.30) (p=0.031), respectively, for patients of N1 stage who received chemotherapy and those who did not. Cox regression analysis demonstrated that age, TNM stage (N stage, not T stage), and chemotherapy were independent risk factors that might affect overall survival in patients with mediastinal lymph node-negative SCLC. These findings suggest that the application of adjuvant chemotherapy following pulmonary lobectomy is associated with improvements of survival prognoses for patients with SCLC. The combination of surgical intervention with conventional therapy should be taken into consideration as a prospective multidisciplinary regimen for early stage SCLC.

A Phase Ib/II Study of Ganetespib With Doxorubicin in Advanced Solid Tumors Including Relapsed-Refractory Small Cell Lung Cancer. Subramaniam DS1, Liu SV1, Crawford J2, Kramer J1, Thompson J1, Wang H2, Giaccone G2. Front Oncol. 2018 Mar 12;8:64. doi: 10.3389/fonc.2018.00064. eCollection 2018.

INTRODUCTION: Small cell lung cancer (SCLC) accounts for 15% of all lung cancers and is characterized by high response rates to cytotoxic chemotherapy and equally high rates of relapse. Many resistance mechanisms have been proposed including resistance to doxorubicin via induction of a heat shock response. Ganetespib is a novel and potent non-geldanamycin heat shock protein 90 (Hsp90) inhibitor. In preclinical studies, synergy between ganetespib and doxorubicin was shown. We conducted a phase Ib/II study of the safety, tolerability, and preliminary efficacy of the combination of ganetespib and doxorubicin. **METHODS:** Patients eligible for the phase Ib portion had advanced tumors that would be appropriate for doxorubicin therapy and those in the phase II portion had relapsed or refractory SCLC. All patients had an ECOG performance status, 0-1 and adequate organ function, including a cardiac ejection fraction ≥50%. Patients who received a lifetime cumulative doxorubicin dose of >150 mg/m2 or who had symptomatic brain metastases were excluded. Patients received ganetespib on Days 1 and 8 and doxorubicin 50 mg/m2 on day 1 in 21-day cycles. **RESULTS:** Eleven patients were enrolled including nine in the phase Ib dose escalation and two in the phase II expansion. The study was terminated by the sponsor. The dose recommended for future study is ganetespib 150 mg/m2 in combination with doxorubicin at a dose of 50 mg/m2. The most common adverse events of the combination were grade 1/2 diarrhea, nausea, fatigue, and transaminitis. No dose limiting toxicities were observed. Response rate was 25% and median duration of response was 137 days. **CONCLUSION:** Ganetespib plus doxorubicin was a well-tolerated combination and there remains potential for the clinical development of Hsp90 inhibitors in SCLC.

PALLIATIVE AND SUPPORTIVE CARE

Patients with advanced cancer and depression report a significantly higher symptom burden than non-depressed patients.
Grotmol KS1, Lie HC2, Loge JH1, Aass N3, Haugen DF4, Stone PC5, Kaasa S6, Hjermstad MJ1. Palliat Support Care. 2018 Jan 10:1-7. doi: 10.1017/S1478951517001183. [Epub ahead of print]

OBJECTIVE: Clinical observations indicate that patients with advanced cancer and depression report higher symptom burden than nondepressed patients. This is rarely examined empirically. Study aim was to investigate the association between self-reported depression disorder (DD) and symptoms in patients with advanced cancer controlled for prognostic factors. **METHOD:** The sample included 935 patients, mean age 62, 52% males, from an international multicentre observational study (European Palliative Care Research Collaborative - Computerised Symptom Assessment and Classification of Pain, Depression and Physical Function). DD was assessed by the Patient Health Questionnaire-9 and scored with Diagnostic and Statistical Manual of Mental Disorder-5 algorithm for major depressive disorder, excluding somatic symptoms. Symptom burden was assessed by summing scores on somatic Edmonton Symptom Assessment Scale (ESAS) symptoms, excluding depression, anxiety, and well-being. Item-by-item scores and symptom burden of those with and without DD were compared using nonparametric Mann-Whitney U tests. The relative importance of sociodemographic, medical, and prognostic factors and DD in predicting symptom burden was assessed by hierarchical, multiple regression analyses. Result Patients with DD reported significantly higher scores on ESAS items and a twofold higher symptom burden compared with those without. Factors associated with higher symptom burden were as follows. **DIAGNOSIS:** lung ($\beta = 0.15$, $p < 0.001$) or breast cancer ($\beta = 0.08$, $p < 0.05$); poorer prognosis: high C-reactive protein ($\beta = 0.08$, $p < 0.05$), lower Karnofsky Performance Status ($\beta = -0.14$, $p < 0.001$), and greater weight loss ($\beta = -0.15$, $p < 0.001$); taking opioids ($\beta = 0.11$, $p < 0.01$); and having DD ($\beta = 0.23$, p

< 0.001). The full model explained 18% of the variance in symptom burden. DD explained 4.4% over and above that explained by all the other variables. Significance of results Depression in patients with advanced cancer is associated with higher symptom burden. These results encourage improved routines for identifying and treating those suffering from depression.

[Does depression treatment improve the survival of depressed patients with cancer? A long-term follow-up of participants in the SMaRT Oncology-2 and 3 trials.](#) Mulick A1, Walker J2, Puntis S2, Burke K2, Symeonides S3, Gourley C3, Wanat M2, Frost C1, Sharpe M4. Lancet Psychiatry. 2018 Apr;5(4):321-326. doi: 10.1016/S2215-0366(18)30061-0. Epub 2018 Mar 12.

BACKGROUND: Comorbid major depression has been associated with worse survival in patients with cancer. However, we do not know if treating depression improves survival. In the SMaRT Oncology-2 (good prognosis cancers) and SMaRT Oncology-3 (lung cancer, a poor prognosis cancer) trials, we found that a depression treatment programme, Depression Care for People with Cancer (DCPC), was effective in reducing comorbid major depression. In this analysis, we aimed to identify whether DCPC also had an effect on survival. **METHODS:** The trials were conducted in three cancer centres and their associated clinics in Scotland, UK. In SMaRT Oncology-2, outpatients with good prognosis cancers and major depression were randomly assigned in a 1:1 ratio to DCPC or usual care, with stratification (by trial centre) and minimisation (by age, primary cancer, and sex) with allocation concealment. In SMaRT Oncology-3, outpatients with lung cancer and major depression were randomly assigned (1:1 ratio) to DCPC or usual care with stratification (by trial centre) and minimisation (by age, sex, and cancer type) with allocation concealment. For this analysis, we obtained long-term data on deaths (all causes) in the SMaRT Oncology-2 and 3 trial participants, censored at July 31, 2015, and analysed survival as a trial outcome. We estimated unadjusted hazard ratios (HRs) for each trial using Cox regression, and pooled the log HRs in a fixed-effects meta-analysis. **FINDINGS:** We recruited 642 participants; between May 12, 2008, and May 13, 2011, 500 participants were recruited to the SMaRT Oncology-2 trial and between Jan 5, 2009, and Sept 9, 2011, 142 participants were recruited to the SMaRT Oncology-3 trial. We followed up SMaRT Oncology-2 and SMaRT Oncology-3 participants for a median of 5 years and 1 year, respectively. 135 (27%) of 500 SMaRT Oncology-2 participants and 114 (80%) of 142 SMaRT Oncology-3 participants died within this period. We found no significant effect of DCPC on survival in the total follow-up period for either SMaRT Oncology 2 (HR 1·02, 95% CI 0·72-1·42, p=0·93) or SMaRT Oncology-3 (HR 0·82, 95% CI 0·56-1·18, p=0·28; pooled HR 0·92, 95% CI 0·72-1·18, p=0·51). **INTERPRETATION:** DCPC is highly effective in improving depression and quality of life in depressed patients with cancer, but there was no evidence for a significant effect on survival. Despite the absence of an effect on length of life, the management of depression remains important for its beneficial effect on quality of life. **FUNDING:** NIHR CLAHRC Oxford, Cancer Research UK, and the Chief Scientist Office of the Scottish Government.

[18F-FDG PET/CT Can Predict Development of Thyroiditis due to Immunotherapy for Lung Cancer.](#) Eshghi N1, Garland L1, Nia ES2, Betancourt R1, Krupinski E3, Kuo PH1. J Nucl Med Technol. 2018 Mar 29. pii: jnmt.117.204933. doi: 10.2967/jnmt.117.204933. [Epub ahead of print]

OBJECTIVE: For patients undergoing immunotherapy with nivolumab for lung cancer, determine if increased 18F-FDG uptake in the thyroid gland predicts development of thyroiditis with subsequent hypothyroidism. Secondarily, determine if 18F-FDG uptake in the thyroid gland correlates with administered cycles of nivolumab. **MATERIALS AND METHODS:** Retrospective chart review over 2 years found 18 lung cancer patients treated with nivolumab and with 18F-FDG PET/CT scans pre- and during therapy. Standardized uptake value (SUV) mean and maximum and total lesion glycolysis (TLG) of the thyroid gland were measured. SUVs were also measured for the pituitary gland, liver and spleen. Patients obtained monthly thyroid testing. PET/CT parameters were analyzed by unpaired t-test for

differences between two groups (patients who developed hypothyroidism and those who did not). Correlation between development of thyroiditis and number of cycles of nivolumab received was also tested. **RESULTS:** Six of eighteen patients developed hypothyroidism. T-test comparing the two groups (patients who developed hypothyroidism and those who did not) demonstrated significant differences in SUVmean (P = 0.04), SUVmax (P = 0.04) and TLG (P = 0.02) of the thyroid gland. Two of four patients who developed thyroiditis and had increased 18F-FDG uptake in the thyroid gland, had normal TSH at time of follow-up 18F-FDG PET/CT. Patients who developed thyroiditis with subsequent hypothyroidism stayed longer on therapy (10.6 cycles) compared to patients without thyroiditis (7.6 cycles), but the trend was not statistically significant. No significant difference in PET/CT parameters was observed for pituitary gland, liver or spleen. **CONCLUSION**:18F-FDG PET/CT can predict the development of thyroiditis with subsequent hypothyroidism before laboratory testing. Further study is required to confirm the positive trend between thyroiditis and duration of therapy.

[Cancer Pain Management Education Rectifies Patients' Misconceptions of Cancer Pain, Reduces Pain, and Improves Quality of Life.](#) Koh SJ1, Keam B2, Hyun MK3, Ju Seo J4, Uk Park K5, Oh SY6, Ahn J4, Lee JY7, Kim J8. Pain Med. 2018 Mar 26. doi: 10.1093/pm/pny039. [Epub ahead of print]
OBJECTIVES: More than half of the patients have reported improper management of breakthrough cancer pain. Empirical evidence is lacking concerning the effectiveness of cancer pain education on breakthrough pain control. This study aimed to examine the effects of individual pain education on pain control, use of short-acting analgesics for breakthrough pain, quality of life outcomes, and rectification of patients' misconceptions regarding cancer pain. **DESIGN:** A quasi-experimental design was used. In total, 176 (102 inpatients and 74 outpatients) and 163 (93 inpatients and 70 outpatients) cancer patients completed questionnaires on pain intensity, quality of life, use of short-acting medication for breakthrough pain, and misconceptions about cancer pain and opioid use before and immediately and/or seven days after individual pain education. **RESULTS:** The mean age of the participants was 60.9 years (±11.2), and 56.3% were male. The most common cancers were lung cancer (17.0%), colon cancer (15.9%), and breast cancer (12.5%). The subjects' reasons for attrition were conditional deterioration, death, or voluntary withdrawal (N = 13, 7.4%). Following the education, there was a significant reduction in overall pain intensity over 24 hours (P < 0.001). The outpatients showed more use of short-acting analgesics for breakthrough pain. Sleep quality change was most significantly associated with intervention; other quality of life aspects (e.g., general feelings and life enjoyment) also improved. Pain education also significantly reduced misconceptions regarding cancer pain management. **CONCLUSIONS:** The present educational intervention was effective in encouraging short-acting analgesic use for breakthrough pain, improving quality of life outcomes, and rectifying patients' misconceptions about analgesic use.

[Sleepless from the Get Go: Sleep Problems Prior to Initiating Cancer Treatment.](#) Zhou ES1,2, Clark K3, Recklitis CJ4,5, Obenchain R3, Loscalzo M3. Int J Behav Med. 2018 Mar 15. doi: 10.1007/s12529-018-9715-2. [Epub ahead of print]
PURPOSE: Cancer patients are likely to experience sleep problems. Understanding their perception of sleep problems is important as subjective symptom experience is associated with treatment-seeking behavior. We explored the prevalence of sleep problems and its correlates in a large sample of cancer patients at an important but understudied stage of their cancer journey: prior to initiating treatment. **METHODS:** Cancer patients (5702) (67.5% female; 76.9% White; 23.0% Hispanic), following diagnosis and prior to initiating cancer treatment, completed an electronic screening instrument. Patients across eight different cancer diagnoses (breast, gastrointestinal, gynecological, head and neck, hematological, lung, prostate, urinary) rated their sleep problems on a five-point scale, with those reporting "severe" or "very severe" sleep problems classified as having high sleep problems. **RESULTS:** Overall, 12.5% of

patients reported high sleep problems. Across diagnoses, the proportion of patients reporting high sleep problems ranged from 4.3 to 13.8%, with prostate cancer patients least likely and gastrointestinal cancer patients most likely to report high sleep problems. Older age, having a partner, higher education, and higher household income were associated with a lower likelihood of experiencing sleep problems. Being female, Black, Hispanic, and reporting anxiety or depression was associated with an increased likelihood of sleep problems. **CONCLUSIONS:** A sizeable proportion of cancer patients experience significant problems with their sleep before any treatment has occurred. This clinical issue cannot be ignored as treatment is likely to worsen existing sleep problems. Oncology providers should routinely screen for sleep-related problems. Identifying and treating patients for sleep problems during a vulnerable period early in their cancer trajectory should be an essential component of clinical care.

[Efficacy of a Propolis-Based Syrup (FARINGEL) in Preventing Radiation-Induced Esophagitis in Locally Advanced Lung Cancer.](#) Ippolito E, Floreno B, Rinaldi CG, Trodella L, Meroni FL, Iurato A, D'Angelillo RM, Ramella S, Fiore M. Chemotherapy. 2018 Mar 19;63(2):76-82. doi: 10.1159/000487897. [Epub ahead of print]

AIM: To evaluate the efficacy of a propolis-based syrup, FARINGEL®, in preventing radiation-induced esophagitis in locally advanced lung cancer patients. **METHODS:** Patients were treated with concurrent chemoradiotherapy (CRT) using involved-field radiotherapy (RT). Every patient received FARINGEL at the beginning of CRT until the first follow-up. The data of the study group were compared with the data of a control group treated without the administration of the syrup. **RESULTS:** Forty-five patients were enrolled. Forty-one (91.1%) completed the protocol and were evaluable for esophagitis. Grade ≥2 toxicity occurred in 9/41 patients (22%). No differences in overall toxicity were detected between the study group and the control group (n = 55, 60.9 vs. 54.5%; p = ns). Grade 2-3 esophagitis was lower in the study group in comparison with the control group (22 and 38%, respectively), but statistical significance was not reached (p = 0.09). However, the onset of grade ≥2 esophagitis was delayed in the study group compared to the control group, occurring at higher doses of RT (41.8 vs. 25.4 Gy; p < 0.001). Furthermore, the mean number of interruption days for esophagitis was lower in the study group than in the control group (0.6 ± 2.0 vs. 2.1 ± 3.6; p = 0.025). **CONCLUSION:** FARINGEL was well-tolerated and delayed esophagitis that was induced by CRT for locally advanced lung cancer.

[Impact of Socioeconomic Status on Pretreatment Weight Loss and Survival in Non-Small-Cell Lung Cancer.](#) Lau SKM1, Gannavarapu BS1, Carter K1, Gao A1, Ahn C1, Meyer JJ1, Sher DJ1, Jatoi A1, Infante R1, Iyengar P1. J Oncol Pract. 2018 Mar 20:JOP2017025239. doi: 10.1200/JOP.2017.025239. [Epub ahead of print]

PURPOSE: Socioeconomic status (SES) influences health care outcomes, but the influence of primary payer on cancer-associated wasting is unknown. We hypothesized that primary payer as an indicator of SES would influence pretreatment cancer-associated weight loss and treatment outcomes. **MATERIALS AND METHODS:** Retrospective review of medical records identified 1,366 patients with non-small-cell lung cancer (NSCLC) consecutively treated at a tertiary care health system between January 1, 2006 and December 31, 2013. Insurance status was obtained from an institutional tumor registry. Cancer-associated weight loss was based on the validated international consensus definition of cachexia. Multivariable regression analyses were used to identify prognostic factors of pretreatment cancer-associated weight loss and survival. **RESULTS:** The cohort included a representative group of patients with a median age at diagnosis of 64 years, 47% females, and 33% patients of nonwhite race. Pretreatment cancer-associated weight loss was present at the time of NSCLC diagnosis in 17%, 14%, 32%, and 38% of patients with stage I, II, III, and IV disease, respectively. Pretreatment cancer-associated weight loss was associated with increasing age at diagnosis, black race, single marital status, tobacco use, and disease stage. Compared with private insurance, Medicaid insurance (odds ratio, 2.17; 95% CI, 1.42 to 3.30) and lack of

insurance (odds ratio, 2.32; 95% CI, 1.50 to 3.58) were associated with pretreatment cancer-associated weight loss. Among cachectic patients, comorbidity, histology, tumor grade, and disease stage were prognostic of survival on multivariable analysis; however, primary payer was not. **CONCLUSION:** Pretreatment cancer-associated weight loss is common in patients with NSCLC, and its presence is significantly associated with lower SES. However, among patients with pretreatment cancer-associated weight loss, SES was not predictive of survival. Early use of cancer cachexia-directed therapies may improve outcomes, and further study on the biologic mechanisms of cancer cachexia will provide novel therapeutic avenues.

[Changes in exercise tolerance and quality of life are unrelated in lung cancer survivors who undergo video-assisted thoracic surgery.](#) Anami K1,2, Horie J3, Hirayama Y4, Yamashita N5, Ito K6. J Phys Ther Sci. 2018 Mar;30(3):467-473. doi: 10.1589/jpts.30.467. Epub 2018 Mar 2.
PURPOSE: The associations between changes in respiratory function, exercise tolerance, and quality of life (QOL) in patients with lung cancer who undergo lobectomy using video-assisted thoracoscopic surgery (VATS) are unclear. This study aimed to investigate the relationships between exercise tolerance and QOL in patients who underwent VATS. **SUBJECTS AND METHODS:** Thirty-six patients with lung cancer were followed for 3 months after VATS. Patients were evaluated before and 1, 4, and 12 weeks after surgery. Respiratory function, grip strength, and knee extension strength, as well as the results of timed up and go, 6-minute walk, and cardiopulmonary exercise tests, were evaluated using the 36-item short-form health survey. Longitudinal changes in physical performance and QOL were analyzed, as was the relationship between the change in physical function and QOL. **RESULTS:** The physical and social aspects of QOL significantly decreased at week 4 post-surgery, but recovered to pre-surgical levels by week 12. In contrast, physical (non-respiratory) function recovered to pre-surgical levels by week 4. There was no correlation between the percentages of change in QOL and those related to physical function. **CONCLUSION:** Our preliminary study highlights the fact that early recovery of physical function is possible after VATS, but does not necessarily correlate with early QOL recovery. It is therefore necessary to perform perioperative interventions to promptly restore QOL after surgery.

[Relationships Between Smoking Status and Psychological Distress, Optimism, and Health Environment Perceptions at Time of Diagnosis of Actual or Suspected Lung Cancer.](#)
Choi SH1, Chan RR, Lehto RH. Cancer Nurs. 2018 Mar 13. doi: 10.1097/NCC.0000000000000579. [Epub ahead of print]
BACKGROUND: While much research and practice resources have addressed smoking cessation among cancer patients, less emphasis has been placed on personal psychological and environment factors associated with smoking at the time of diagnosis. **OBJECTIVE:** The aim of this study was to examine differences in psychological distress, optimism, and perceptions of the health environment/illness experience based on smoking status in patients with current, former, and no smoking history with newly diagnosed suspected or actual lung cancer. **METHODS:** Data were derived from a descriptive study of 52 patients (34 men and 18 women aged 37-83 years) undergoing diagnostic evaluation for actual or suspected lung cancer. Descriptive statistics were used to characterize data. Analysis of variance, χ, and Spearman correlation tests were used to determine relationships among main study variables (smoking status, anxiety, worry, perceived cognitive functioning, optimistic outlook, health environment/illness experience perceptions). **RESULTS:** Current smoking status was associated with higher psychological distress (anxiety and worry) among patients facing a new suspected or actual cancer diagnosis. **CONCLUSIONS:** The study was able to provide important information relative to smoking status and psychological distress at the time of diagnosis of suspected or actual lung cancer. Findings demonstrate needs for assessment and targeted interventions to reduce psychological distress and to promote long-term adaptation in patients smoking at time of diagnosis. **IMPLICATIONS FOR PRACTICE:** Nurses are

positioned to provide support and resources for cancer patients. It is critical that smoking cessation interventions also address nicotine craving, emotion regulation, and adaptive coping skills.

[Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer.](#) Bar-Lev Schleider L1, Mechoulam R2, Lederman V3, Hilou M3, Lencovsky O4, Betzalel O3, Shbiro L4, Novack V5. Eur J Intern Med. 2018 Mar;49:37-43. doi: 10.1016/j.ejim.2018.01.023.

BACKGROUND: Cancer is a major public health problem as the leading cause of death. Palliative treatment aimed to alleviate pain and nausea in patients with advanced disease is a cornerstone of oncology. In 2007, the Israeli Ministry of Health began providing approvals for medical cannabis for the palliation of cancer symptoms. The aim of this study is to characterize the epidemiology of cancer patients receiving medical cannabis treatment and describe the safety and efficacy of this therapy. **METHODS:** We analyzed the data routinely collected as part of the treatment program of 2970 cancer patients treated with medical cannabis between 2015 and 2017. **RESULTS:** The average age was 59.5 ± 16.3 years, 54.6% women and 26.7% of the patients reported previous experience with cannabis. The most frequent types of cancer were: breast (20.7%), lung (13.6%), pancreatic (8.1%) and colorectal (7.9%) with 51.2% being at stage 4. The main symptoms requiring therapy were: sleep problems (78.4%), pain (77.7%, median intensity 8/10), weakness (72.7%), nausea (64.6%) and lack of appetite (48.9%). After six months of follow up, 902 patients (24.9%) died and 682 (18.8%) stopped the treatment. Of the remaining, 1211 (60.6%) responded; 95.9% reported an improvement in their condition, 45 patients (3.7%) reported no change and four patients (0.3%) reported deterioration in their medical condition. **CONCLUSIONS:** Cannabis as a palliative treatment for cancer patients seems to be well tolerated, effective and safe option to help patients cope with the malignancy related symptoms.

[The effect of nabilone on appetite, nutritional status, and quality of life in lung cancer patients: a randomized, double-blind clinical trial.](#) Turcott JG1, Del Rocío Guillen Núñez M2, Flores-Estrada D1, Oñate-Ocaña LF3, Zatarain-Barrón ZL1, Barrón F1, Arrieta O4. Support Care Cancer. 2018 Mar 17. doi: 10.1007/s00520-018-4154-9. [Epub ahead of print]

BACKGROUND: Over one half of the patients diagnosed with advanced lung cancer experience anorexia. In addition to its high incidence, cancer-induced anorexia promotes the development of the anorexia-cachexia syndrome, which is related to poor clinical outcomes. Recently, drugs derived from cannabinoids, such as Nabilone, have been recognized for their appetite improvement properties; however, clinical trials to support their use in cancer patients are necessary. **METHODS:** This is a randomized, double-blind, placebo-controlled clinical trial to assess the effect of Nabilone vs. placebo on the appetite, nutritional status, and quality of life in patients diagnosed with advanced Non-small cell lung cancer (NSCLC) (NCT02802540). **RESULTS:** A total of 65 patients from the outpatient clinic at the National Institute of Cancer (INCan) were assessed for eligibility and 47 were randomized to receive Nabilone (0.5 mg/2 weeks followed by 1.0 mg/6 weeks) or placebo. After 8 weeks of treatment, patients who received Nabilone increased their caloric intake (342-kcal) and had a significantly higher intake of carbohydrates (64 g) compared to patients receiving placebo ($p = 0.040$). Quality of life also showed significant improvements in patients in the experimental arm of the trial, particularly in role functioning ($p = 0.030$), emotional functioning ($p = 0.018$), social functioning ($p = 0.036$), pain ($p = 0.06$), and insomnia ($p = 0.020$). No significant change in these scales was seen in the control group. **CONCLUSION:** Nabilone is an adequate and safe therapeutic option to aid in the treatment of patients diagnosed with anorexia. Larger trials are necessary in order to draw robust conclusions in regard to its efficacy in lung cancer patients.

[**Lung cancer and family-centered patient concerns.**](#) Feliciano J1, Becker B2, Shukla M2, Bodurtha J3. Support Care Cancer. 2018 Mar 21. doi: 10.1007/s00520-018-4159-4. [Epub ahead of print]

BACKGROUND: The risk factors, diagnosis, management, and outcomes for lung cancer (LC) are a family experience. Genetic and environmental factors interact to predispose certain groups to LC, including family member, and the family or caregiving unit experiences the disease course as an interdependent group. This qualitative study examined the concerns and preferences of LC patients about incorporating family in addressing their lung cancer experiences and cancer risks. **METHODS:** This project aims to identify concerns and preferences for addressing family history documentation, risk assessment, prevention, and follow-up issues for LC patients and their family. We held focus groups (FG) to discuss the format and timing of addressing these preferences and concerns. The qualitative data was analyzed using a grounded theory approach. **RESULTS:** 7 FG totaling 17 participants were conducted. The mean age was 64. All patients had advanced lung cancer. Participants included five males; nine African-Americans; three current, 11 former and three never smokers. Five participants had parents or grandparents with LC. Two had siblings with LC. Six themes were identified: (1) Varied journeys to LC diagnosis. (2) Mixed patient perceptions of cancer causation. (3) Limited documentation and utilization of family history. (4) Diverse attitudes toward smoking cessation. (5) A range of discussions about cancer risk, prevention, and screening. (6) Implications for implementation of family-centered cancer care and health promotion. **CONCLUSIONS:** The diagnosis of LC, its management, and outcomes occur in the family context. The diagnosis represents a potential teachable moment with opportunity to reduce the risk of LC development or improve early detection in a population at higher risk of developing lung cancer. Lung cancer patients are interested in discussing risk factors, prevention, and diagnosis of lung cancer for their relatives.

COMPLEMENTARY & ALTERNATIVE THERAPY

[**Lemongrass essential oil and citral inhibit Src/Stat3 activity and suppress the proliferation/survival of small-cell lung cancer cells, alone or in combination with chemotherapeutic agents.**](#)
Maruoka T1, Kitanaka A2, Kubota Y3, et al. Int J Oncol. 2018 Mar 13. doi: 10.3892/ijo.2018.4314. [Epub ahead of print]

Small-cell lung cancer (SCLC) is intractable due to its high propensity for relapse. Novel agents are thus needed for SCLC treatment. Lemongrass essential oil (LG-EO) and its major constituent, citral, have been reported to inhibit the proliferation and survival of several types of cancer cells. However, the precise mechanisms through which LG-EO and citral exert their effects on SCLC cells have not been fully elucidated. SCLC cells express Src and have high levels of Src-tyrosine kinase (Src-TK) activity. In most SCLC cell lines, constitutive phosphorylation of Stat3(Y705), which is essential for its activation, has been detected. Src-TK can phosphorylate Stat3(Y705), and activated Stat3 promotes the expression of the anti-apoptotic factors Bcl-xL and Mcl-1. In the present study, LG-EO and citral prevented Src-TK from phosphorylating Stat3(Y705), resulting in decreased Bcl-xL and Mcl-1 expression, in turn suppressing the proliferation/survival of SCLC cells. To confirm these findings, the wild-type-src gene was transfected into the LU135 SCLC cell line (LU135 wt-src), in which Src and activated phospho-Stat3(Y705) were overexpressed. The suppression of cell proliferation and the induction of apoptosis by treatment with LG-EO or citral were significantly attenuated in the LU135-wt-src cells compared with the control LU135-mock cells. The signal transducer and activator of transcription 3 (Stat3) signaling pathway is also associated with intrinsic drug resistance. LU135-wt-src cells were significantly resistant to conventional chemotherapeutic agents compared with LU135-mock cells. The combined effects of citral and each conventional chemotherapeutic agent on SCLC cells were also evaluated. The combination treatment exerted additive or more prominent effects on LU135-wt-src, LU165 and MN1112 cells, which are

relatively chemoresistant SCLC cells. These findings suggest that either LG-EO or citral, alone or in combination with chemotherapeutic agents, may be a novel therapeutic option for SCLC patients.

Ameliorative effects of Tai Chi on cancer-related fatigue: a meta-analysis of randomized controlled trials. Song S1, Yu J1, Ruan Y2, Liu X1, Xiu L1, Yue X3. Support Care Cancer. 2018 Mar 21. doi: 10.1007/s00520-018-4136-y. [Epub ahead of print]
PURPOSE: This meta-analysis investigated the effectiveness of Tai Chi on cancer-related fatigue (CRF). **METHODS:** Nine databases (PubMed, Web of Science, Ovid, the Cochrane Library, Embase, and four Chinese databases) were searched to identify randomized controlled trials (RCTs) that evaluated the effects of Tai Chi on CRF. The reference lists given in the identified RCTs were also reviewed to identify potentially relevant studies. **RESULTS:** Six RCTs involving 373 patients were included. The change in short- and long-term CRF (SCRF and LCRF, respectively) was calculated as the change in the mean score for CRF from baseline to the end of intervention period and to the end of post-intervention follow-up, respectively. Pooled results suggested that Tai Chi had a significant positive effect on standard mean difference (i.e., SCRF; SMD = - 0.54; $p < 0.0001$), but the impact on LCRF remained unclear. Subgroup analyses of SCRF indicated positive effects of Tai Chi among patients with breast (SMD = - 0.81; $p < 0.00001$) and lung cancer (SMD = - 0.50; $p = 0.002$), but not prostate cancer ($p = 0.98$). Tai Chi also had effects on SCRF that were superior to physical exercise and psychological support (SMD = - 0.49 and - 0.84, respectively; both $p < 0.05$). A longer intervention time (8-12 weeks) benefited SCRF more than a shorter time (SMD = - 1.08 and - 0.36, respectively; both $p < 0.05$). **CONCLUSION:** Tai Chi for more than 8 weeks has short-term ameliorative effects on CRF, especially among patients with breast and lung cancer. Its beneficial effects are superior to physical exercise and psychological support. It remains unclear whether there are long-term benefits, and further study is needed.

Structural characterization of a polysaccharide from the flower buds of Tussilago farfara, and its effect on proliferation and apoptosis of A549 human non-small lung cancer cell line. Qu H1, Yang W2, Li J3. Int J Biol Macromol. 2018 Mar 2;113:849-858. doi: 10.1016/j.ijbiomac.2018.03.005. [Epub ahead of print]
In present study, we purified a polysaccharide, TFPB1, from the flower buds of Tussilago farfara using DEAE-cellulose 52 anion-exchange and Sephacryl S-300 HR gel filtration chromatography. TFPB1 was a homogeneous polysaccharide with a molecular weight of 37.8kDa and composed of rhamnose, galacturonic acid, glucose, galactose, and arabinose, in a ratio of 13:13:1:7:12. Methylation and NMR results demonstrated that TFPB1 contained a rhamnogalacturonan I backbone consisting of a repeat disaccharide unit →4)-α-D-GalAp-(1→2)-α-L-Rhap-(1→, substituted by various type II arabinogalactan branches including terminal galactose, (1→3)-β-D-galactan and (1→5)-α-L-arabinan, attached to the O-4 of (1→2)-α-L-Rhap. TFPB1 was found to inhibit cell proliferation of A549 cells and induce cell apoptosis in vitro. Furthermore, TFPB1 downregulated the phosphorylation of Akt, and upregulated caspase-3, Fas, FasL, and Bax expression, but downregulated Bcl-2 expression. Therefore, TFPB1 exhibited anti-proliferative and anti-apoptotic effect partly depending on the suppression of Akt signaling pathway. These findings provided us a potential chemotherapeutic strategy for the treatment of human non-small cell lung cancer.

Regulatory roles of OASL in lung cancer cell sensitivity to Actinidia chinensis Planch root extract (acRoots). Lv J1, Wang L2, Shen H3, Wang X4,5. Cell Biol Toxicol. 2018 Mar 5. doi: 10.1007/s10565-018-9422-4. [Epub ahead of print]
Lung cancer is one of the most common malignancies worldwide. Actinidia chinensis Planch root extract (acRoots) was found to have the capacity of the anti-tumor, although the molecular mechanisms remain unclear. The present study aims to investigate the molecular mechanisms by which lung cancer cells sense

to inhibitory effects of acRoots with a special focus on immune-associated gene profiles. We firstly provide a preclinical evidence that acRoots can significantly inhibit lung cancer cell proliferation and apoptosis via the PI3K-OASL signal pathway. The heterogeneous alterations of immune-associated gene profiles of lung cancer cell types were measured after treatment with various doses of acRoots. The OASL gene was identified as the key regulator in molecular networks of acRoots-treated lung cancer cells and validated. The OASL gene plays an important role in the regulation of lung cancer cell sensitivity to acRoots, which modulated by the PI3K signal pathway. Thus, our data indicate that OASL can be one of the decisive regulators to maintain lung cancer cell susceptibility to acRoots and may be associated with the development of drug resistance. The regulation of OASL can be an alternative strategy to improve drug efficacy during cancer therapies.

[Naturopathic Oncology Care for Thoracic Cancers: A Practice Survey.](#) Seely D1,2, Ennis JK1,2, McDonell E1,2, Zhao L1,2. Integr Cancer Ther. 2018 Mar 1:1534735418759420. doi: 10.1177/1534735418759420. [Epub ahead of print]
BACKGROUND AND OBJECTIVES: There is a lack of information on therapies recommended by naturopathic doctors (NDs) for lung and gastroesophageal cancer care. Study objectives were to: (1) identify the most common interventions considered for use by NDs; (2) identify interventions NDs recommend to support key therapeutic goals; and (3) identify potential contraindications between integrative and conventional therapies. **METHODS:** Oncology Association of Naturopathic Physicians (OncANP) members (n = 351) were invited to complete an electronic survey. Respondents provided information on interventions considered for thoracic cancer pre- and postoperatively across 4 therapeutic domains (supplemental natural health products, physical, mental/emotional, and nutritional), therapeutic goals, and contraindications. This survey was part of the development of the Thoracic Perioperative Integrative Surgical Evaluation trial. **RESULTS:** Forty-four NDs completed the survey (12.5% response rate), all of whom were trained at accredited colleges in North America and the majority of whom were Fellows of the American Board of Naturopathic Oncology (FABNO) (56.8%). NDs identified significantly more interventions in the postoperative compared to preoperative setting. The most frequently identified interventions included modified citrus pectin, arnica, omega-3 fatty acids, vitamin D, probiotics, exercise, acupuncture, meditation, stress reduction, low glycemic index diet, and Mediterranean diet. Potential contraindications with conventional treatment (surgery, chemotherapy, radiotherapy) differed across natural health products. **CONCLUSIONS:** These findings highlight naturopathic interventions with a high level of use in thoracic cancer care, describe and characterize therapeutic goals and the interventions used to achieve these goals, and provide insight on how practice changes relative to conventional cancer treatment phase.

MISCELLANEOUS WORKS

[Survival among Lung Cancer Patients in the U.S. Military Health System: A Comparison with the SEER population.](#) Lin J1, Kamamia C2, Brown D3, Shao S2, McGlynn KA4, Nations JA2, Carter CA2, Shriver CD2, Zhu K2. Cancer Epidemiol Biomarkers Prev. 2018 Mar 12. pii: cebp.0822.2017. doi: 10.1158/1055-9965.EPI-17-0822. [Epub ahead of print]
BACKGROUND: The U.S. military health system (MHS) provides universal health care access to its beneficiaries. However, whether the universal access has translated into improved patient outcome is unknown. This study compared survival of non-small cell lung cancer (NSCLC) patients in the MHS with that in the U.S. general population. **METHODS:** The MHS data were obtained from The Department of Defense's (DoD) Automated Central Tumor Registry (ACTUR) and the U.S. population data were drawn from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. The study subjects were NSCLC patients diagnosed between January 1, 1987 and December 31, 2012 in

ACTUR and a sample of SEER patients who were matched to the ACTUR patients on age group, sex, race, and year of diagnosis group with a matching ratio of 1:4. Patients were followed through December 31, 2013. **RESULTS:** 16,257 NSCLC patients were identified from ACTUR and 65,028 matched patients from SEER. Compared with SEER patients, ACTUR patients had significantly better overall survival (Log Rank P<0.001). The better overall survival among the ACTUR patients remained after adjustment for potential confounders (HR=0.78, 95% CI=0.76 to 0.81). The survival advantage of the ACTUR patients was present regardless of cancer stage, grade, age group, sex or race.
CONCLUSIONS: The MHS's universal care and lung cancer care programs may have translated into improved survival among NSCLC patients. **IMPACT:** This study supports improved survival outcome among NSCLC patients with universal care access.

[Project Transform: engaging patient advocates to share their perspectives on improving research, treatment and policy.](#) Bridges JFP1,2, Janssen EM1, Ferris A3, Dy SM1,4. Curr Med Res Opin. 2018 Mar 9:1-8. doi: 10.1080/03007995.2018.1440199. [Epub ahead of print]
OBJECTIVE: Incorporating the patient perspective into lung cancer research, policy and treatment is becoming increasingly recognized as important. This project sought to create an engagement partnership with lung cancer patient advocates and to explore their views on transforming lung cancer healthcare systems, treatment and policy to be more patient centered. **METHODS:** A patient action committee (PAC) of patient advocates living with lung cancer was engaged through group meetings, in-person and phone interviews, and email correspondence. Group meetings (two 1 hour meetings, one 3 hour meeting) served to discuss engagement strategies and project goals, while individual interviews (n = 19) (30-75 minutes) provided in-depth exploration of individuals' perspectives. Meetings and interviews were recorded to identify priorities for addressing issues within lung cancer research, treatment and policy. PAC members corroborated the results through email and in-person meetings. **RESULTS:** PAC members identified three general objectives: (i) for healthcare systems, increasing access to care through accessible, coordinated and affordable care, (ii) for treatment, addressing patient needs in treatment and research through patient education, shared decisions and clinical trials, and (iii) for policy, shining a light on lung cancer through screening policies, public awareness and research funding. **CONCLUSION:** Patient advocates expressed their views that lung cancer is a neglected disease that is not highly prioritized in healthcare systems, treatment approaches and public perceptions. This project represents an integral step in developing an ongoing partnership between researchers and these advocates.

[Progress in the Treatment and Outcomes for Early-Stage Non-Small Cell Lung Cancer.](#) Shin JY1, Yoon JK2, Marwaha G2. Lung. 2018 Mar 17. doi: 10.1007/s00408-018-0110-1. [Epub ahead of print]
PURPOSE: The purpose of this study is to assess temporal trends in population-based treatment and survival rates in patients with early-stage non-small cell lung cancer (NSCLC). **METHODS:** Data were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Chi-square test, Kaplan-Meier method, and Cox regression models were employed in SPSS 23.0. **RESULTS:** Fifty-seven thousand and eighty-eight NSCLC patients with early-stage disease from 1988 to 2014 were identified. 6409 (11.2%) were diagnosed in 1988-1994, 5800 (10.2%) 1995-1999, 13,031 (22.8%) 2000-2004, 15,786 (27.7%) 2005-2009, and 16,062 (28.1%) 2010-2014. We observed a significant increase in the proportion of older patients, adenocarcinoma histology, and rate of wedge resection over the study period. The five-year overall survival (OS) for the entire cohort was 63.3%. Those undergoing resection without adjuvant therapy had the highest outcomes. Lobectomy was associated with better outcomes compared to wedge resection or pneumonectomy. A significant difference in five-year OS by year of diagnosis (1988-1994: 58.8% vs. 1995-1999: 60.6% vs. 2000-2004: 63.2% vs. 2005-2009: 66.1%; p < 0.001) was observed. This significant OS difference was also observed regardless of age, surgery type, and T stage, but also only in those with adenocarcinoma. On multivariable analysis, year of diagnosis, age, gender,

race, treatment and surgery type, histology, T stage, and tumor grade remained independent prognostic factors for OS. **CONCLUSIONS:** Overall survival for early-stage NSCLC has significantly improved over the recent decades despite an increasing proportion of older patients and those undergoing sublobar resection or SBRT. This finding may be limited to those with adenocarcinoma.

[Smoking-related health beliefs and smoking behavior in the National Lung Screening Trial.](#)
Kaufman AR1, Dwyer LA2, Land SR3, Klein WMP4, Park ER5. Addict Behav. 2018 Mar 14;84:27-32. doi: 10.1016/j.addbeh.2018.03.015. [Epub ahead of print]
Understanding the association between smoking-related health beliefs and smoking cessation in the context of lung screening is important for effective cessation treatment. The purpose of the current study is to explore how current smokers' self-reported smoking-related health cognitions (e.g., self-efficacy) and emotions (e.g., worry) are related to cessation. This study utilized longitudinal data from current smokers (age 55-74) in a sub-study of the National Lung Screening Trial (NLST; 2002-2006; N = 2738). Logistic regression analyses examined associations of cessation at last assessment with smoking-related health cognitions and emotions, demographics, and two-way interactions among smoking-related health cognition and emotion variables, gender, and age. Over 37% (n = 1028) of smokers had quit at their last assessment of smoking status. Simple logistic regressions showed the likelihood of quitting was greater among participants reporting higher perceived severity of smoking-related diseases (OR = 1.17, p = .04), greater self-efficacy for quitting (OR = 1.32, p < .001), and fewer perceived barriers to quitting (OR = 0.82, p = .01). Likelihood of quitting was lower among non-Hispanic Black participants (versus non-Hispanic White participants) (OR = 0.68, p = .04) and higher among older participants (OR = 1.03, p = .002). Multiple logistic regression showed that participants reporting greater self-efficacy for quitting (B = 0.09, p = .05), fewer perceived barriers to quitting (B = -0.22, p = .01), and who were older (B = 0.03, p < .01) were more likely to quit smoking. These results suggest that, among heavy smokers undergoing lung screening, smoking-related health cognitions and emotions are associated with smoking cessation. These health beliefs must be considered an integral component of cessation in screening settings.

[Clinical Features and Management of Acquired Resistance to PD-1 Axis Inhibitors in Twenty-Six Patients with Advanced Non-Small Cell Lung Cancer.](#) Gettinger SN1, Wurtz A2, Goldberg SB2, et al. J Thorac Oncol. 2018 Mar 22. pii: S1556-0864(18)30210-7. doi: 10.1016/j.jtho.2018.03.008. [Epub ahead of print]
INTRODUCTION: With expanding indications for PD-1 axis inhibitors in non-small cell lung cancer (NSCLC), acquired resistance (AR) to these therapies is increasingly being encountered. We sought to characterize clinical patterns of AR to PD-1 axis inhibitors in patients with advanced NSCLC, and evaluate subsequent outcome and management strategies for such patients. **METHODS:** Patients with NSCLC who developed AR to PD-1 axis inhibitor therapy initiated between December 2009 and February 2016 at one institution were identified and examined by clinical and radiographic features. AR was defined as progressive disease after initial response by either RECIST v1.1 or immune-related response criteria. **RESULTS:** Twenty-six patients with AR to PD-1 axis inhibitor therapy were identified and evaluated. Median time to AR was 313 days; 2-year survival rate from AR was 70% (95%CI, 0.53-0.92). Twenty patients (77%) experienced AR in LNs, including eleven patients with LN-only progression. Twenty-three (88%) patients had recurrence limited to one (54%) or two (35%) sites of disease. Fourteen patients (54%) continued PD-1 axis inhibitor therapy beyond progression. Three patients were re-challenged with same PD-1 axis inhibitor after holiday from and progression off therapy, two again responded. Fifteen patients (58%) received local therapy to site(s) of AR, eleven continued respective PD-1 axis inhibitor after local therapy. Two-year survival rate from AR among these 15 patients was 92% (95%CI, 0.77-1). **CONCLUSION:** Acquired resistance to PD-1 axis inhibitors is often limited to one or two sites, when local therapy and continuation of PD-1 axis inhibitor therapy can result

in prolonged benefit. Lymph node metastases appear to be particularly susceptible sites to AR. When progression of disease following response occurs after holiday from PD-1 axis inhibitor, re-challenge can again lead to tumor regression.

Underutilization and disparities in access to EGFR testing among Medicare patients with lung cancer from 2010 - 2013. Lynch JA1,2, Berse B3,4, Rabb M5, Mosquin P5, Chew R5, West SL5, Coomer N5, Becker D6,7, Kautter J3. BMC Cancer. 2018 Mar 20;18(1):306. doi: 10.1186/s12885-018-4190-3.

BACKGROUND: Tumor testing for mutations in the epidermal growth factor receptor (EGFR) gene is indicated for all newly diagnosed, metastatic lung cancer patients, who may be candidates for first-line treatment with an EGFR tyrosine kinase inhibitor. Few studies have analyzed population-level testing. **METHODS:** We identified clinical, demographic, and regional predictors of EGFR & KRAS testing among Medicare beneficiaries with a new diagnosis of lung cancer in 2011-2013 claims. The outcome variable was whether the patient underwent molecular, EGFR and KRAS testing. Independent variables included: patient demographics, Medicaid status, clinical characteristics, and region where the patient lived. We performed multivariate logistic regression to identify factors that predicted testing. **RESULTS:** From 2011 to 2013, there was a 19.7% increase in the rate of EGFR testing. Patient zip code had the greatest impact on odds to undergo testing; for example, patients who lived in the Boston, Massachusetts hospital referral region were the most likely to be tested (odds ratio (OR) of 4.94, with a 95% confidence interval (CI) of 1.67-14.62). Patient demographics also impacted odds to be tested. Asian/Pacific Islanders were most likely to be tested (OR 1.63, CI 1.53-1.79). Minorities and Medicaid patients were less likely to be tested. Medicaid recipients had an OR of 0.74 (CI 0.72-0.77). Hispanics and Blacks were also less likely to be tested (OR 0.97, CI 0.78-0.99 and 0.95, CI 0.92-0.99), respectively. Clinical procedures were also correlated with testing. Patients who underwent transcatheter biopsies were 2.54 times more likely to be tested (CI 2.49-2.60) than those who did not undergo this type of biopsy. **CONCLUSIONS:** Despite an overall increase in EGFR testing, there is widespread underutilization of guideline-recommended testing. We observed racial, income, and regional disparities in testing. Precision medicine has increased the complexity of cancer diagnosis and treatment. Targeted interventions and clinical decision support tools are needed to ensure that all patients are benefitting from advances in precision medicine. Without such interventions, precision medicine may exacerbate racial disparities in cancer care and health outcomes.

Time-to-Treatment-Failure and Related Outcomes among 1000+ Advanced Non-Small Cell Lung Cancer Patients: Comparisons Between Older Versus Younger Patients. Gajra A1, Zemla TJ2, Jatoi A2, et al. J Thorac Oncol. 2018 Mar 30. pii: S1556-0864(18)30254-5. doi: 10.1016/j.jtho.2018.03.020. [Epub ahead of print]

BACKGROUND: Time-to-treatment-failure (TTF) is the interval from chemotherapy initiation to premature discontinuation. We evaluated TTF based on age. **METHODS:** Pooled analyses were conducted with, first-line chemotherapy trials for advanced non-small cell lung cancer (CALGB 9730, 30203, and 30801). Comparisons -- with age 65+ and 70+ years -- were performed for TTF (primary endpoint), reasons for early chemotherapy cessation, grade 3+ adverse events, and overall survival. **RESULTS:** Among 1006 patients, 460 (46%) were 65+ years of age. 145 older patients (32% of this age cohort) completed all six, planned chemotherapy cycles, as did 170 (32%) younger patients. Median TTF was 2.9 months (95% confidence interval (CI) = (2.7, 3.2)) in older and 3 months (95% CI= (2.9, 3.5)) in younger patients; adjustment for performance status and stratification by chemotherapy by trial yielded no statistically significant age-based difference in TTF. However, reasons for early chemotherapy cessation differed between age groups (multivariate p = 0.004). Older patients were less likely to discontinue from cancer progression (41% versus 55%) and more likely from toxicity or patient choice (16% and 15%,

respectively) compared to younger patients (13% and 6%, respectively). Older patients were more likely to experience grade 3+ adverse events (86% versus 79%) with no statistically significant difference in survival. An age cut point of 70+ showed no difference in TTF, a lower trend of early cessation due to cancer progression, and somewhat shorter older patient survival. **CONCLUSION:** TTF was comparable between older and younger patients; but different, age-based, and potentially modifiable reasons account for it.

Cancer survival among Alaska Native people. Nash SH1, Meisner ALW2, Zimpelman GL1, Barry M2,3, Wiggins CL2,4. Cancer. 2018 Mar 26. doi: 10.1002/cncr.31350. [Epub ahead of print]
BACKGROUND: Recent cancer survival trends among American Indian and Alaska Native (AN) people are not well understood; survival has not been reported among AN people since 2001. **METHODS:** This study examined cause-specific survival among AN cancer patients for lung, colorectal, female breast, prostate, and kidney cancers. It evaluated whether survival differed between cancers diagnosed in 1992-2002 (the earlier period) and cancers diagnosed in 2003-2013 (the later period) and by the age at diagnosis (<65 vs ≥65 years), stage at diagnosis (local or regional/distant/unknown), and sex. Kaplan-Meier and Cox proportional hazards models were used to estimate univariate and multivariate-adjusted cause-specific survival for each cancer. **RESULTS:** An improvement was observed in 5-year survival over time from lung cancer (hazard ratio [HR] for the later period vs the earlier period, 0.83; 95% confidence interval [CI], 0.72-0.97), and a marginally nonsignificant improvement was observed for colorectal cancer (HR, 0.81; 95% CI, 0.66-1.01). Site-specific differences in survival were observed by age and stage at diagnosis. **CONCLUSIONS:** This study presents the first data on cancer survival among AN people in almost 2 decades. During this time, AN people have experienced improvements in survival from lung and colorectal cancers. The reasons for these improvements may include increased access to care (including screening) as well as improvements in treatment. Improving cancer survival should be a priority for reducing the burden of cancer among AN people and eliminating cancer disparities. Cancer 2018. © 2018 American Cancer Society.