Caring Ambassadors Lung Cancer Program
Literature Review, June 2018

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Circulating cotinine concentrations and lung cancer risk in the Lung Cancer Cohort Consortium (LC3). Larose TL1,2, Guida F1, Fanidi A1,3, et al. Int J Epidemiol. 2018 Jun 12. doi: 10.1093/ije/dyy100. [Epub ahead of print]
BACKGROUND: Self-reported smoking is the principal measure used to assess lung cancer risk in epidemiological studies. We evaluated if circulating cotinine-a nicotine metabolite and biomarker of recent tobacco exposure-provides additional information on lung cancer risk. **METHODS:** The study was conducted in the Lung Cancer Cohort Consortium (LC3) involving 20 prospective cohort studies. Pre-diagnostic serum cotinine concentrations were measured in one laboratory on 5364 lung cancer cases and 5364 individually matched controls. We used conditional logistic regression to evaluate the association between circulating cotinine and lung cancer, and assessed if cotinine provided additional risk-discriminative information compared with self-reported smoking (smoking status, smoking intensity, smoking duration), using receiver-operating characteristic (ROC) curve analysis. **RESULTS:** We observed a strong positive association between cotinine and lung cancer risk for current smokers [odds ratio (OR) per 500 nmol/L increase in cotinine (OR500): 1.39, 95% confidence interval (CI): 1.32-1.47]. Cotinine concentrations consistent with active smoking ($\geq$115 nmol/L) were common in former smokers (cases: 14.6%; controls: 9.2%) and rare in never smokers (cases: 2.7%; controls: 0.8%). Former and never smokers with cotinine concentrations indicative of active smoking ($\geq$115 nmol/L) also showed increased lung cancer risk. For current smokers, the risk-discriminative performance of cotinine combined with self-reported smoking (AUCintegrated: 0.69, 95% CI: 0.68-0.71) yielded a small improvement over self-reported smoking alone (AUCsmoke: 0.66, 95% CI: 0.64-0.68) (P = 1.5x10-9). **CONCLUSIONS:** Circulating cotinine concentrations are consistently associated with lung cancer risk for current smokers and provide additional risk-discriminative information compared with self-report smoking alone.

Assessing Therapeutic Efficacy of MEK Inhibition in a KRAS G12C-Driven Mouse Model of Lung Cancer. Li S1, Liu S2, Deng J3, et al. Clin Cancer Res. 2018 Jun 26. pii: clincanres.3438.2017. doi: 10.1158/1078-0432.CCR-17-3438. [Epub ahead of print]

PURPOSE: Despite the challenge to directly target mutant KRAS due to its high GTP affinity, some agents are under development against downstream signaling pathways, such as MEK inhibitors. However, it remains controversial whether MEK inhibitors can boost current chemotherapy in KRAS-mutant lung tumors in clinic. Considering the genomic heterogeneity among lung cancer patients, it is valuable to test potential therapeutics in KRAS-mutation driven mouse models. **EXPERIMENTAL DESIGN:** We first compared the pERK1/2 level in lung cancer samples with different KRAS substitutions and generated a new genetically engineered mouse model whose tumor was driven by KRAS G12C, the most common KRAS mutation in lung cancer. Next, we evaluated the efficacy of selumetinib or its combination with chemotherapy, in KRAS G12C tumors compared to KRAS G12D tumors. Moreover, we generated KRAS G12C/p53 R270H model to explore the role of a dominant negative p53 mutation detected in patients in responsiveness to MEK inhibition. **RESULTS:** We determined higher pERK1/2 in KRAS G12C lung tumors compared to KRAS G12D. Using mouse models, we further identified that KRAS G12C tumors are significantly more sensitive to selumetinib compared with Kras G12D tumors. MEK inhibition significantly increased chemotherapeutic efficacy and progression-free survival of KRAS G12C mice. Interestingly, p53 co-mutation rendered KRAS G12C lung tumors less sensitive to combination treatment with selumetinib and chemotherapy. **CONCLUSIONS:** Our data demonstrate that unique KRAS mutations and concurrent mutations in tumor-suppressor genes are important factors for lung tumor responses to MEK inhibitor. Our preclinical study supports further clinical evaluation of combined MEK inhibition and chemotherapy for lung cancer patients harboring KRAS G12C and wildtype p53 status.

[A Novel Long Noncoding RNA (lncRNA), LL22NC03-N64E9.1, Promotes the Proliferation of Lung Cancer Cells and is a Potential Prognostic Molecular Biomarker for Lung Cancer.](#) Jing H1, Qu X1, Liu L2, Xia H1. Med Sci Monit. 2018 Jun 23;24:4317-4323. doi: 10.12659/MSM.908359.

BACKGROUND: The aim of this study was to investigate the expression of a novel long noncoding RNA (lncRNA), LL22NC03-N64E9.1, and its effect on the phenotype of lung cancer cells and tissues using The Cancer Genome Atlas (TCGA) RNA sequencing data and other publicly available profiling data. **MATERIAL AND METHODS:** The lung cancer dataset GSE30219 was downloaded from the Gene Expression Omnibus (GEO) repository. Differentially expressed lncRNA, LL22NC03-N64E9.1, in 48 lung cancer tissue samples and adjacent normal lung tissues, normal lung cell lines BEAS-2B and A549, and lung cancer cell lines, H1703, and H292, were detected by quantitative reverse transcription polymerase chain reaction (PCR) (qRT-PCR). Interference efficiency was performed using small interfering RNA (siRNA). Tumor levels of lncRNA, LL22NC03-N64E9.1, and clinicopathological parameters were statistically analyzed. **RESULTS:** Analysis of the GSE30219 test cohort showed that lncRNA, LL22NC03-N64E9.1 expression was significantly increased in lung cancer. In clinical tissue samples, the level of LL22NC03-N64E9.1 in patients with lung cancer was significantly increased compared with adjacent normal lung tissues (P<0.001). The level of LL22NC03-N64E9.1 in patients with lung cancer was significantly correlated with tumor size and TNM stage (P<0.05), but not with age, sex and the presence of lymph node metastasis (P>0.05). In the H292 cells, following knockdown of LL22NC03-N64E9.1, cell proliferation and cloning were reduced. **CONCLUSIONS:** Expression of lncRNA, LL22NC03-N64E9.1, promoted proliferation of lung cancer cells in vitro, was highly expressed in lung cancer tissues and was associated with increased overall survival (OS), tumor size, and tumor stage in patients with lung cancer.

[Androgen Receptor and Ki67 Expression and Survival Outcomes in Non-small Cell Lung Cancer.](#) Grant L1, Banerji S1,2,3, Murphy L1,2,3, ET AL. Horm Cancer. 2018 Jun 18. doi: 10.1007/s12672-018-0336-7. [Epub ahead of print]

Lung cancer is the most common cause of cancer-related deaths worldwide with non-small cell lung cancer (NSCLC) making up most of these cases. Males have poorer overall survival compared to women following a lung cancer diagnosis. Many studies have focused on the effects of estrogen to explain higher survival rates among women, but few have looked at the effects of androgens. We describe the expression of the androgen receptor (AR) and Ki67 in lung cancer specimens in the Manitoba Tumor Bank (MTB) and correlate these factors with patient outcome. Using the MTB, we performed immunohistochemistry on lung cancer tissue to determine expression of the AR and Ki67. These were then correlated with patient outcome. Of the 136 cases, 55% were female and 55% were adenocarcinoma. AR expression was not independently associated with outcome. Ki67 was associated with a significantly higher hazard ratio for death and recurrence (HR 2.19, 95% CI 1.30-3.70; HR 1.92, 95% CI 1.07-3.46, respectively). AR expression modified the effect of Ki67 on outcome, such that when both were expressed, there was no association with recurrence or survival (HR 2.39, 95% CI 1.31-4.36 for AR- Ki67+ vs HR 1.54, 95% CI 0.44-5.37 for AR+ Ki67+). Ki67 was associated with poorer outcomes alone. AR status alone was not associated with outcome. Although the mechanism remains unclear, AR status seems to negate the association of a high Ki67 and poor outcome.

[Identification of recurrence-associated microRNAs in stage I lung adenocarcinoma.](#) Sim J1, Kim Y2, Kim H2, Shin SJ2, Kim DH3, Paik SS2, Jang K2.

Medicine (Baltimore). 2018 Jun;97(25):e10996. doi: 10.1097/MD.0000000000010996.

Lung cancer is the most common cause of cancer-associated death worldwide. Postoperative relapse and subsequent metastasis result in a high mortality rate, even in early stage lung cancer. MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression at the post-transcriptional level and are frequently dysregulated in various cancers. The aim of this study was to identify recurrence-associated miRNAs in early stage lung cancer. To screen for differentially expressed miRNAs related to postoperative recurrence, miRNA microarray data derived from stage I lung adenocarcinoma formalin-fixed paraffin-embedded (FFPE) tissue samples (n=6) and publically available the Cancer Genome Atlas (TCGA) data were analyzed. An independent sample (n=29) was used to validate candidate miRNAs by quantitative real-time polymerase chain reaction (qRT-PCR). In miRNA expression profiling, we identified 60 significantly dysregulated miRNAs in the relapsed group. Additionally, 20 dysregulated miRNAs were found using TCGA data set. Three miRNAs (let-7g-5p, miR-143-3p, and miR-374a-5p) were associated with postoperative recurrence in both microarray and TCGA data sets. All 3 candidate miRNAs were validated in the independent cohort of stage I adenocarcinoma by qRT-PCR. We discovered 3 recurrence-associated miRNAs of stage I lung adenocarcinoma samples using FFPE tissue, which showed possible clinical utility as biomarkers predicting recurrence after curative surgery. Further investigation of the functional properties of these miRNAs is needed.

[Serum 25-hydroxyvitamin D levels and risk of lung cancer and histologic types: a Mendelian randomisation analysis of the HUNT study.](#) Sun YQ1, Brumpton BM2,3,4, Bonilla C4, Lewis SJ4, Burgess S5,6, Skorpen F1, Chen Y7, Nilsen TIL8,9, Romundstad PR8, Mai XM8. Eur Respir J. 2018 Jun 7;51(6). pii: 1800329. doi: 10.1183/13993003.00329-2018. Print 2018 Jun.

We aimed to investigate potential causal associations between serum 25-hydroxyvitamin D (25(OH)D) levels and incidence of lung cancer overall and histologic types.We performed a Mendelian randomisation analysis using a prospective cohort study in Norway, including 54 580 individuals and 676 incident lung cancer cases. A 25(OH)D allele score was generated based on the vitamin D-increasing alleles rs2282679, rs12785878 and rs10741657. Hazard ratios with 95% confidence intervals for incidence of lung cancer and histologic types were estimated in relation to the allele score. The inverse-variance weighted method using summarised data of individual single nucleotide polymorphisms was applied to calculate the Mendelian randomisation estimates.The allele score accounted for 3.4% of the variation in serum

25(OH)D levels. There was no association between the allele score and lung cancer incidence overall, with HR 0.99 (95% CI 0.93-1.06) per allele score. A 25 nmol·L-1 increase in genetically determined 25(OH)D level was not associated with the incidence of lung cancer overall (Mendelian randomisation estimate HR 0.96, 95% CI 0.54-1.69) or any histologic type.Mendelian randomisation analysis did not suggest a causal association between 25(OH)D levels and risk of lung cancer overall or histologic types in this population-based cohort study.

[A Prospective Study of Dietary Polyunsaturated Fatty Acids Intake and Lung Cancer Risk.](#) Luu HN1,2, Cai H1, Murff HJ1,3, et al. Int J Cancer. 2018 Jun 15. doi: 10.1002/ijc.31608. [Epub ahead of print]
Animal studies have shown that polyunsaturated fatty acids (PUFAs) have antineoplastic and anti-inflammatory properties. Results from epidemiologic studies on specific types of PUFAs for lung cancer risk, however, are inconclusive. We prospectively evaluated the association of specific types of dietary PUFA intakes and lung cancer risk in two population-based cohort studies, the Shanghai Women's Health Study (SWHS) and Shanghai Men's Health Study (SMHS) with a total of 121,970 study participants (i.e., 65,076 women and 56,894 men). Dietary fatty acid intakes were derived from data collected at the baseline using validated food frequency questionnaires (FFQs). Cox proportional hazards model was performed to assess the association between PUFAs and lung cancer risk. Total, saturated and monounsaturated fatty acid intakes were not significantly associated with lung cancer risk. Total PUFAs intake was inversely associated with lung cancer risk [HRs and respective 95% CIs for quintiles 2 to 5 versus quintile 1: 0.84 (0.71-0.98), 0.97 (0.83-1.13), 0.86 (0.74-1.01) and 0.85 (0.73-1.00), Ptrend =0.11]. However, DHA intake was positively associated with lung cancer risk [HRs and 95% CIs: 1.01 (0.86-1.19), 1.20 (1.03-1.41), 1.21 (1.03-1.42) and 1.24 (1.05-1.47), Ptrend =0.001]. The ratio of n-6 PUFAs to n-3 PUFAs (i.e., 7:1) was inversely associated with lung cancer risk, particularly among never-smokers and adenocarcinoma patients. Total PUFAs and the ratio between n-6 PUFAs and n-3 PUFAs were inversely associated with lung cancer risk. Our current study highlights an important public health impact of PUFA intakes toward intervention/prevention programs of lung cancer. This article is protected by copyright. All rights reserved.

[Tumor-Targeted Nanoparticles Deliver a Vitamin D-Based Drug Payload for the Treatment of EGFR Tyrosine Kinase Inhibitor-Resistant Lung Cancer.](#) Liu C1, Shaurova T2, Shoemaker S2, Petkovich M3, Hershberger PA2, Wu Y1. Mol Pharm. 2018 Jun 26. doi: 10.1021/acs.molpharmaceut.8b00307. [Epub ahead of print]
Mutation in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR) gene drives the development of lung cancer. EGFR tyrosine kinase inhibitors (EGFR TKIs), including erlotinib and afatinib, are initially effective in treating EGFR mutant nonsmall cell lung cancer (NSCLC). However, drug resistance quickly develops due to several mechanisms, including induction of the epithelial-mesenchymal transition (EMT). No effective therapies are currently available for patients who develop EMT-associated EGFR TKI resistance. 1,25-Dihydroxyvitamin D3 (1,25D3) promotes epithelial differentiation and inhibits growth of NSCLC cells. 1,25D3 thus represents a promising agent for the treatment of EMT-associated EGFR TKI resistance. However, 1,25D3 induces the expression of 24-hydroxylase (24OHase), which decreases 1,25D3 activity. CTA091, a potent and selective 24OHase inhibitor, has been developed to attenuate this adverse effect. CTA091 also suppresses renal 24OHase activity and so may promote hypercalcemia. To exploit favorable effects of 1,25D3 plus CTA091 in tumor cells while avoiding problematic systemic effects of 24OHase inhibition, we developed EGFR-targeted, liposomal nanoparticles (EGFR-LP) to offer tumor-targeted co-delivery of 1,25D3 and CTA091. We then established an EMT-associated model of EGFR TKI resistance, and showed that such nanoparticles improved cellular uptake of 1,25D3 and CTA091, drove pro-epithelial signaling by

upregulating E-cadherin (CDH1), and significantly inhibited the growth of EGFR TKI resistant cells. Our results demonstrated that the delivery of vitamin D-based drug payloads via tumor-targeted EGFR-LP has promise as a new therapy for EFGR TKI resistant lung cancer. Future studies will focus on in vivo evaluation of biological activity, therapeutic benefits, and systemic toxicity prior to clinical translation.

SCREENING, DIAGNOSIS AND STAGING

Feasibility and Safety of CT-guided Intrathoracic and Bone Re-biopsy for Non-small Cell Lung Cancer.
Matsumoto T1, Hasebe T1, Baba Y2, ET AL. Anticancer Res. 2018 Jun;38(6):3587-3592. doi: 10.21873/anticanres.12632.
AIM: This study aimed to retrospectively determine the feasibility and safety of computed tomography (CT)-guided intrathoracic and bone re-biopsy for patients with non-small cell lung cancer (NSCLC). **MATERIALS AND METHODS:** Seventeen patients underwent CT-guided intrathoracic or bone re-biopsy for the determination of epidermal growth factor receptor (EGFR) T790M mutation and/or programmed cell death-ligand 1 (PD-L1) expression. The characteristics of each lesion, success rate of analyses, and complications were investigated. **RESULTS:** Specimens from 16 out of the 17 patients were adequate for evaluation of EGFR T790M mutation and/or PD-L1 expression. The mean diameter of the lesions was 40 mm, the mean procedural time was 24 minutes, and the median number of punctures was 2. There were no significant differences in lesion characteristics and success rates between CT-guided intrathoracic and bone re-biopsies. No serious complications occurred. **CONCLUSION:** Both CT-guided intrathoracic and bone re-biopsies for patients with NSCLC were feasible and safe.

IASLC Statement Paper: Liquid Biopsy for Advanced Non-Small Cell Lung Cancer (NSCLC).
Rolfo C1, Mack PC2, Scagliotti GV3, et al. J Thorac Oncol. 2018 Jun 6. pii: S1556-0864(18)30680-4. doi: 10.1016/j.jtho.2018.05.030. [Epub ahead of print]
The isolation of circulating cell-free tumoral DNA (ctDNA) in plasma and its subsequent molecular analysis is a powerful tool that can help improve clinical outcomes across multiple cancer types, including non-small cell lung cancer (NSCLC). Assays of this nature that utilize blood as opposed to tumor samples are frequently referred to as liquid biopsies. An increasing number of new platforms have been recently developed that improve not only the fidelity of the molecular analysis of the liquid biopsy but also the number of tests performed on a single specimen. ctDNA assays for detection of both epidermal growth factor receptor (EGFR) sensitizing and resistance mutations have already entered clinical practice and many other molecular tests - such as resistance mutations for ALK rearrangements - are likely to do so in the near future. Due to an abundance of new evidence, an appraisal was warranted to review strengths and weaknesses, to describe what is already in clinical practice and what has yet to be implemented, and to highlight areas in need of further investigation. A multidisciplinary panel of experts in the field of thoracic oncology with interest and expertise in liquid biopsy and molecular pathology, was convened by the International Association for the Study of Lung Cancer (IASLC) to evaluate current available evidence with the aim of producing a set of recommendations for the use of liquid biopsy for molecular analysis in in guiding the clinical management of advanced NSCLC patients as well as identifying unmet needs.

Invasive Mediastinal Staging for Lung Cancer by Society of Thoracic Surgeons Database Participants.
Krantz SB1, Howington JA2, Wood DE3, Kim KW4, Kosinski AS5, Cox ML5, Kim S5, Mulligan MS3, Farjah F3. Ann Thorac Surg. 2018 Jun 5. pii: S0003-4975(18)30742-2. doi: 10.1016/j.athoracsur.2018.05.012. [Epub ahead of print]
BACKGROUND: Prior studies suggest underutilization of invasive mediastinal staging for lung cancer. We hypothesized that Society of Thoracic Surgeons General Thoracic Surgery Database (STS-GTSD)

participants would have higher rates of invasive staging compared to previous reports. **METHODS:** We conducted a retrospective cohort study (2012-2016) of lung cancer patients staged by computed tomography and positron-emission tomography and first treated with an anatomic resection. We defined invasive staging by the use of mediastinoscopy, endosonography, and/or thoracoscopy. Standardized incidence ratios (SIRs) were used to compare participant-level rates of invasive staging, and Poisson regression was used to identify factors associated with invasive staging. **RESULTS:** Among 29,015 patients across 256 participating STS-GTSD sites, 34% (95% confidence interval [CI] 33-34%) underwent invasive staging. The overall rate of invasive staging did not change between 2012 and 2016 (p-trend=0.16). Increasing clinical stage and features suggestive of a central tumor were associated with invasive staging (p<0.001). Rates of invasive staging among patients with clinical stage ≥IB or features suggestive of a central tumor were 43% (95% CI 42-44%) and 52% (95% CI 50-54%), respectively. There was over 40-fold variation in rates of invasive staging across 251 centers contributing at least 10 cases (lowest SIR=0.08; highest SIR=3.26)-66 sites (26%) performed IMS less often than average and 77 sites (31%) performed invasive staging more often than average. **CONCLUSIONS:** STS-GTSD participants performed invasive mediastinal staging more frequently than prior reports, and yet only in a minority of patients. Rates of invasive mediastinal staging vary widely across STS-GTSD participants.

[Screening Patterns and Mortality Differences in Patients With Lung Cancer at an Urban Underserved Community.](#) Su CT1, Bhargava A2, Shah CD1, et al. Clin Lung Cancer. 2018 Jun 5. pii: S1525-7304(18)30139-6. doi: 10.1016/j.cllc.2018.05.019. [Epub ahead of print]
BACKGROUND: The landmark National Lung Screening Trial demonstrated significant reduction in lung cancer-related mortality. However, European lung cancer screening (LCS) trials have not confirmed such benefit. We examined LCS patterns and determined the impact of LCS-led diagnosis on the mortality of newly diagnosed patients with lung cancer in an underserved community. **PATIENTS AND METHODS:** Medical records of patients diagnosed with primary lung cancer in 2013 through 2016 (n = 855) were reviewed for primary care provider (PCP) status and LCS eligibility and completion, determined using United States Preventative Services Task Force guidelines. Univariate analyses of patient characteristics were conducted between LCS-eligible patients based on screening completion. Survival analyses were conducted using Kaplan-Meier and multivariate Cox regression. **RESULTS:** In 2013 through 2016, 175 patients with primary lung cancer had an established PCP and were eligible for LCS. Among them, 19% (33/175) completed screening prior to diagnosis. LCS completion was associated with younger age (P = .02), active smoking status (P < .01), earlier stage at time of diagnosis (P < .01), follow-up in-network cancer treatment (P = .03), and surgical management (P < .01). LCS-eligible patients who underwent screening had improved all-cause mortality compared with those not screened (P < .01). Multivariate regression showed surgery (hazard ratio, 0.31; P = .04) significantly affected mortality. **CONCLUSION:** To our knowledge, this is the first study to assess LCS patterns and mortality differences on patients with screen-detected lung cancer in an urban underserved setting since the inception of United States Preventative Services Task Force guidelines. Patients with a LCS-led diagnosis had improved mortality, likely owing to cancer detection at earlier stages with curative treatment, which echoes the finding of prospective trials.

[Circulating tumour DNA in EGFR-mutant non-small-cell lung cancer.](#) Cabanero M1,2, Tsao MS1,2. Curr Oncol. 2018 Jun;25(Suppl 1):S38-S44. doi: 10.3747/co.25.3761. Epub 2018 Jun 13.
The advent of targeted therapy in non-small-cell lung cancer (nsclc) has made the routine molecular diagnosis of EGFR mutations crucial for optimal patient management. Obtaining tumour tissue for biomarker testing, especially in the setting of re-biopsy, can present many challenges. A potential alternative source of tumour dna is circulating cell-free tumour-derived dna (ctdna). Although ctdna is present in low quantities in plasma, the convenience of sample acquisition and the increasing reliability of

detection methods make this approach a promising one. The various performance characteristics of both digital and nondigital platforms are still variable, and a standardized approach is needed that will make those platforms reliable clinical tools for the detection of EGFR sensitizing mutations and resistance mutations, including the T790M resistance mutation. Information derived from ctdna can be used to assess tumour burden, to identify genomic-based resistance mechanisms, and to track dynamic changes during therapy.

[The Contribution of Fluorine 18F-FDG PET/CT to Lung Cancer Diagnosis, Staging and Treatment Planning.](#) Budak E1, Çok G2, Akgün A3. Mol Imaging Radionucl Ther. 2018 Jun 7;27(2):73-80. doi: 10.4274/mirt.53315.
OBJECTIVE: Lung cancer is the most common cause of cancer-related death throughout the world, and the correct choice of treatment based on early diagnosis and staging increases the chance of survival. The present study aims to investigate the contribution of fluorine 18-fluorodeoxyglucose-positron emission tomography/computed tomography (18F-FDG PET/CT) to the management of lung cancer. **METHODS:** In this study, 50 patients who underwent 18F-FDG PET/CT for lung cancer diagnosis and staging between February 2012 and February 2014 were included. The maximum standardized uptake value (SUVmax) of the primary lung lesion along with other findings of 18F-FDG PET/CT and the results of histopathologic and conventional examinations were evaluated retrospectively. The mean survival time of patients was determined, and the findings were compared by using statistical methods. **RESULTS:** Histopathologic examinations revealed 51 lung cancers in 50 patients. The sensitivity, accuracy and positive predictive value of 18F-FDG PET/CT in detecting primary malignancy were 94%, 94%, 100%, respectively. Adenocarcinoma (n=23, 16.8±13.5) and squamous cell carcinoma (n=15, 17.9±5.6) did not differ significantly regarding their mean SUVmax values (p=0.2). A statistically significant positive correlation (r=0.4) was identified between tumor size and SUVmax value for 51 tumors (p=0.002). The 18F-FDG PET/CT result was true negative in nine, false positive in six, true positive in two, and false negative in four patients who underwent histopathologic evaluation of their lymph nodes. The 18F-FDG PET/CT changed treatment planning in 34% of the patients. No significant relationship was identified between SUVmax value of the tumor and patient survival in patients (p=0.118). **CONCLUSION:** The present study concluded that PET/CT was an efficient method in the diagnosis and staging of lung cancer since it provided useful information in addition to conventional methods. It was also observed that PET/CT scanning resulted in a change in therapeutic plans in the majority of patients. However, there was no statistically significant relationship between survival and the SUVmax of the primary mass.

[Prognostic impact of incisional or excisional biopsy of cervical lymph node metastases of solid tumors.](#) Shinohara S1, Takebayashi S1, Kikuchi M1, Michida T1, Hayashi K1, Yamamoto R1, Saida K1, Mizuno K1, Fujiwara K1, Naito Y1. Jpn J Clin Oncol. 2018 Jun 1;48(6):529-534. doi: 10.1093/jjco/hyy056.
OBJECTIVES: In performing an open biopsy of a neck mass, an incisional biopsy may increase the risk of cancer cell seeding and dissemination that, ultimately, worsens a patient's survival. The aim of this study was to compare the impact of incisional and excisional biopsies of cervical lymph node metastases of solid tumors on patients' survival. **METHODS:** A retrospective review was made of patients with cervical metastases of solid tumors who underwent an open biopsy for a diagnosis between 2005 and 2015. Sixty-four patients met the criteria out of 524 open biopsy cases undertaken during the period. Survival analyses were estimated from 33 cases whose initial symptoms were the presence of a neck mass, using two modes of biopsy: excisional and incisional. **RESULTS:** The 2-year overall survival rates in incisional and excisional biopsy groups were 65% and 43%, respectively, and 2-year disease-specific survival rates were 74% and 43%, respectively. The differences were not significant. For lung cancer or head and neck cancer subgroups, survival differences between incisional and excisional biopsy groups

were also not significant. **CONCLUSIONS:** A carefully targeted physical examination and performing a fine needle aspiration are essential to establish a diagnosis for the etiology of an unknown neck mass. In performing an open biopsy, the effect of an incisional biopsy on patients' survival was no worse than that of an excisional biopsy, despite the latter being theoretically preferable.

Current Status and Problems of T790M Detection, a Molecular Biomarker of Acquired Resistance to EGFR Tyrosine Kinase Inhibitors, with Liquid Biopsy and Re-biopsy. Komiya K1, Nakashima C1, Nakamura T1, et al. Anticancer Res. 2018 Jun;38(6):3559-3566. doi: 10.21873/anticanres.12628. **BACKGROUND/AIM:** The purpose of this study was to consider appropriate application of liquid and re-biopsy through analysis of current status in practice. **PATIENTS AND METHODS:** We performed a retrospective analysis of 22 patients with epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer who exhibited 1st/2nd generation EGFR-tyrosine kinase inhibitors resistance. The cobas® method was used to detect T790M with re-biopsy and the mutation-biased PCR and quenched probe method was used with liquid biopsy. **RESULTS:** T790M detection rate was 52% with re-biopsy and 58% with liquid biopsy. The concordance between tissue and plasma was 58%. One patient who was T790M-positive with liquid biopsy showed heterogeneity among metastatic lesions in terms of osimertinib efficacy, as revealed by T790M detection with re-biopsy. **CONCLUSION:** Liquid biopsy reflects the whole body, whereas re-biopsy is useful for spatial diagnosis. Considering these characteristics, a combination of liquid and re-biopsy contribute to enhanced treatment.

Initial results of a lung cancer screening demonstration project: a local program evaluation. Fabbrini AE1, Lillie SE, Partin MR, Fu SS, Clothier BA, Bangerter AK, Nelson DB, Doro EA, Bell BJ, Rice KL. Am J Manag Care. 2018 Jun;24(6):272-277. **OBJECTIVES:** To describe participation rates, results, and lessons learned from a lung cancer screening (LCS) demonstration project. **STUDY DESIGN:** Prospective observational study at 1 of 8 centers participating in a national Veterans Health Administration LCS demonstration project. **METHODS:** An electronic health record (EHR) algorithm and tobacco pack-year (TPY) information prompt identified patients potentially eligible for LCS. LCS invitation was planned to consist of shared decision-making materials, an invitation letter to call the LCS manager, a reminder letter, and an outreach phone call for nonresponders. The outreach call was subsequently dropped due to time constraints on the LCS manager. Lung nodules and incidental findings on LCS low-dose computed tomography (LDCT) were recorded in templated radiology reports and tracked with EHR notes. **RESULTS:** Of 6133 potentially eligible patients, we identified 1388 patients with eligible TPY information: 918 were invited for LCS and 178 (19%) completed LCS. LCS completion was more likely in patients in the mailing-plus-call outreach group (phase I) compared with the mail-only group (phase II) (22% vs 9%; P <.001). Among those completing an LDCT, 61% had lung nodules requiring follow-up: 43% of the nodules were less than 4 mm in diameter, 12 patients required further diagnostic evaluation, and 2 had lung malignancies. There were 179 incidental LDCT findings in 116 patients, and 20% were clinically significant. **CONCLUSIONS:** Important considerations in LCS are accurate identification of eligible patients, balancing invitation approaches with resource constraints, and establishing standardized methods for tracking numerous small lung nodules and incidental findings detected by LDCT.

Assessing the inter-observer variability of Computer-Aided Nodule Assessment and Risk Yield (CANARY) to characterize lung adenocarcinomas. Nakajima EC1, Frankland MP2, Johnson TF3, et al. PLoS One. 2018 Jun 1;13(6):e0198118. doi: 10.1371/journal.pone.0198118. eCollection 2018. Lung adenocarcinoma (ADC), the most common lung cancer type, is recognized increasingly as a disease spectrum. To guide individualized patient care, a non-invasive means of distinguishing indolent from aggressive ADC subtypes is needed urgently. Computer-Aided Nodule Assessment and Risk Yield

(CANARY) is a novel computed tomography (CT) tool that characterizes early ADCs by detecting nine distinct CT voxel classes, representing a spectrum of lepidic to invasive growth, within an ADC. CANARY characterization has been shown to correlate with ADC histology and patient outcomes. This study evaluated the inter-observer variability of CANARY analysis. Three novice observers segmented and analyzed independently 95 biopsy-confirmed lung ADCs from Vanderbilt University Medical Center/Nashville Veterans Administration Tennessee Valley Healthcare system (VUMC/TVHS) and the Mayo Clinic (Mayo). Inter-observer variability was measured using intra-class correlation coefficient (ICC). The average ICC for all CANARY classes was 0.828 (95% CI 0.76, 0.895) for the VUMC/TVHS cohort, and 0.852 (95% CI 0.804, 0.901) for the Mayo cohort. The most invasive voxel classes had the highest ICC values. To determine whether nodule size influenced inter-observer variability, an additional cohort of 49 sub-centimeter nodules from Mayo were also segmented by three observers, with similar ICC results. Our study demonstrates that CANARY ADC classification between novice CANARY users has an acceptably low degree of variability, and supports the further development of CANARY for clinical application.

[Safety of Electromagnetic Navigation Bronchoscopy in Patients With COPD: Results From the NAVIGATE Study.](#) Towe CW1, Nead MA2, Rickman OB3, Folch EE4, Khandhar SJ5, Perry Y1, Linden PA1. J Bronchology Interv Pulmonol. 2018 Jun 12. doi: 10.1097/LBR.0000000000000522. [Epub ahead of print]

BACKGROUND: Electromagnetic navigation bronchoscopy (ENB) aids in the localization of lung lesions for biopsy and/or to guide fiducial or dye marking for stereotactic radiation or surgical localization. This study assessed ENB safety in patients with chronic obstructive pulmonary disease (COPD) and/or poor lung function. **METHODS:** NAVIGATE is a prospective, multicenter, observational study of ENB. This substudy analyzed the 1-month follow-up of the first 1000 enrolled subjects. COPD was determined by medical history. Pulmonary function testing (PFT) results were collected if available within 30 days of the procedure. Procedure-related complications were captured. **RESULTS:** The analysis included 448 subjects with COPD and 541 without COPD (COPD data missing in 11). One-month follow-up was completed in 93.3%. Subjects with COPD tended to be older, male, and have history of tobacco exposure, asthma, and recent pneumonia. Nodule size, location, and procedure time were similar between groups. There was no statistically significant difference in the procedure-related composite complication rate between groups (7.4% with COPD, 7.8% without COPD, P=0.90). Common Terminology Criteria for Adverse Events scale grade ≥2 pneumothorax was not different between groups (2.7% with COPD, 3.7% without COPD, P=0.47). COPD was not a significant multivariate predictor of complications. Severity of forced expiratory volume in 1 second (FEV1) or diffusing capacity of the lung for carbon monoxide impairment was not associated with increased composite procedure-related complications (ppFEV1P=0.66, ppDLCO P=0.36). **CONCLUSIONS:** In this analysis, complication rates following ENB procedures were not increased in patients with COPD or poor pulmonary function. Because pneumothorax risk is not elevated, ENB may be the preferred method to biopsy peripheral lung lesions in patients with COPD and/or poor pulmonary function testing.

[Comparison of detection methods of EGFR T790M mutations using plasma, serum, and tumor tissue in EGFR-TKI-resistant non-small cell lung cancer.](#) Kobayashi K1, Naoki K1,2, Manabe T1, et al. Onco Targets Ther. 2018 Jun 6;11:3335-3343. doi: 10.2147/OTT.S161745. eCollection 2018.

BACKGROUND: Osimertinib, a third-generation epidermal growth factor receptor-tyrosine kinase inhibitor, exerts remarkable effects against EGFR T790M resistance mutation-positive non-small cell lung cancer. Identifying T790M mutation by re-biopsy is essential before prescribing osimertinib. Tissue biopsy is the golden standard for this purpose, but several factors limit its success rate. The liquid biopsy with blood, using circulating tumor DNA, has been an alternative method. However, the true biological

meaning and equivalence of liquid biopsy and tumor biopsy are still under investigation. Especially, the usefulness of serum samples to detect T790M mutation is not yet been known. **PATIENTS AND METHODS:** We prospectively evaluated the sensitivity, specificity, and parallelism of the detection of EGFR mutations in tissue re-biopsy and liquid biopsy (plasma and serum), simultaneously, from June 2016 to May 2017. EGFR mutations in tumor re-biopsy were evaluated by COBAS ver2 and PNA-LNA PCR clamp method, and those in liquid biopsy were evaluated with COBAS ver2. **RESULTS:** Fifteen patients were enrolled. In 10 patients whose EGFR mutation was detected in liquid biopsy, the original EGFR mutation (exon 19 del or L858R) was detected in all patients. Detection of EGFR mutation by COBAS ver2 and by PNA-LNA method was almost the same in tissue re-biopsy. The detection rate of T790M was lower than that of the original EGFR mutation in liquid biopsy compared to that in tissue re-biopsy. The detection of T790M in serum exhibited a higher specificity (67%) and positive predictive value (50%) than that in plasma (50% and 40%, respectively). The detection sensitivity was similar in plasma and serum. **CONCLUSION:** Plasma, serum, and tissue genotyping can have complementary roles for detecting EGFR-T790M using COBAS ver2. Repeated tests with different samples and different methods may improve accuracy of T790M detection and will lead to the maximum benefit for the patient.

[**Differences in smoking prevalence and eligibility for low-dose computed tomography (LDCT) lung cancer screening among older U.S. adults: role of sexual orientation.**](#) Matthews AK1, McCabe SE2, Lee JGL3, Veliz P2. Cancer Causes Control. 2018 Jun 15. doi: 10.1007/s10552-018-1044-x. [Epub ahead of print]
The purpose of this study was to determine the past-year prevalence estimates of cigarette smoking and eligibility for low-dose computed tomography (LDCT) lung cancer screening among older U.S. adults and examine potential variations in these estimates by sexual orientation. Data were from the 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC-III) and included in-person interviews with a nationally representative sample of non-institutionalized adults aged 18 and older. Eligibility for LDCT was based on U.S. Centers for Medicare and Medicaid Services (CMS) guidelines. Analyses included participants aged 55-77 (n = 9,635). Overall, 17.5% of older adult respondents reported past-year smoking. Overall rates of past-year cigarette smoking were influenced by sex and sexual orientation with males reporting higher rates compared to females. Among both males and females, smoking was most prevalent among bisexual individuals. Eligibility for LDCT was also higher among males compared to females and among bisexually identified adults relative to homosexual and heterosexual-identified adults. Overall, 11.2% of older U.S. adults met eligibility for LDCT lung cancer screening. Eligibility for LDCT lung screening is associated with sexual orientation; the highest rates of eligibility are among bisexual women and men (26.9 and 24.5%, respectively). The current study found variations in cigarette smoking and eligibility for LDCT lung cancer screening (a proxy for chronic high-risk smoking) among older U.S. adults based on sexual orientation. Efforts to increase screening should take into account these differences.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[**Is There a Role for VATS Sleeve Lobectomy in Lung Cancer?**](#) Merchant NN1, McKenna R Jr2, Onugha O2. Surg Technol Int. 2018 Jun 1;32:225-229.
Lung cancer is the second most commonly diagnosed cancer and continues to be the leading cause of death for both men and women, with non-small cell lung cancer (NSCLC) accounting for 85% of all lung cancer cases. Once a lung mass is visualized on imaging, accurate staging is required for determination of treatment options and, when possible, surgical resection is recommended as it has been proven to have the

best survival rates versus non-surgical treatment. If a patient has advanced or metastatic disease, therapeutic options include chemotherapy and radiation, while immunotherapy and specific agents that target tumor mutations are only recommended for appropriate candidates. Additionally, surgical options differ based on whether the tumor is peripherally or centrally located in the lung parenchyma. This article will review relevant literature concerning current surgical techniques for resection of centrally located NSCLC using thoracotomy and will emphasize the benefits and challenges of a video-assisted thoracic surgery (VATS) approach.

[**Preparing Cancer Patients and Family Caregivers for Lung Surgery: Development of a Multimedia Self-Management Intervention.**](#) Sun V1, Kim JY2, Raz DJ2, et al. J Cancer Educ. 2018 Jun;33(3):557-563. doi: 10.1007/s13187-016-1103-5.

The surgical treatment of lung malignancies often results in persistent symptoms, psychosocial distress, and decrements in quality of life (QOL) for cancer patients and their family caregivers (FCGs). The potential benefits of providing patients and FCGs with preparatory education that begins in the preoperative setting have been explored in multiple medical conditions, with positive impact observed on postoperative recovery, psychological distress, and QOL. However, few studies have explored the benefits of preparatory educational interventions to promote self-management in cancer surgery, including lung surgery. This paper describes the systematic approach used in the development of a multimedia self-management intervention to prepare cancer patients and their FCGs for lung surgery. Intervention development was informed by (1) contemporary published evidence on the impact of lung surgery on patients and FCG, (2) our previous research that explored QOL, symptoms, and caregiver burden after lung surgery, (3) the use of the chronic care self-management model (CCM) to guide intervention design, and (4) written comments and feedback from patients and FCGs that informed intervention development and refinement. Pilot-testing of the intervention is in process, and a future randomized trial will determine the efficacy of the intervention to improve patient, FCG, and system outcomes.
PMCID: PMC5573658 [Available on 2019-06-01]

[**Image-guided video-assisted thoracoscopic small lung tumor resection using near-infrared marking.**](#) Wen CT1, Liu YY2, Fang HY1, Hsieh MJ1, Chao YK3. Surg Endosc. 2018 Jun 4. doi: 10.1007/s00464-018-6252-7. [Epub ahead of print]

BACKGROUND: Localization of non-visible, non-palpable small pulmonary nodules during video-assisted thoracoscopic surgery (VATS) remains challenging. We sought to investigate the feasibility and safety of image-guided video-assisted thoracoscopic surgery (iVATS) with near-infrared (NIR) marking in a hybrid operating room (OR). **METHODS:** Both localization and surgery were performed by a single team of thoracic surgeons. Diluted indocyanine green (ICG; quantity: 0.3-0.5 mL; dye concentration: 0.125 mg/mL) was injected percutaneously to pinpoint the tumor's location under cone beam computed tomography (CBCT) guidance using a laser-guided navigation system. Real-time fluorescence images were intraoperatively obtained using a NIR thoracoscopic camera to guide subsequent resection. **RESULTS:** Between March and December 2017, 26 patients underwent NIR marking of small pulmonary nodules for iVATS. The median tumor size was 7 mm (interquartile range [IQR] 5.3-10.8 mm), whereas their median distance from the pleural surface was 5 mm (IQR 0.3-10.5 mm). Seven nodules (35%) were solid, whereas 17 (65%) were ground-glass opacities. All lesions were identifiable on intraoperative CBCT. The median time required for NIR localization was 13 min. An NIR(+) "tattoo" was identified in all cases, and no intraoperative conversion to thoracotomy occurred. The final pathological diagnoses were primary lung cancer (n = 11), metastatic cancer (n = 6), and benign lung tumor (n = 9). Adverse events were not observed, and the median length of post-operative stay was 4 days (IQR 3-4 days). **CONCLUSIONS:** Our data show that iVATS with NIR marking is useful, has no adverse effects, and can successfully localize difficult-to-identify small pulmonary nodules.

[Survival rates after lobectomy versus sublobar resection for early-stage right middle lobe non-small cell lung cancer.](#) Lv X1, Cao J1, Dai X2, Rusidanmu A1. Thorac Cancer. 2018 Jun 21. doi: 10.1111/1759-7714.12782. [Epub ahead of print]
BACKGROUND: Lung cancer in the right middle lobe has a poorer prognosis than tumors located in other lobes. The optimal surgical procedure for early-stage non-small cell lung cancer (NSCLC) in the right middle lobe has not yet been elucidated. The aim of this study was to compare survival rates after lobectomy and sublobar resection for early-stage right middle lobe NSCLC. **METHODS:** Patients who underwent lobectomy or sublobar resection for stage IA right middle lobe NSCLC tumors ≤ 2 cm between 2004 and 2014 were identified from the Surveillance, Epidemiology and End Results database of 18 registries. Cox regression model analysis was used to evaluate the prognostic factors. The lung cancer-specific survival (LCSS) and overall survival (OS) rates between the two groups were compared. **RESULTS:** A total of 861 patients met our criteria, including 662 (76.9%) patients who underwent lobectomy and 199 (23.1%) patients who underwent sublobar resection. No statistical differences in LCSS and OS rates were identified between the groups of patients with stage IA right middle lobe NSCLC ≤ 1 cm. For tumors > 1-2 cm, lobectomy was associated with more favorable LCSS and OS rates compared to sublobar resection. **CONCLUSION:** Lobectomy and sublobar resection deliver a comparable prognosis for patients with stage IA right middle lobe NSCLC ≤ 1 cm. For tumors > 1-2 cm, lobectomy showed better survival rates than sublobar resection.

[Does Race Influence Risk Assessment and Recommendations for Lung Resection? A Randomized Trial.](#) Ferguson MK1, Demchuk C2, Wroblewski K3, Huisingh-Scheetz M4, Thompson K4, Farnan J4, Acevedo J5. Ann Thorac Surg. 2018 Jun 11. pii: S0003-4975(18)30828-2. doi: 10.1016/j.athoracsur.2018.04.087. [Epub ahead of print]
BACKGROUND: Racial disparities in utilization of surgical therapy for lung cancer exist in the United States. Videos of standardized patients (SPs) can help identify factors that influence physicians' surgical risk estimation. We hypothesized that physician race and SP race in videos influence surgeon decision making. **METHODS:** Four race-neutral clinical vignettes representing lung resection candidates were paired with risk-level concordant short silent videos of SPs. Vignette/video combinations were classified as low or high risk. Trainees and practicing thoracic surgeons read a race-neutral vignette, provided an initial estimate of the percent risk of major surgical complications, viewed a video randomized to black or white SP, provided a final estimate of risk, and scored the likelihood that they would recommend surgery. Changes in risk estimates were assessed. **RESULTS:** Participants included 113 surgeons (38 practicing surgeons, 75 trainees); 76 were white non-Hispanic (67%), 37 were in other self-identified racial categories. Percentage changes between initial and final risk estimates were not significantly related to patient race (p=0.11) or surgeon race (white vs other; p=0.52). Videos of black SPs were associated with a similar likelihood of recommending surgery compared to that of videos of white SPs (p=0.90). Physician race (white vs other) was not related to the likelihood of recommending surgery (p=0.79). **CONCLUSIONS:** Neither patient nor physician race was significantly associated with risk estimation or surgical recommendations. These findings do not provide an explanation for documented racial disparities in lung cancer therapy. Further investigation is needed to identify mechanism underlying these disparities.

Phase II study of carboplatin, pemetrexed, and bevacizumab in advanced nonsquamous non-small-cell lung cancer. Laslett NF1, Park S1, Masters GA1, et al. Cancer Med. 2018 Jun 14. doi: 10.1002/cam4.1569. [Epub ahead of print]

Lung cancer remains the leading cause of cancer death throughout the world. Despite new chemotherapeutic, immunomodulating and molecularly targeted agents, patients with locally advanced or metastatic disease still have a poor prognosis. This trial looked to combine antiangiogenic therapy with a first-line cytotoxic chemotherapy doublet, hoping to extend median progression-free survival (PFS) while minimizing toxicity in patients with advanced nonsquamous non-small-cell lung cancer (NSCLC). In this single institution, single-arm study, 51 patients (age >18 yo) were followed from 2007 to 2012. Patients with stage IV nonsquamous NSCLC and patients with recurrent unresectable disease (nonradiation candidates) were eligible. Treatment consisted of carboplatin AUC 5 IV 30-60 minutes, pemetrexed 500/mg2 IV 10 minutes, bevacizumab 15 mg/kg IV (90 minutes 1st dose, 60 minutes 2nd dose, 30 minutes subsequent doses). Treatment was administered every 21 days and planned for 6 cycles, in the absence of disease progression or unacceptable toxicities. Growth factor support was not permitted prophylactically but allowed for toxicities, as were dose reductions. Maintenance treatment for those with stable disease or better consisted of Bevacizumab 15 mg/kg every 3 weeks for up to 1 year. Between November 2007 and March 2012, 51 patients were followed in the phase II trial of carboplatin, pemetrexed, and bevacizumab. Patients were enrolled over a 24-month period. After the end of treatment visits, subjects were followed at least every 3 months for survival data. The median follow-up period was 49 weeks (6 weeks to 178), and the median number of treatment cycles was 6 (range, 1-6). Among the 50 patients assessable for response, median overall survival was 49 weeks (95% CI, 0-62.7) with median PFS of 28 weeks (95% CI, 0-132.4). A complete or partial response was seen in 28 (59.5%) patients. Grade 3-4 treatment-related adverse events occurred in 9 (17.6%) of 51 patients; the most common were thrombocytopenia (4 [7.8%]) and neutropenia (3 [5.9%]). Three (5.8%) of 51 patients were discontinued because of treatment-related adverse events (grade 3 diarrhea, thrombocytopenia, dehydration, fatigue, and grade 4 respiratory distress), and 1 patient (1.9%) was found to be ineligible due to anticoagulation use. A novel 3-drug combination for advanced nonsquamous NSCLC shows promising efficacy with modest toxicity.

Switch maintenance therapy with docetaxel and bevacizumab after induction therapy with cisplatin, pemetrexed, and bevacizumab in advanced non-squamous non-small cell lung cancer: a phase II study. Nishimoto K1, Karayama M1,2, Inui N3,4, et al. Med Oncol. 2018 Jun 16;35(7):108. doi: 10.1007/s12032-018-1172-x.

Switch maintenance therapy, using alternative agents that were not administered during induction chemotherapy, is a treatment option for advanced non-squamous non-small cell lung cancer (NSCLC). Bevacizumab is known to increase the efficacy of other chemotherapeutic agents; however, switch maintenance therapy with docetaxel and bevacizumab has not been adequately studied. The goal of this study was to evaluate the efficacy and safety of switch maintenance therapy with docetaxel and bevacizumab following induction therapy with cisplatin, pemetrexed, and bevacizumab. Chemotherapy-naïve non-squamous NSCLC patients received induction therapy of four cycles of cisplatin (75 mg/m2), pemetrexed (500 mg/m2), and bevacizumab (15 mg/kg). Patients who achieved disease control after induction therapy then received maintenance therapy with docetaxel (50 mg/m2) and bevacizumab (15 mg/kg) until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival from enrollment. This study enrolled 49 NSCLC patients, among which 38 (77.6%) completed the four cycles of induction therapy and received maintenance therapy. The median progression-free survival from enrollment was 7.8 months (95% confidence interval: 4.7-11.0 months). The most common

toxicities of grade 3 or higher were neutropenia (68.4%), leukopenia (50.0%), febrile neutropenia (31.8%), and hypertension. Switch maintenance therapy with docetaxel and bevacizumab following induction therapy with cisplatin, pemetrexed, and bevacizumab demonstrated modest efficacy and frequent hematologic toxicity in non-squamous NSCLC patients.

[Liquid chromatography-tandem mass spectrometric assay for therapeutic drug monitoring of the EGFR inhibitors afatinib, erlotinib and osimertinib, the ALK inhibitor crizotinib and the VEGFR inhibitor nintedanib in human plasma from non-small cell lung cancer patients.](#) Reis R1, Labat L2, Allard M3, et al. J Pharm Biomed Anal. 2018 Jun 1;158:174-183. doi: 10.1016/j.jpba.2018.05.052. [Epub ahead of print]

A new method for the quantitative analysis by liquid chromatography-tandem mass spectrometry (LC-MS/MS) of five tyrosine kinase inhibitors (afatinib, crizotinib, osimertinib, erlotinib and nintedanib) used in the treatment of non-small cell lung cancer (NSCLC) was developed and validated in human plasma. Separation was performed on an Accucore® C18 (2.1 × 50 mm; 2.6 μm) column using a gradient elution of water acidified with 0.1% (v/v) formic acid (A) and acetonitrile containing 0.1% (v/v) formic acid (B) at a flow rate of 500 μL/min. The analytes were detected in the selected reaction monitoring mode of a triple quadrupole mass spectrometer after positive ionization with heated electrospray interface. After addition of three isotopically labeled internal standards, plasma pretreatment consisted in a simple protein precipitation. This method presented satisfactory results in terms of sensitivity, specificity, precision (intra- and inter-assay coefficient of variation from 2.6% to 10.6%), accuracy (from 96.1% to 108.5%), recovery and matrix effects. The lower limit of quantification and the linearity of these five tyrosine kinases inhibitors are suitable with the expected concentrations in clinical practice. This new bioanalytical method can be used in daily clinical practice for therapeutic drug monitoring of these tyrosine kinase inhibitors in NSCLC patients.

[Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC.](#) Socinski MA1, Jotte RM1, Cappuzzo F1, et al. N Engl J Med. 2018 Jun 14;378(24):2288-2301. doi: 10.1056/NEJMoa1716948. Epub 2018 Jun 4.

BACKGROUND: The cancer-cell-killing property of atezolizumab may be enhanced by the blockade of vascular endothelial growth factor-mediated immunosuppression with bevacizumab. This open-label, phase 3 study evaluated atezolizumab plus bevacizumab plus chemotherapy in patients with metastatic nonsquamous non-small-cell lung cancer (NSCLC) who had not previously received chemotherapy. **METHODS:** We randomly assigned patients to receive atezolizumab plus carboplatin plus paclitaxel (ACP), bevacizumab plus carboplatin plus paclitaxel (BCP), or atezolizumab plus BCP (ABCP) every 3 weeks for four or six cycles, followed by maintenance therapy with atezolizumab, bevacizumab, or both. The two primary end points were investigator-assessed progression-free survival both among patients in the intention-to-treat population who had a wild-type genotype (WT population; patients with EGFR or ALK genetic alterations were excluded) and among patients in the WT population who had high expression of an effector T-cell (Teff) gene signature in the tumor (Teff-high WT population) and overall survival in the WT population. The ABCP group was compared with the BCP group before the ACP group was compared with the BCP group. **RESULTS:** In the WT population, 356 patients were assigned to the ABCP group, and 336 to the BCP group. The median progression-free survival was longer in the ABCP group than in the BCP group (8.3 months vs. 6.8 months; hazard ratio for disease progression or death, 0.62; 95% confidence interval [CI], 0.52 to 0.74; P<0.001); the corresponding values in the Teff-high WT population were 11.3 months and 6.8 months (hazard ratio, 0.51 [95% CI, 0.38 to 0.68]; P<0.001). Progression-free survival was also longer in the ABCP group than in the BCP group in the entire intention-to-treat population (including those with EGFR or ALK genetic alterations) and among patients with low or negative programmed death ligand 1 (PD-L1) expression, those with low Teff gene-

signature expression, and those with liver metastases. Median overall survival among the patients in the WT population was longer in the ABCP group than in the BCP group (19.2 months vs. 14.7 months; hazard ratio for death, 0.78; 95% CI, 0.64 to 0.96; P=0.02). The safety profile of ABCP was consistent with previously reported safety risks of the individual medicines. **CONCLUSIONS:** The addition of atezolizumab to bevacizumab plus chemotherapy significantly improved progression-free survival and overall survival among patients with metastatic nonsquamous NSCLC, regardless of PD-L1 expression and EGFR or ALK genetic alteration status. (Funded by F. Hoffmann-La Roche/Genentech; IMpower150 ClinicalTrials.gov number, NCT0236614).

[Development and validation of response markers to predict survival and pleurodesis success in patients with malignant pleural effusion (PROMISE): a multicohort analysis.](#)

Psallidas I1, Kanellakis NI2, Gerry S3, et al. Lancet Oncol. 2018 Jun 13. pii: S1470-2045(18)30294-8. doi: 10.1016/S1470-2045(18)30294-8. [Epub ahead of print]

BACKGROUND: The prevalence of malignant pleural effusion is increasing worldwide, but prognostic biomarkers to plan treatment and to understand the underlying mechanisms of disease progression remain unidentified. The PROMISE study was designed with the objectives to discover, validate, and prospectively assess biomarkers of survival and pleurodesis response in malignant pleural effusion and build a score that predicts survival. **METHODS:** In this multicohort study, we used five separate and independent datasets from randomised controlled trials to investigate potential biomarkers of survival and pleurodesis. Mass spectrometry-based discovery was used to investigate pleural fluid samples for differential protein expression in patients from the discovery group with different survival and pleurodesis outcomes. Clinical, radiological, and biological variables were entered into least absolute shrinkage and selection operator regression to build a model that predicts 3-month mortality. We evaluated the model using internal and external validation. **FINDINGS:** 17 biomarker candidates of survival and seven of pleurodesis were identified in the discovery dataset. Three independent datasets (n=502) were used for biomarker validation. All pleurodesis biomarkers failed, and gelsolin, macrophage migration inhibitory factor, versican, and tissue inhibitor of metalloproteinases 1 (TIMP1) emerged as accurate predictors of survival. Eight variables (haemoglobin, C-reactive protein, white blood cell count, Eastern Cooperative Oncology Group performance status, cancer type, pleural fluid TIMP1 concentrations, and previous chemotherapy or radiotherapy) were validated and used to develop a survival score. Internal validation with bootstrap resampling and external validation with 162 patients from two independent datasets showed good discrimination (C statistic values of 0·78 [95% CI 0·72-0·83] for internal validation and 0·89 [0·84-0·93] for external validation of the clinical PROMISE score). **INTERPRETATION:** To our knowledge, the PROMISE score is the first prospectively validated prognostic model for malignant pleural effusion that combines biological and clinical parameters to accurately estimate 3-month mortality. It is a robust, clinically relevant prognostic score that can be applied immediately, provide important information on patient prognosis, and guide the selection of appropriate management strategies. **FUNDING:** European Respiratory Society, Medical Research Funding-University of Oxford, Slater & Gordon Research Fund, and Oxfordshire Health Services Research Committee Research Grants. Copyright © 2018 Elsevier Ltd. All rights reserved.

[Comparative effectiveness from a single-arm trial and real-world data: alectinib versus ceritinib.](#)

Davies J1, Martinec M2, Delmar P2, Coudert M3, Bordogna W2, Golding S2, Martina R4, Crane G1. J Comp Eff Res. 2018 Jun 26. doi: 10.2217/cer-2018-0032. [Epub ahead of print]

AIM: To compare the overall survival of anaplastic lymphoma kinase-positive non-small-cell lung cancer patients who received alectinib with those who received ceritinib. **MATERIALS & METHODS:** Two treatment arms (alectinib [n = 183] and ceritinib [n = 67]) were extracted from clinical trials and an electronic health record database, respectively. Propensity scores were applied to balance baseline

characteristics. Kaplan-Meier and multivariate Cox regression were conducted. **RESULTS:** After propensity score adjustment, baseline characteristics were balanced. Alectinib had a prolonged median overall survival (alectinib = 24.3 months and ceritinib = 15.6 months) and lower risk of death (hazard ratio: 0.65; 95% CI: 0.48-0.88). **CONCLUSION:** Alectinib was associated with prolonged overall survival versus ceritinib, which is consistent with efficacy evidence from clinical trials.

[**Clinical outcomes of African American patients with advanced or metastatic non-small cell lung cancer on Nivolumab in a single community-based cancer center.**](#) Tiu AC1, Potdar R2, Djibo DA3, Masab M3, Dourado C2. Med Oncol. 2018 Jun 18;35(7):109. doi: 10.1007/s12032-018-1171-y.
African Americans (AA) have the highest incidence and mortality rates with lung cancer. They are diagnosed at an earlier age with more advanced disease. Programmed cell death protein-1 inhibitor, Nivolumab, was approved as a second-line agent after failure of platinum-based therapy for advanced or metastatic non-small cell lung cancer (NSCLC). The original studies leading to the approval of Nivolumab had insufficient AA patients, thus there is still inadequate knowledge on treatment outcomes among AA patients. Our primary study endpoints were to determine the median overall survival, 1-year overall survival rate, median progression-free survival, and 1-year progression-free survival rate of patients with advanced or metastatic non-small cell lung cancer on Nivolumab. Our secondary study endpoints were to determine the overall tumor response rate, median time to response, median duration of response, and incidence of treatment-related adverse events of grade 3 or 4. In this retrospective study, we reviewed the charts of 38 patients, 29 of which were AA, with advanced or metastatic NSCLC who received Nivolumab from March 1, 2015 until November 30, 2017 from a single community-based cancer center and compared our results with historical data. Adenocarcinoma was the most common histology (71%) among all patients. Seven (18%) continued to use Nivolumab while 21 (55%) discontinued the treatment mainly due to progression of the disease. The median overall survival was 21.4 months (95% CI 13.5-27.4) and 17.6 months (95% CI 11.5-27.6) for all the patients and AA, respectively. Both have statistically significant difference (P < 0.001) compared to the historical studies of Borghaei et al. and Brahmer et al. At 1 year, the overall survival rate was 73% (95% CI 50-86) and 66% (95% CI 40-82) for all patients and AA, respectively. The median progression-free survival was also statistically significant (P < 0.001) between all the patients 6.3 months (95% CI 2.8-8), AA 6.0 months (95% CI 2.3-8.0), and the said historical studies. The 1-year progression-free survival rate was 23% (95% CI 10-39) and 28% (95% CI 12-47) for all patients and AA, respectively. Overall tumor response rate which includes complete and partial responses was 21% (95% CI 10-37) and 24% (95% CI 10-43) for all patients and AA, respectively. The median time to response was 3 and 2.8 months for all patients and AA, respectively. The median duration of response was 3.8 and 4.0 months for all patients and AA, respectively. Treatment-related adverse events of grade 3 or 4 were reported in 8 and 10% in all patients and AA, respectively, similar to the rates previously shown. AA patients with advanced or metastatic NSCLC on Nivolumab had increased overall survival and progression-free survival with similar grade 3 or 4 treatment-related adverse events. Providing adequate access to immunotherapy is indispensable to maximize survival benefit for AA patients.

[**Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study.**](#) Novello S1, Mazières J2, Oh IJ3, et al. Ann Oncol. 2018 Jun 1;29(6):1409-1416. doi: 10.1093/annonc/mdy121.
BACKGROUND: This is the first trial to directly compare efficacy and safety of alectinib versus standard chemotherapy in advanced/metastatic anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer (NSCLC) patients who have progressed on, or were intolerant to, crizotinib. **PATIENTS AND METHODS:** ALUR (MO29750; NCT02604342) was a randomized, multicenter, open-label, phase III trial of alectinib versus chemotherapy in advanced/metastatic ALK-positive NSCLC patients

previously treated with platinum-based doublet chemotherapy and crizotinib. Patients were randomized 2 : 1 to receive alectinib 600 mg twice daily or chemotherapy (pemetrexed 500 mg/m2 or docetaxel 75 mg/m2, both every 3 weeks) until disease progression, death, or withdrawal. Primary end point was investigator-assessed progression-free survival (PFS). **RESULTS:** Altogether, 107 patients were randomized (alectinib, n = 72; chemotherapy, n = 35) in 13 countries across Europe and Asia. Median investigator-assessed PFS was 9.6 months [95% confidence interval (CI): 6.9-12.2] with alectinib and 1.4 months (95% CI: 1.3-1.6) with chemotherapy [hazard ratio (HR) 0.15 (95% CI: 0.08-0.29); P < 0.001]. Independent Review Committee-assessed PFS was also significantly longer with alectinib [HR 0.32 (95% CI: 0.17-0.59); median PFS was 7.1 months (95% CI: 6.3-10.8) with alectinib and 1.6 months (95% CI: 1.3-4.1) with chemotherapy]. In patients with measurable baseline central nervous system (CNS) disease (alectinib, n = 24; chemotherapy, n = 16), CNS objective response rate was significantly higher with alectinib (54.2%) versus chemotherapy (0%; P < 0.001). Grade ≥3 adverse events were more common with chemotherapy (41.2%) than alectinib (27.1%). Incidence of AEs leading to study-drug discontinuation was lower with alectinib (5.7%) than chemotherapy (8.8%), despite alectinib treatment duration being longer (20.1 weeks versus 6.0 weeks). **CONCLUSION:** Alectinib significantly improved systemic and CNS efficacy versus chemotherapy for crizotinib-pretreated ALK-positive NSCLC patients, with a favorable safety profile.

[Brigatinib in Patients with Alectinib-Refractory ALK-Positive Non-Small Cell Lung Cancer: A Retrospective Study.](#) Lin JJ1, Zhu VW2, Schoenfeld AJ3, et al. J Thorac Oncol. 2018 Jun 20. pii: S1556-0864(18)30714-7. doi: 10.1016/j.jtho.2018.06.005. [Epub ahead of print]
BACKGROUND: The second-generation ALK inhibitor alectinib recently demonstrated superior efficacy compared to the first-generation ALK inhibitor crizotinib in advanced anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer (NSCLC), establishing alectinib as the new standard first-line therapy. Brigatinib, another second-generation ALK inhibitor, has demonstrated substantial activity in patients with crizotinib-refractory ALK-positive NSCLC; however, its activity in the alectinib-refractory setting is unknown. **METHODS:** A multicenter, retrospective study was performed at three institutions. Patients were eligible if they had advanced, alectinib-refractory ALK-positive NSCLC and were treated with brigatinib. Medical records were reviewed to determine clinical outcomes. **RESULTS:** Twenty-two patients were eligible for this study. Confirmed objective responses to brigatinib were observed in 3 of 18 patients (17%) with measurable disease. Nine patients (50%) had stable disease on brigatinib. The median progression-free survival was 4.4 months [95% confidence interval (CI), 1.8-5.6 months] with a median duration of treatment of 5.7 months (95% CI, 1.8-6.2 months). Among nine patients in this study who underwent post-alectinib/pre-brigatinib biopsies, five had an ALK I1171X or V1180L resistance mutation; of these, one had a confirmed partial response and three had stable disease on brigatinib. One patient had an ALK G1202R mutation in a post-alectinib/pre-brigatinib biopsy, and had progressive disease as the best overall response to brigatinib. **CONCLUSIONS:** Brigatinib has limited clinical activity in alectinib-refractory ALK-positive NSCLC. Additional studies are needed to establish biomarkers of response to brigatinib and to identify effective therapeutic options for alectinib-resistant ALK-positive NSCLC patients.

[Brief report: Early use of systemic corticosteroids in patients with advanced NSCLC treated with nivolumab.](#) Scott SC1, Pennell NA2. J Thorac Oncol. 2018 Jun 20. pii: S1556-0864(18)30711-1. doi: 10.1016/j.jtho.2018.06.004. [Epub ahead of print]
BACKGROUND: Checkpoint inhibitors augment the immune system's natural surveillance mechanisms and have increasing applications in non-small cell lung cancer (NSCLC). Immunosuppressive

corticosteroids are also frequently used in this population to treat unwanted inflammation. Based on this mechanistic opposition, we investigated the interaction between nivolumab and corticosteroids in patients with advanced NSCLC. **METHODS:** A retrospective chart review of 210 NSCLC patients treated with nivolumab at the Cleveland Clinic was performed. Use of systemic corticosteroids (equivalent to >10 mg prednisone per day) during nivolumab therapy was associated with objective outcomes of number of nivolumab cycles and overall survival. **RESULTS:** Sixty-six patients (31%) received concurrent systemic corticosteroids during nivolumab therapy. The most common indications included sequelae from active or treated brain metastases (27%) and COPD or other respiratory disease (21%). For patients with early exposure to steroids within the first 30 days of nivolumab therapy (12%, n=25), the median number of nivolumab cycles was two, compared to five cycles in patients not exposed to corticosteroids (p=0.002). Median overall survival for patients on steroids during the first 30 days was 4.3 months, compared to 11 months for patients not on steroids, hazard ratio for death 2.30 (95% CI 1.27-4.16, p=0.006) in multivariate analysis. **CONCLUSION:** Nearly one-third of NSCLC patients treated with nivolumab were prescribed concurrent corticosteroids during the course of nivolumab therapy. Patients exposed to corticosteroids during the first cycle of nivolumab received fewer total cycles of nivolumab, suggesting decreased clinical benefit, and had shorter overall survival.

[Phase II Trial of Carboplatin and Pemetrexed Plus Bevacizumab with Maintenance Bevacizumab as a First-line Treatment for Advanced Non-squamous Non-small Cell Lung Cancer in Elderly Patients.](#) Takeoka H1, Yamada K2, Naito Y3, et al. Anticancer Res. 2018 Jun;38(6):3779-3784. doi: 10.21873/anticanres.12661.
BACKGROUND/AIM: The combination of platinum-doublet chemotherapy with bevacizumab has been established as a first-line treatment option in non-elderly patients with non-squamous (non-sq) non-small cell lung cancer (NSCLC). However, the safety and efficacy of this regimen have not yet been fully established in elderly patients. **PATIENTS AND METHODS:** Chemo-naïve patients with non-sq NSCLC, aged ≥75 years, having a good performance status (Eastern Cooperative Oncology Group performance status 0-1) and adequate organ function were considered eligible. Patients received carboplatin (area under the curve=5 mg/ml/min), pemetrexed (500 mg/m2), and bevacizumab (15 mg/kg) every 3 weeks for up to 4 cycles, followed by maintenance bevacizumab. The primary endpoint was the objective response rate (ORR; target=50%, threshold=30%; Simon's two-stage design), and the secondary endpoints were safety, progression-free survival (PFS), and overall survival (OS). **RESULTS:** Twelve patients were enrolled from June 2013 to July 2017. The study was closed because of slow patient accrual. The median patient age was 80 years. Eleven patients (92%) completed 4 cycles of induction chemotherapy. Seven patients achieved a partial response (PR), yielding an ORR of 58%. The median PFS was 8.4 [95% confidence interval (CI)=4.4-10.5] months, and the median OS was 33.9 (95%CI=13.2-43.3) months. Toxicities were generally mild and consistent with previous reports. There were no treatment-related deaths. **CONCLUSION:** A regimen comprising carboplatin and pemetrexed plus bevacizumab followed by maintenance bevacizumab is feasible and potentially efficacious in elderly patients with non-sq NSCLC.

[Nivolumab-induced thyroid dysfunction in patients with lung cancer.](#) [Article in English, Spanish]Ramos-Levi AM1, Rogado J2, Sanchez-Torres JM2, Colomer R2, Marazuela M3. Endocrinol Diabetes Nutr. 2018 Jun 14. pii: S2530-0164(18)30109-5. doi: 10.1016/j.endinu.2018.05.005. [Epub ahead of print]
BACKGROUND: Nivolumab is an anti-cancer monoclonal antibody that inhibits PD1 and modulates T-cell response. It has been shown to significantly improve survival in several types of cancer, but clinical trials have also reported an increased risk of developing immune-related adverse events (IRAEs). Endocrine IRAEs may be particularly relevant. **OBJECTIVE:** To comprehensively evaluate the clinical

presentation of endocrine IRAEs in patients with lung cancer treated with nivolumab. Potential risk factors are analyzed, and strategies for IRAE management are proposed. **METHODS:** Forty consecutive patients treated with nivolumab for advanced non-small cell lung cancer (NSCLC) were studied, paying particular attention to development of endocrine IRAEs (thyroid, hypophyseal, adrenal, or pancreatic) and clinical outcome. **RESULTS:** Thyroid function changes were found in 9 patients (22.5%), of which six developed hypothyroidism and three had hyperthyroidism after a median of 3.8 and 2.3 cycles of nivolumab respectively. Only one patient had thyroid-related symptoms. Thyroid autoimmunity was negative in all cases. Hyperthyroid patients showed no uptake in iodine scintigraphy, and their hormone values returned to normal in less than six months. Nivolumab was discontinued for toxicity in one patient. One patient with hyperthyroidism also developed autoimmune diabetes, and one patient with hypothyroidism also had hypogonadism. After a median follow-up of 7.6 months, 25 patients (62.5%) showed response to nivolumab. Univariate and multivariate analyses showed no differences between patients who developed thyroid changes and those who did not. **CONCLUSIONS:** Thyroid changes after treatment with nivolumab are common and warrant active laboratory monitoring. The underlying mechanisms and their relevance deserve further research.

NSCLC - RADIOTHERAPY

Use of PET and Other Functional Imaging to Guide Target Delineation in Radiation Oncology.

Verma V1, Choi JI2, Sawant A3, Gullapalli RP4, Chen W4, Alavi A5, Simone CB 2nd6. Semin Radiat Oncol. 2018 Jun;28(3):171-177. doi: 10.1016/j.semradonc.2018.02.001.

Molecular and functional imaging is increasingly being used to guide radiotherapy (RT) management and target delineation. This review summarizes existing data in several disease sites of various functional imaging modalities, chiefly positron emission tomography/computed tomography (PET/CT), with respect to RT target definition and management. For gliomas, differentiation between postoperative changes and viable tumor is discussed, as well as focal dose escalation and reirradiation. Head and neck neoplasms may also benefit from precise PET/CT-based target delineation, especially for cancers of unknown primary; focal dose escalation is also described. In lung cancer, PET/CT can influence coverage of tumor volumes, dose escalation, and adaptive management. For cervical cancer, PET/CT as an adjunct to magnetic resonance imaging planning is discussed, as are dose escalation and delineation of avoidance targets such as the bone marrow. The emerging role of choline-based PET for prostate cancer and its impact on dose escalation is also described. Lastly, given the essential role of PET/CT for target definition in lymphoma, phase III trials of PET-directed management are reviewed, along with novel imaging modalities. Taken together, molecular and functional imaging approaches offer a major step to individualize radiotherapeutic care going forward.

Stereotactic body radiation therapy (SBRT) improves local control and overall survival compared to conventionally fractionated radiation for stage I non-small cell lung cancer (NSCLC). von

Reibnitz D1, Shaikh F1, Wu AJ1, et al. Acta Oncol. 2018 Jun 6:1-7. doi: 10.1080/0284186X.2018.1481292. [Epub ahead of print]

BACKGROUND: Stereotactic body radiotherapy (SBRT) has been adopted as the standard of care for inoperable early-stage non-small cell lung cancer (NSCLC), with local control rates consistently >90%. However, data directly comparing the outcomes of SBRT with those of conventionally fractionated radiotherapy (CONV) is lacking. **MATERIAL AND METHODS:** Between 1990 and 2013, 497 patients (525 lesions) with early-stage NSCLC (T1-T2N0M0) were treated with CONV (n = 127) or SBRT (n = 398). In this retrospective analysis, five endpoints were compared, with and without adjusting for clinical and dosimetric factors. Competing risks analysis was performed to estimate and compare the cumulative incidence of local failure (LF), nodal failure (NF), distant failure (DF) and disease

progression. Overall survival (OS) was estimated by the Kaplan-Meier method and compared by the Cox regression model. Propensity score (PS) matched analysis was performed based on seven patient and clinical variables: age, gender, Karnofsky performance status (KPS), histology, T stage, biologically equivalent dose (BED), and history of smoking. **RESULTS:** The median dose delivered for CONV was 75.6 Gy in 1.8-2.0 Gy fractions (range 60-90 Gy; median BED = 89.20 Gy) and for SBRT 48 Gy in four fractions (45-60 Gy in three to five fractions; median BED = 105.60 Gy). Median follow-up was 24.4 months, and 3-year LF rates were 34.1% with CONV and 13.6% with SBRT (p < .001). Three-year OS rates were 38.9 and 53.1%, respectively (p = .018). PS matching showed a significant improvement of OS (p = .0497) for SBRT. T stage was the only variable correlating with all five endpoints. **CONCLUSION:** SBRT compared to CONV is associated with improved LF rates and OS. Our data supports the continued use and expansion of SBRT as the standard of care treatment for inoperable early-stage NSCLC.

[**The Integration of Radiotherapy With Immunotherapy for the Treatment of Non-Small Cell Lung Cancer.**](#) Ko EC1, Raben D2, Formenti SC3. Clin Cancer Res. 2018 Jun 26. pii: clincanres.3620.2018. doi: 10.1158/1078-0432.CCR-17-3620. [Epub ahead of print]
Five-year survival rates for non-small cell lung cancer (NSCLC) range from 14% to 49% for stage I to stage IIIA disease, and are <5% for stage IIIB/IV disease. Improvements have been made in the outcomes of patients with NSCLC due to advancements in radiotherapy (RT) techniques, the use of concurrent chemotherapy with radiation, and the emergence of immunotherapy as first- and second-line treatment in the metastatic setting. RT remains the mainstay treatment in patients with inoperable early-stage NSCLC, and is given concurrently or sequentially with chemotherapy in patients with locally advanced unresectable disease. There is emerging evidence that RT not only provides local tumor control, but may also influence systemic control. Multiple preclinical studies have demonstrated that RT induces immunomodulatory effects in the local tumor microenvironment, supporting a synergistic combination approach with immunotherapy to improve systemic control. Immunotherapy options that could be combined with RT include programmed cell death-1/programmed cell death ligand-1 blockers, as well as investigational agents such as OX-40 agonists, toll-like receptor agonists, indoleamine 2,3-dioxygenase-1 inhibitors, and cytokines. Here, we describe the rationale for the integration of RT and immunotherapy in patients with NSCLC, present safety and efficacy data that support this combination strategy, review planned and ongoing studies, and highlight unanswered questions and future research needs.
PMID: 29945993

[**Postoperative re-irradiation using stereotactic body radiotherapy for metastatic epidural spinal cord compression.**](#) Ito K1,2, Nihei K1, Shimizuguchi T1, Ogawa H1, Furuya T1, Sugita S3, Hozumi T3, Keisuke Sasai2, Karasawa K1. J Neurosurg Spine. 2018 Jun 15:1-7. doi: 10.3171/2018.1.SPINE171155. [Epub ahead of print]
OBJECTIVE: This study aimed to clarify the outcomes of postoperative re-irradiation using stereotactic body radiotherapy (SBRT) for metastatic epidural spinal cord compression (MESCC) in the authors' institution and to identify factors correlated with local control. **METHODS:** Cases in which patients with previously irradiated MESCC underwent decompression surgery followed by spine SBRT as re-irradiation between April 2013 and May 2017 were retrospectively reviewed. The surgical procedures were mainly performed by the posterior approach and included decompression and fixation. The prescribed dose for spine SBRT was 24 Gy in 2 fractions. The primary outcome was local control, which was defined as elimination, shrinkage, or no change of the tumor on CT or MRI obtained approximately every 3 months after SBRT. In addition, various patient-, treatment-, and tumor-specific factors were evaluated to determine their predictive value for local control. **RESULTS:** Twenty-eight cases were identified in the authors' institutional databases as meeting the inclusion criteria. The histology of the primary disease was thyroid cancer in 7 cases, lung cancer in 6, renal cancer in 3, colorectal cancer in 3,

and other cancers in 9. The most common previous radiation dose was 30 Gy in 10 fractions (15 cases). The mean interval since the most recent irradiation was 16 months (range 5-132 months). The median duration of follow-up after SBRT was 13 months (range 4-38 months). The 1-year local control rate was 70%. In the analysis of factors related to local control, Bilsky grade, number of vertebral levels in the treatment target, the interval between the latest radiotherapy and SBRT, recursive partitioning analysis (RPA), the prognostic index for spinal metastases (PRISM), and the revised Tokuhashi score were not significantly correlated with local control. The favorable group classified by the Rades prognostic score achieved a significantly higher 1-year local control rate than the unfavorable group (1-year local control rate: 100% vs 33%; p < 0.01). Radiation-induced myelopathy and vertebral compression fracture were observed in 1 and 3 patients, respectively. No other grade 3 or greater toxicities were encountered. **CONCLUSIONS:** The results indicate that spine SBRT as postoperative re-irradiation was effective, and it was especially useful for patients classified as having a good survival prognosis according to the Rades score.

[Decreased Risk of Radiation Pneumonitis With Coincident Concurrent Use of Angiotensin-converting Enzyme Inhibitors in Patients Receiving Lung Stereotactic Body Radiation Therapy.](#)
Alite F1, Balasubramanian N1, Adams W1, Surucu M1, Mescioglu I2, Harkenrider MM1. Am J Clin Oncol. 2018 Jun;41(6):576-580. doi: 10.1097/COC.0000000000000324.
OBJECTIVES: Angiotensin-converting enzyme inhibitors (ACEi) have demonstrated decreased rates of radiation-induced lung injury in animal models and clinical reports have demonstrated decreased pneumonitis in the setting of conventionally fractionated radiation to the lung. We tested the role of ACEi in diminishing rates of symptomatic (grade ≥2) pneumonitis in the setting of lung stereotactic body radiation therapy (SBRT). **METHODS:** We analyzed patients treated with thoracic SBRT to 48 to 60 Gy in 4 to 5 fractions from 2006 to 2014. We reviewed pretreatment and posttreatment medication profiles to document use of ACEi, angiotensin receptor blockers, bronchodilators, aspirin, PDE-5 inhibitors, nitrates, and endothelin receptor antagonists. Pneumonitis was graded posttreatment based on Common Terminology Criteria for Adverse Events Version 4.0. Univariate and multivariate analysis was performed and time to development of pneumonitis was evaluated by the Kaplan-Meier method. **RESULTS:** A total of 189 patients were evaluated with a median follow-up of 24.8 months. The overall 1-year rate of symptomatic pneumonitis was 13.2%. The 1-year rate of symptomatic pneumonitis was 4.2% for ACEi users versus 16.3% in nonusers (P=0.03). On univariate analysis, the odds of developing grade 2 or greater pneumonitis were significantly lower for patients on ACEi (P=0.03). On multivariate analysis, after controlling for clinicopathologic characteristics and dosimetric endpoints, there was a significant association between ACEi use and decreased risk of clinical pneumonitis (P=0.04). Angiotensin receptor blockers or other bronchoactive medications did not show significant associations with development of pneumonitis. **CONCLUSIONS:** Incidental concurrent use of ACEi demonstrated efficacy in diminishing rates of symptomatic pneumonitis in the setting of lung SBRT.

SMALL CELL LUNG CANCER - SCLC

[Talazoparib is a Potent Radiosensitizer in Small Cell Lung Cancer Cell Lines and Xenografts.](#) Laird JH1, Lok BH2, Ma J3, Bell A4, de Stanchina E5, Poirier JT6, Rudin CM7. Clin Cancer Res. 2018 Jun 26. pii: clincanres.0401.2018. doi: 10.1158/1078-0432.CCR-18-0401. [Epub ahead of print]
PURPOSE: Small cell lung cancer (SCLC) is an aggressive malignancy with a critical need for novel therapies. Our goal was to determine whether PARP inhibition could sensitize SCLC cells to ionizing radiation (IR) and if so, to determine the contribution of PARP trapping to radiosensitization.
METHODS AND MATERIALS: Short-term viability assays and clonogenic survival assays (CSA) were used to assess radiosensitization in six SCLC cell lines. Doses of veliparib and talazoparib with

equivalent enzymatic inhibitory activity but differing PARP trapping activity were identified and compared in CSAs. Talazoparib, IR, and their combination were tested in three patient-derived xenograft (PDX) models. **RESULTS:** Talazoparib radiosensitized 5 of 6 SCLC cell lines in short-term viability assays and confirmed in 3 of 3 cell lines by CSAs. Concentrations of 200 nM talazoparib and 1600 nM veliparib similarly inhibited PAR polymerization; however, talazoparib exhibited greater PARP trapping activity that was associated with superior radiosensitization. This observation further correlated with an increased number of double-stranded DNA breaks induced by talazoparib as compared to veliparib. Finally, a dose of 0.2 mg/kg talazoparib in vivo caused tumor growth inhibition in combination with IR but not as a single agent in 3 SCLC PDX models. **CONCLUSIONS:** PARP inhibition effectively sensitizes SCLC cell lines and PDXs to IR, and PARP trapping activity enhances this effect. PARP inhibitors, especially those with high PARP trapping activity, may provide a powerful tool to improve the efficacy of radiation therapy in SCLC.

[Cardiac mortality in limited-stage small cell lung cancer.](#) Verma V1, Fakhreddine MH2, Haque W3, Butler EB3, Teh BS3, Simone CB 2nd4. Radiother Oncol. 2018 Jun 19. pii: S0167-8140(18)30311-6. doi: 10.1016/j.radonc.2018.06.011. [Epub ahead of print]
INTRODUCTION: Life expectancy of patients with limited-stage small cell lung cancer (LS-SCLC) continues to rise; thus, characterization of long-term toxicities is essential. Although there are emerging data linking cardiac irradiation doses with survival for non-small cell lung cancer, there are currently minimal data on cardiac-specific mortality (CSM) in LS-SCLC. The goal of this investigation was to evaluate CSM between left- and right-sided cases. **METHODS:** The Surveillance, Epidemiology, and End Results database was queried for stage I-III primary SCLC patients receiving radiotherapy; CSM was compared between left- and right-sided diseases. Accounting for mortality from other causes, Gray's test compared cumulative incidences of CSM between both groups. Multiple multivariate models examined the independent effect of laterality on CSM, including the Fine and Gray competing risk model and the Cox proportional hazards model. **RESULTS:** Of 19,692 patients, 7991 (41%) were left-sided and 11,701 (59%) were right-sided. Left-sided patients experienced significantly higher CSM overall (3.3% vs. 2.6%, p = 0.004). Laterality was an independent predictor of CSM in the overall population in the Fine and Gray competing risk model (p = 0.006) as well as the Cox proportional hazards model (p = 0.007). The overall hazard ratio for CSM by disease laterality was 1.27 (95% confidence interval, 1.08-1.50). Laterality had no statistical association with non-cardiac mortality in the Fine and Gray competing risk model (p = 0.130). **CONCLUSIONS:** Although causation between radiotherapy and CSM in LS-SCLC cannot be stated based on these data, we encourage clinical attentiveness to cardiac-sparing radiotherapy for LS-SCLC, along with further investigation evaluating dosimetric correlates for cardiotoxicity.

[Comparison of carboplatin plus etoposide with amrubicin monotherapy for extensive-disease small cell lung cancer in the elderly and patients with poor performance status.](#) Igawa S1, Shirasawa M1, Ozawa T1, et al. Thorac Cancer. 2018 Jun 5. doi: 10.1111/1759-7714.12772. [Epub ahead of print]
BACKGROUND: Carboplatin plus etoposide (CE) is a standard treatment for elderly patients with extensive-disease small cell lung cancer (ED-SCLC). However, amrubicin monotherapy (AMR) may be a feasible alternative. We compared the efficacies and safety profiles of CE and AMR for ED-SCLC in elderly patients and chemotherapy-naive patients with poor performance status (PS). **METHODS:** The records of SCLC patients who received CE or AMR as first-line chemotherapy were retrospectively reviewed and their treatment outcomes evaluated. **RESULTS:** Eighty-four patients (median age 72 years; 42 each received CR and AMR) were analyzed; 34 patients had a PS score of 2. There were no significant differences in patient characteristics between the treatment groups. The median progression-free survival rates of patients in the CE and AMR groups were 5.8 and 4.8 months, respectively (P = 0.04); overall survival was 14.0 and 8.5 months, respectively (P = 0.089). Twenty-three CE group patients received

AMR as second-line chemotherapy; their median overall survival from first-line chemotherapy was 18.5 months. Grade 3 or higher neutropenia occurred more frequently in patients treated with AMR (64% vs. 40%; P = 0.02), as did febrile neutropenia (14% vs. 7%). **CONCLUSIONS:** CE remains a suitable first-line treatment for ED-SCLC in elderly patients or those with poor PS in comparison with AMR.

Randomized, Double-Blind, Phase II Study of Temozolomide in Combination With Either Veliparib or Placebo in Patients With Relapsed-Sensitive or Refractory Small-Cell Lung Cancer.
Pietanza MC1, Waqar SN1, Krug LM1, et al. J Clin Oncol. 2018 Jun 15:JCO2018777672. doi: 10.1200/JCO.2018.77.7672. [Epub ahead of print]
PURPOSE: Both temozolomide (TMZ) and poly (ADP-ribose) polymerase (PARP) inhibitors are active in small-cell lung cancer (SCLC). This phase II, randomized, double-blind study evaluated whether addition of the PARP inhibitor veliparib to TMZ improves 4-month progression-free survival (PFS). **PATIENTS AND METHODS**: A total of 104 patients with recurrent SCLC were randomly assigned 1:1 to oral veliparib or placebo 40 mg twice daily, days 1 to 7, and oral TMZ 150 to 200 mg/m2/day, days 1 to 5, of a 28-day cycle until disease progression, unacceptable toxicity, or withdrawal of consent. Response was determined by imaging at weeks 4 and 8, and every 8 weeks thereafter. Improvement in PFS at 4 months was the primary end point. Secondary objectives included overall response rate (ORR), overall survival (OS), and safety and tolerability of veliparib with TMZ. Exploratory objectives included PARP-1 and SLFN11 immunohistochemical expression, MGMT promoter methylation, and circulating tumor cell quantification. **RESULTS:** No significant difference in 4-month PFS was noted between TMZ/veliparib (36%) and TMZ/placebo (27%; P = .19); median OS was also not improved significantly with TMZ/veliparib (8.2 months; 95% CI, 6.4 to 12.2 months; v 7.0 months; 95% CI, 5.3 to 9.5 months; P = .50). However, ORR was significantly higher in patients receiving TMZ/veliparib compared with TMZ/placebo (39% v 14%; P = .016). Grade 3/4 thrombocytopenia and neutropenia more commonly occurred with TMZ/veliparib: 50% versus 9% and 31% versus 7%, respectively. Significantly prolonged PFS (5.7 v 3.6 months; P = .009) and OS (12.2 v 7.5 months; P = .014) were observed in patients with SLFN11-positive tumors treated with TMZ/veliparib. **CONCLUSION:** Four-month PFS and median OS did not differ between the two arms, whereas a significant improvement in ORR was observed with TMZ/veliparib. SLFN11 expression was associated with improved PFS and OS in patients receiving TMZ/veliparib, suggesting a promising biomarker of PARP-inhibitor sensitivity in SCLC.

PALLIATIVE AND SUPPORTIVE CARE

Psychosocial consequences of diagnosis and treatment of lung cancer and evaluation of the need for a lung cancer specific instrument using focus group methodology. Looijmans M1, van Manen AS1, Traa MJ1,2, Kloover JS3, Kessels BLJ3, de Vries J4,5. Support Care Cancer. 2018 Jun 9. doi: 10.1007/s00520-018-4291-1. [Epub ahead of print]
OBJECTIVES: Patients with lung cancer (LC) have high rates of psychosocial symptoms and international guidelines recommend regular psychosocial screening during treatment. This study evaluates psychosocial consequences of diagnosis and treatment of LC in a qualitative way and evaluates the need for a LC specific screening instrument. **METHODS:** Focus group meetings with LC patients were divided by treatment type. Patients discussed psychological and social consequences of diagnosis and treatment. Major themes were identified using content analysis. Themes were re-evaluated in a subsequent focus group, in accordance with the European Organization for Research and Treatment of Cancer (EORTC) guidelines. **RESULTS:** Patients reported a range of psychosocial consequences, such as frustration due to physical limitations, fear of recurrence, sadness of leaving behind partner and children, and disappointing social support. Patients treated with palliative intent specifically indicated insecurities about the future. Patients from all treatment modalities indicated a need for family support

during treatment. No themes specific to LC arose. **CONCLUSIONS:** Patients with LC are coping with a range of psychosocial consequences, independent of the type of treatment they receive. Fear of recurrence/metastasis and insecurity about the future were more prominent in patients receiving palliative chemotherapy. Themes were not specific to LC; therefore, a screening instrument specific for the LC population does not seem required. However, the current standard for screening is considered insufficiently sensitive and a stepped screening approach with specific screening tools and a clinical interview is suggested as usual care.

[A Patient-Centered Activity Regimen Improves Participation in Physical Activity Interventions in Advanced-Stage Lung Cancer.](#) Bade BC1, Hyer JM2, Bevill BT2, Pastis A3, Rojewski AM2, Toll BA2, Silvestri GA2. Integr Cancer Ther. 2018 Jun 1:1534735418781739. doi: 10.1177/1534735418781739. [Epub ahead of print]

INTRODUCTION: Physical activity (PA) is a potential therapy to improve quality of life in patients with advanced-stage lung cancer (LC), but no PA regimen has been shown to be beneficial, clinically practical, and sustainable. We sought to test the hypothesis that a patient-centered activity regimen (PCAR) will improve patient participation and PA more effectively than weekly phone calls.
METHODS: In patients with advanced-stage LC, we implemented a walking-based activity regimen and motivated patients via either weekly phone calls (n = 29; FitBit Zip accelerometer) or PCAR (n = 15; FitBit Flex, an educational session, and twice-daily gain-framed text messages). Data collection over a 4-week period was compared, and a repeated-measures, mixed-effects model for activity level was constructed. **RESULTS:** Subjects receiving PCAR more frequently used the device (100% vs 79%) and less frequently had missing data (11% vs 38%). "More active" and "less active" groups were created based on mean step count in the first week. "Less active" patients in the PCAR group increased their PA level, whereas PA level fell in the "more active" group. Most subjects found PCAR helpful (92%) and would participate in another activity study (85%). **DISCUSSION:** Compared with weekly phone calls, PCAR has higher patient participation, is more likely to improve PA in "less active" subjects, and has high patient satisfaction. A multifaceted PA regimen may be a more efficacious mechanism to study PA in advanced LC. PCAR should be used in a randomized controlled trial to evaluate for improvements in symptom burden, quality of life, and mood.

[Lung Cancer Cachexia: Can Molecular Understanding Guide Clinical Management?](#) Sørensen J1. Integr Cancer Ther. 2018 Jun 1:1534735418781743. doi: 10.1177/1534735418781743. [Epub ahead of print]

Cachexia has been recognized for a long time as an adverse effect of cancer. It is associated with reduced physical function, reduced tolerance to anticancer therapy, and reduced survival. This wasting syndrome is mainly known for an ongoing loss of skeletal muscle leading to progressive functional impairment and is driven by a variable combination of reduced food intake and abnormal metabolism. Cytokines derived from host immune system or the tumor itself is believed to play a role in promoting cancer cachexia. Circulating levels of cytokines, including IL-1α, IL-6, and TNFα have been identified in cancer patients but they probably only represent a small part of a changed and abnormal metabolism. Murine models have shown that browning of white adipose tissue (WAT) takes place early in the progression of cancer cachexia. Thus, browning of white adipose tissue is believed to be a strong contributor to the increased energy expenditure common in cachectic patients. Despite the severe implications of cancer cachexia for the patients and extensive research efforts, a more coherent and mechanistic explanation of the syndrome is lacking, and for many clinicians, cancer cachexia is still a vague concept. From a lung cancer perspective this commentary reviews the current knowledge on cancer cachexia mechanisms and identifies specific ways of clinical management regarding food intake, systemic inflammation, and muscular dysfunction. Much of what we know comes from preclinical studies. More translational research

is needed for a future cancer cachexia screening tool to guide clinicians, and here possible variables for a cancer cachexia screening tool are considered.

COMPLEMENTARY & ALTERNATIVE THERAPY

[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 Jun;34(3):207-218. doi: 10.1007/s10565-018-9422-4. Epub 2018 Mar 5.

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.
PMID: 29508110

MISCELLANEOUS WORKS

[Inhaled corticosteroids in COPD and the risk of lung cancer.](#) Lee YM1, Kim SJ2, Lee JH2, Ha E1. Int J Cancer. 2018 Jun 26. doi: 10.1002/ijc.31632. [Epub ahead of print]

Inhaled corticosteroids (ICS) might reduce the risk of lung cancer by controlling airway inflammation in patients with chronic obstructive pulmonary disease (COPD) because both are associated with chronic inflammation. The objective was to assess the impact of ICS on lung cancer risk reduction in COPD patients. We performed a nested case-control study based on the database of the National Health Insurance Service-National Sample Cohort, a nationally representative cohort of 1,125,691 participants in Korea followed over 11 years. The eligible population was patients aged 30 to 89 years who were newly diagnosed with COPD and initiated inhaled medications after diagnosis. Cases were defined as individuals diagnosed with lung cancer after the initiation of inhaled medications and were matched with controls by propensity score at a 1:4 ratio. We identified 265 individuals with lung cancer, matched with 1,060 controls. Use of ICS was associated with reduced risk of lung cancer (adjusted hazard ratio [aHR] 0.74, 95% CI 0.57-0.96). The high cumulative ICS dose group, defined as those above the third quartile of ICS dose distribution, had a lower risk of lung cancer than the low cumulative dose group (aHR 0.51, 95% CI 0.34-0.75). The effect of ICS on lung cancer risk reduction was more remarkable in former smokers than current smokers. Additionally, the result was consistent in men regardless of the classification according to ICS use, while it was not significant in women. ICS, particularly at high cumulative dose, might be associated with decreased risk of lung cancer in patients with COPD. This article is protected by copyright. All rights reserved.

[Death Or Debt? National Estimates Of Financial Toxicity In Persons With Newly-Diagnosed Cancer.](#) Gilligan AM1, Alberts DS2, Roe DJ3, Skrepnek GH4. Am J Med. 2018 Jun 12. pii: S0002-9343(18)30509-6. doi: 10.1016/j.amjmed.2018.05.020. [Epub ahead of print]

PURPOSE: To evaluate the impact of cancer upon a patient's depletion of net worth and incursion of debt in the U.S. **METHODS:** This longitudinal study used the Health and Retirement Study (HRS) from 1998-2014. Persons ≥50 years with newly-diagnosed malignancies were included, excluding minor skin cancers. Multivariable generalized linear models were employed to assess changes in net worth and debt (consumer, mortgage, home equity) at two-and four-years following diagnosis (Year+2, Year+4) after controlling for demographic and clinically-related variables, cancer-specific attributes, economic factors, and mortality. A two-year period prior to cancer diagnosis served as an historical control. **RESULTS:** Across 9.5 million total estimated new diagnoses of cancer from 2000-2012, individuals averaged 68.6±9.4 years with slight majorities being married (54.7%), not retired (51.1%), and Medicare beneficiaries (56.6%). At Year+2, 42.4% depleted their entire life's assets, with higher adjusted odds associated with worsening cancer, requirement of continued treatment, socio-economic factors (i.e., increasing age/income/household size, female sex), clinical characteristics (i.e., current smoker, worse self-reported health, hypertension, diabetes, lung disease), Medicaid, and uninsured (p<0.05); average losses were -\$92,098. At Year+4, financial insolvency extended to 38.2%, with several consistent socio-economic, cancer-related, and clinical characteristics remaining significant predictors of complete asset depletion. **CONCLUSION:** Using nationally-representative data, this investigation of an estimated 9.5 million newly-diagnosed persons with cancer ≥50 years of age found a substantial proportion incurring financial toxicity. As large financial burdens have been found to adversely affect access to care and outcomes among cancer patients, the active development of approaches to mitigate these effects among already vulnerable groups remain of key importance.

[**Postoperative Management of Multiple Primary Cancers Associated with Non-small Cell Lung Cancer.**](#) Shoji F1,2, Yamazaki K3, Miura N3, Katsura M3, Oku Y3, Takeo S3, Maehara Y2. Anticancer Res. 2018 Jun;38(6):3773-3778. doi: 10.21873/anticanres.12660.

BACKGROUND/AIM: Modern treatment for primary cancers has improved survival. Therefore, increased numbers of patients with multiple primary cancers (MPC) associated with lung cancer may be expected. The aim of the present study was to report MPC associated with lung cancer and discuss patients' characteristics and postoperative management. **PATIENTS AND METHODS:** Overall, 973 consecutive patients who underwent surgery for non-small cell lung cancer (NSCLC) were retrospectively studied. **RESULTS:** NSCLC with MPC was observed in 148 patients (15.2%). MPC comprised 24 synchronous (2.5%) and 124 metachronous (12.7%) diseases. Of the 124 metachronous patients, NSCLC was detected before cancers were detected in other organs (lung cancer first (LCF)) in 25 (20.2%) patients and subsequently in other organs after treatment (other organs, primary cancer-first (OCF)) in 99 (79.8%) patients. MPC was significantly associated with advanced age (p<0.0001) and chronic obstructive pulmonary disease (COPD) (p=0.0040). The leading sites of MPC in patients with synchronous tumors and those with OCF were the digestive organs. In contrast, the leading site of MPC in patients with LCF was the lung. In the latter, at least two primary lung cancers were detected within 5 years as well as 5 years after surgery for the treatment of the first detected lung cancer, while primary cancers of other organs were detected within 5 years. **CONCLUSION:** Advanced age and COPD may represent a high-risk of MPCs. Therefore, we recommend careful follow-up to detect MPC in the lung as well as the digestive organs beyond 5 years after treatment of the first cancer.

[**Oral bisphosphonate use and lung cancer incidence among postmenopausal women.**](#) Tao MH1, Chen S1, Freudenheim JL2, et al. Ann Oncol. 2018 Jun 1;29(6):1476-1485. doi: 10.1093/annonc/mdy097.

BACKGROUND: Bisphosphonates are common medications for the treatment of osteoporosis in older populations. Several studies, including the Women's Health Initiative (WHI), have found inverse associations of bisphosphonate use with risk of breast and endometrial cancer, but little is known about its association with other common malignancies. The objective of this study was to evaluate the association

of bisphosphonate use on the incidence of lung cancer in the WHI. **PATIENTS AND METHODS:** The association between oral bisphosphonate use and lung cancer risk was examined in 151 432 postmenopausal women enrolled into the WHI in 1993-1998. At baseline and during follow-up, participants completed an inventory of regularly used medications including bisphosphonates. **RESULTS:** After a mean follow-up of 13.3 years, 2511 women were diagnosed with incident lung cancer. There was no evidence of a difference in lung cancer incidence between oral bisphosphonate users and never users (adjusted hazard ratio = 0.91; 95% confidence intervals, 0.80-1.04; P = 0.16). However, an inverse association was observed among those who were never smokers (hazard ratio = 0.57, 95% confidence interval, 0.39-0.84; P < 0.01). **CONCLUSION:** In this large prospective cohort of postmenopausal women, oral bisphosphonate use was associated with significantly lower lung cancer risk among never smokers, suggesting bisphosphonates may have a protective effect against lung cancer. Additional studies are needed to confirm our findings.

Radon and lung cancer: What does the public really know? Vogeltanz-Holm N1, Schwartz GG2. J Environ Radioact. 2018 Jun 5;192:26-31. doi: 10.1016/j.jenvrad.2018.05.017. [Epub ahead of print] Radon causes approximately 21,000 deaths annually from lung cancer, making it the second most important cause of lung cancer after smoking. However, the extent of public knowledge about radon is unclear. We systematically reviewed the epidemiologic literature in order to assay the public's understanding about radon and specifically, whether radon is known to cause lung cancer. Radon knowledge has most often been gauged via telephone and in-person responses to the question, "Have you heard about radon?" Our review of 20 such studies reveals that although many individuals have "heard about" radon, many segments of the population, particularly individuals younger than thirty and those with less education, do not know what radon is. Of those who have heard about radon, the majority of respondents in many studies did not know that radon causes lung cancer. Conversely, misinformation about radon is common; approximately 50% of respondents in many studies reported the erroneous belief that radon causes headaches. This suggests that the public has confused the effects of radon with those of carbon monoxide. Rates of radon testing and mitigation are correpondingly low and appear to reflect cognitive defense mechanisms by which individuals believe that their risks from radon are lower than the risks faced by others. Our review suggests that public information materials about radon require revision. Specifically, these should emphasize that radon causes lung cancer and that household carbon monoxide detectors do not detect it. Radon education provided by realtors at the time of residential home sales may be a promising venue to increase radon testing and remediation.

Potential Micronutrients and Phytochemicals against the Pathogenesis of Chronic Obstructive Pulmonary Disease and Lung Cancer. Zhai T1, Li S2, Hu W3, Li D4, Leng S5. Nutrients. 2018 Jun 25;10(7). pii: E813. doi: 10.3390/nu10070813.
Lung cancer and chronic obstructive pulmonary disease have shared etiology, including key etiological changes (e.g., DNA damage and epigenetics change) and lung function impairment. Focusing on those shared targets may help in the prevention of both. Certain micronutrients (vitamins and minerals) and phytochemicals (carotenoids and phenols) have potent antioxidant or methyl-donating properties and thus have received considerable interest. We reviewed recent papers probing into the potential of nutrients with respect to lung function preservation and prevention of lung cancer risk, and suggest several hypothetical intervention patterns. Intakes of vitamins (i.e., A, C, D, E, B12), carotenoids, flavonoids, curcumins, resveratrol, magnesium, and omega-3 fatty acids all show protective effects against lung function loss, some mainly by improving average lung function and others through reducing decline rate. Dietary interventions early in life may help lung function reserve over the lifespan. Protective nutrient interventions among smokers are likely to mitigate the effects of cigarettes on lung health. We also discuss their underlying mechanisms and some possible causes for the inconsistent results in

observational studies and supplementation trials. The role of the lung microbiome on lung health and its potential utility in identifying protective nutrients are discussed as well. More prospective cohorts and well-designed clinical trials are needed to promote the transition of individualized nutrient interventions into health policy.

[Genome-Wide Association Study of Familial Lung Cancer.](Byun J1, Schwartz AG2, Lusk C2, et al. Carcinogenesis. 2018 Jun 19. doi: 10.1093/carcin/bgy080. [Epub ahead of print]
To identify genetic variation associated with lung cancer risk, we performed a genome-wide association analysis of 685 lung cancer cases that had a family history of two or more first or second degree relatives compared with 744 controls without lung cancer that were genotyped on an Illumina Human OmniExpressExome-8v1 array. To ensure robust results, we further evaluated these findings using data from six additional studies that were assembled through the Transdisciplinary Research on Cancer of the Lung Consortium comprising 1,993 familial cases and 33,690 controls. We performed a meta-analysis after imputation of all variants using the 1000 Genomes Project Phase 1 (version 3 release date September 2013). Analyses were conducted for 9,327,222 SNPs integrating data from the two sources. A novel variant on chromosome 4p15.31 near the LCORL gene and an imputed rare variant intergenic between CDKN2A and IFNA8 on chromosome 9p21.3 were identified at a genome-wide level of significance for squamous cell carcinomas. Additionally, associations of CHRNA3 and CHRNA5 on chromosome 15q25.1 in sporadic lung cancer were confirmed at a genome-wide level of significance in familial lung cancer. Previously identified variants in or near CHRNA2, BRCA2, CYP2A6 for overall lung cancer, TERT, SECISPB2L and RTEL1 for adenocarcinoma and RAD52 and MHC for squamous carcinoma were significantly associated with lung cancer.

[Budget Impact Analysis of Afatinib for First-Line Treatment of Patients with Metastatic Non-Small Cell Lung Cancer with Epidermal Growth Factor Receptor Exon 19 Deletions or Exon 21 Substitution Mutations in a U.S. Health Plan.](Graham J1, Earnshaw S1, Burslem K2, Lim J2. J Manag Care Spec Pharm. 2018 Jun;24(6):544-553. doi: 10.18553/jmcp.2018.24.6.544.
BACKGROUND: Afatinib is 1 of 3 tyrosine kinase inhibitors approved in the United States for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions (del19) or exon 21 (L858R) substitution mutations. In clinical trials, afatinib has demonstrated improvement in progression-free survival versus standard chemotherapy and gefitinib. **OBJECTIVE:** To analyze the impact of increases in afatinib treatment share on the cost and health outcomes in a commercial health plan in the United States. **METHODS:** A decision model was developed to evaluate the budget impact of increases in afatinib share for the first-line treatment of patients with metastatic NSCLC with EGFR del19 or L858R substitution mutations over a 5-year time horizon. The model compared the total annual costs for a health plan with 1 million covered lives in a scenario in which afatinib share increased 5 percentage points annually to one in which all treatment shares remained constant over time. The number of patients eligible for treatment was estimated using published incidence data. Therapies included in the model were afatinib, erlotinib, gefitinib, and the chemotherapy doublet, pemetrexed in combination with cisplatin. The mean time spent by patients in progression-free and progressive disease states was based on survival data from clinical trials and a network meta-analysis. Therapy-related costs included monthly drug acquisition and administration costs and costs of managing adverse reactions. Disease management costs were also assessed in the model. Scenario analyses were performed to assess alternative scenarios of afatinib treatment share. Additionally, a one-way sensitivity analysis was performed to test the robustness of the model, given parameter uncertainty. **RESULTS:** Using the base-case parameter assumptions and a 5-percentage-point annual increase in afatinib treatment share, we estimated the total budget increases in years 1 through 5 to be $1,606, $65,542, $140,564, $209,272, and $303,368, respectively. These budget

increases translated to per-member-per-month increases ranging from $0.00 to $0.03 in years 1 to 5. The increase in afatinib use resulted in the proportion of the treated population (134 patients treated over 5 years) remaining in progression-free disease increasing from 23.7% to 26.2% at the end of year 5, versus if afatinib treatment share had stayed constant. **CONCLUSIONS:** Increasing the treatment share of afatinib in a health plan for the first-line treatment of NSCLC with EGFR del19 or L858R mutations was estimated to increase the proportion of treated patients remaining in progression-free disease, while having small budget impact to the health plan. **DISCLOSURES:** Boehringer Ingelheim Pharmaceuticals funded this study research and was involved in all stages of study conduct, including the analysis of data, and also undertook all costs associated with the development and publication of this manuscript. Graham and Earnshaw are employees of RTI Health Solutions, an independent contract research organization that has received research funding for this and other studies from Boehringer Ingelheim Pharmaceuticals. Lim and Burslem are employees of Boehringer Ingelheim Pharmaceuticals, which developed and produces afatinib, along with other pharmaceutical products.

[**Healthcare utilization and costs associated with COPD among SEER-Medicare beneficiaries with NSCLC.**](#) Shah S1, Blanchette CM1, Coyle JC2, Kowalkowski M3, Arthur ST2, Howden R1,2. J Med Econ. 2018 Jun 1:1-17. doi: 10.1080/13696998.2018.1484370. [Epub ahead of print]
AIM: To estimate the healthcare utilization and costs in elderly lung cancer patients with and without pre-existing chronic obstructive pulmonary disease. **METHODS:** Using SEER-Medicare data, we identified patients with lung cancer between 2006 to 2010, at least 66 years of age, and continuously enrolled in Medicare Parts A and B in the 12 months prior to cancer diagnosis. The diagnosis of pre-existing COPD in lung cancer patients were identified using ICD-9 codes. Healthcare utilization and costs were categorized as inpatient hospitalizations, skilled nursing facility (SNF) use, physician office visits, ER visits, and outpatient encounters for every stage of lung cancer. The adjusted analysis was performed using a generalized linear model for healthcare costs and a negative binomial model for healthcare utilization. **RESULTS:** Inpatient admissions in the COPD group increased for each stage of NSCLC compared to the Non-COPD group per 100 person-months (Stage I: 14.67 vs 9.49 stays, $P < 0.0001$; Stage II: 14.13 vs 10.78 stays, $P < 0.0001$; Stage III: 28.31 vs 18.91 stays, $P < 0.0001$; Stage IV: 49.5 vs 31.24 stays, $P < 0.0001$). A similar trend was observed for outpatient visits with an increase in utilization among COPD group (Stage I: 1136.04 vs 796 visits, $P < 0.0001$; Stage II: 1325.12 vs 983.26 visits, $P < 0.0001$; Stage III: 2025.47 vs 1656.64 visits, $P < 0.0001$; Stage IV: 2825.73 vs 2422.26 visits, $P < 0.0001$). Total direct costs per person-month in patients with pre-existing COPD were significantly higher than the Non-COPD group across all services ($54,799.16 vs $41,862.91). Outpatient visits represented the largest cost category across all services in both groups, with higher costs among the COPD group ($41,203 vs $31,140.08). **CONCLUSION:** Healthcare utilization and costs among lung cancer patients with pre-existing COPD was approximately two to three times higher than the Non-COPD group.

[**Racial disparities in lung cancer survival: The contribution of stage, treatment, and ancestry.**](#)
Jones CC1, Mercaldo SF2, Blume JD2, et al. J Thorac Oncol. 2018 Jun 6. pii: S1556-0864(18)30682-8. doi: 10.1016/j.jtho.2018.05.032. [Epub ahead of print]
INTRODUCTION: Lung cancer is a leading cause of cancer-related death worldwide. Racial disparities in LC survival exist between blacks and whites, yet are limited by categorical definitions of race. We sought to examine the impact of African ancestry on overall survival among black and white non-small cell lung cancer (NSCLC) cases. **METHODS:** Black and white incident NSCLC cases from the prospective Southern Community Cohort Study (N=425) were identified via linkage with state cancer registries in 12 Southern states. Vital status was determined by linkage with the National Death Index and Social Security Administration. We evaluated the impact of African ancestry, estimated using genome-wide ancestry informative markers, on overall survival by calculating the time-dependent area under the

curve (AUC) for Cox proportional hazards models, adjusting for relevant covariates such as stage and treatment. We replicated our findings in an independent population of black NSCLC cases. **RESULTS:** Global African ancestry was not significantly associated with overall survival among NSCLC cases. There was no change in model performance when comparing Cox proportional hazards models with and without African ancestry (AUC=0.79 for each model). Removal of stage and treatment reduced the average time-dependent AUC from 0.79 to 0.65. Similar findings were observed in our replication study. **CONCLUSIONS:** Stage and treatment are more important predictors of survival than African ancestry. These findings suggest that racial disparities in lung cancer survival may disappear with similar early detection efforts for blacks and whites alike.