Caring Ambassadors Lung Cancer Program
Literature Review, March 2017

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Neuroinflammatory and cognitive consequences of combined radiation and immunotherapy in a novel preclinical model.

McGinnis GJ1,2,3, Friedman D4, Young KH4, Torres ER2, Thomas CR Jr3, Gough MJ3,4, Raber J2,3,5,6.

BACKGROUND: Cancer patients often report behavioral and cognitive changes following cancer treatment. These effects can be seen in patients who have not yet received treatment or have received only peripheral (non-brain) irradiation. Novel treatments combining radiotherapy (RT) and immunotherapy (IT) demonstrate remarkable efficacy with respect to tumor outcomes by enhancing the proinflammatory environment in the tumor. However, a proinflammatory environment in the brain mediates cognitive impairments in other neurological disorders and may affect brain function in cancer patients receiving these novel treatments. Currently, gaps exist as to whether these treatments impact the brain in individuals with or without tumors and with regard to the underlying mechanisms. **RESULTS:** Combined treatment with precision RT and checkpoint inhibitor IT achieved control of tumor growth. However, BALB/c mice receiving combined treatment demonstrated changes in measures of anxiety levels, regardless of tumor status. C57BL/6J mice with tumors demonstrated increased anxiety, except following combined treatment. Object recognition memory was impaired in C57BL/6J mice without tumors following combined treatment. All mice with tumors showed impaired object recognition, except those treated with RT alone. Mice with tumors demonstrated impaired amygdala-dependent cued fear memory, while maintaining hippocampus-dependent context fear memory. These behavioral alterations and cognitive impairments were accompanied by increased microglial activation in mice receiving immunotherapy alone or combined with RT. Finally, based on tumor status, there were significant changes in proinflammatory cytokines (IFN-γ, IL-6, IL-5, IL-2, IL-10) and a growth factor (FGF-basic). **MATERIALS AND METHODS:** Here we test the hypothesis that IT combined with peripheral RT have detrimental behavioral and cognitive effects as a result of an enhanced proinflammatory environment in the brain. BALB/c mice with or without injected hind flank CT26 colorectal carcinoma or C57BL/6J mice with or without Lewis Lung carcinoma were used for all experiments. Checkpoint inhibitor IT, using an anti-CTLA-4 antibody, and precision CT-guided peripheral RT alone and combined were used to closely

model clinical treatment. We assessed behavioral and cognitive performance and investigated the immune environment using immunohistochemistry and multiplex assays to analyze proinflammatory mediators. **CONCLUSIONS:** Although combined treatment achieved tumor growth control, it affected the brain and induced changes in measures of anxiety, cognitive impairments, and neuroinflammation.

[The important role of circulating CYFRA21-1 in metastasis diagnosis and prognostic value compared with carcinoembryonic antigen and neuron-specific enolase in lung cancer patients.](#)

Zhang L1, Liu D2, Li L2, et al. BMC Cancer. 2017 Feb 2;17(1):96. doi: 10.1186/s12885-017-3070-6.
BACKGROUND: The roles of carcinoembryonic antigen (CEA), cytokeratin 19 fragments (CYFRA21-1) and neuron-specific enolase (NSE) in metastases occurrence and poor diagnosis in specific histological classifications of lung cancer need further exploring. In this study, we investigated relationship between elevated levels of three biomarkers of CEA, CYFRA21-1 and NSE (individually and in combination) and metastasis, survival status and prognosis in lung cancer patients. **METHODS:** Eight hundred and sixty eight lung cancer patients including adenocarcinoma (ADC, N = 445), squamous cell carcinoma (SCC, N = 215), small cell lung cancer (SCLC, N = 159) and other types (N = 49) were categorized into negative, moderate and high groups according to serum levels of biomarkers, and were then categorized into negative, single, double and triple groups according to any positive combination of three biomarkers. The cutoff values of three biomarkers for groupings were developed on the training group (N = 432) and verified in a validation group (N = 436). Clinical and laboratory characteristics were then assessed for correlation with occurrence of metastasis, survival status and prognosis between the two groups. Further correlation analyses were also conducted by different subtypes (ADC, SCC and SCLC) and tumor stages (I + II, III and IV) of lung cancers. **RESULTS:** The consistent results between training and validation group confirmed the rationality of grouping methods. CYFRA21-1 levels had stronger association with metastases and survival status than CEA and NSE in all lung cancer patients. When stratified by subtypes, these significances only existed in ADC patients for CYFRA21-1. Cox regression analyses showed that CYFRA21-1 and NSE were independent prognostic factors for lung cancer patients. However, only CYFRA21-1 was an independent prognostic factor in ADC and SCLC patients subtypes. Cox-regression results also indicated that CYFRA21-1 could act as independent prognostic factor in different stages (I + II, III and IV) of lung cancer. **CONCLUSION:** CYFRA21-1 was more important in metastasis occurrence and in predicting poor prognosis in lung cancer patients than CEA, NSE and positive numbers of biomarkers.

[Chronic treatment of non-small-cell lung cancer cells with gefitinib leads to an epigenetic loss of epithelial properties associated with reductions in microRNA-155 and -200c.](#) Narita M1, Shimura E1, Nagasawa A1, et al. PLoS One. 2017 Feb 22;12(2):e0172115. doi: 10.1371/journal.pone.0172115. eCollection 2017.

BACKGROUND: The EGFR tyrosine kinase inhibitor gefitinib is used in therapy for non-small-cell lung cancer (NSCLC). However, its application is limited by resistance-accelerated disease progression, which is accompanied by the epithelial-to-mesenchymal transition (EMT). In the present study, we performed multiple expression analyses of microRNAs (miRNAs) and quantified the expression of several related EMT players in gefitinib-resistant NSCLC cells. **METHODS AND RESULTS:** To establish gefitinib-resistant NSCLC cells, gefitinib-sensitive HCC827 cells, which exhibit an in-frame deletion [E746-A750] in EGFR exon 19, were exposed to gefitinib for at least 1.5 months. Next, to profile "gefitinib-resistant HCC827 (HCC827GR)" cells, which have a secondary T790M mutation in EGFR exon 20, a miRNA array analysis was performed in HCC827 and HCC827GR cells. The greatest differences were seen in the levels of miR-155 and miR-200c, which essentially disappeared in HCC827GR cells. In addition to these reductions, the levels of smad2 and zeb1, which are both key players in EMT and targets for miR-155 and miR-200c, respectively, were dramatically increased in

HCC827GR cells. In HCC827GR cells, the expression of epithelial-cadherin (E-cadherin) was greatly reduced with repressive histone modifications, whereas vimentin, which is expressed in mesenchymal cells, was dramatically increased with active histone modifications. In another gefitinib-resistant NSCLC cell line (H1975 cells), similar to the findings in HCC827GR cells, both miR-155 and miR-200c were absent, and the EMT was induced along with epigenetic modifications. Interestingly, the inhibition of both miR-155 and miR-200c in HCC827 cells without gefitinib induced significant increases in smad2 and zeb1 along with a dramatic decrease in E-cadherin and a slight increase in vimentin. Furthermore, although the inhibition of these miRNAs in HCC827 cells decreased gefitinib sensitivity, this dual-inhibition in HCC827 cells without gefitinib did not produce a secondary T790M mutation in EGFR exon 20. **CONCLUSION AND IMPLICATIONS:** These results suggest that chronic treatment of NSCLC cells with gefitinib changes the expression of miRNAs, including dramatic reductions in miR-155 and miR-200c along with an EGFR mutation. Furthermore, this depletion of miR-155 and miR-200c may be associated with the EMT along with histone modifications, and may contribute to the decrease in the sensitivity to gefitinib independent of a secondary EGFR mutation.

Eribulin in non-small cell lung cancer: challenges and potential strategies. Swami U1, Shah U2, Goel S2. Expert Opin Investig Drugs. 2017 Feb 6. doi: 10.1080/13543784.2017.1292250. [Epub ahead of print]
INTRODUCTION: Eribulin is a non-taxane, macrocyclic, synthetic, ketone analog of Halichondrin B with a microtubule inhibitory action specific towards plus ends. It is approved by United States Food and Drug Administration (USFDA) for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen. It is also approved as a third line therapy for patients with metastatic breast cancer who have received a prior treatment with anthracycline and taxane in either adjuvant or metastatic setting. It has also undergone investigation in various cancers including non-small cell lung cancer (NSCLC). Areas covered: This review covers eribulin in detail with regards to pharmacodynamics, mechanism of action, pharmacokinetics, published phase I studies along with special focus on phase II and III studies of eribulin in NSCLC. Expert opinion: Eribulin is a potent chemotherapeutic agent with acceptable and easily manageable toxicity profile. It has shown activity in NSCLC. However, the management of NSCLC is undergoing rapid evolution with introduction of newer immune mediated and targeted agents. The way to move forward is to combine eribulin with novel immune checkpoint inhibitors, targeted agents and chemotherapies in appropriate line of therapy.

Foxk2 inhibits non-small cell lung cancer epithelial-mesenchymal transition and proliferation through the repression of different key target genes. Chen S1, Jiang S2, Hu F2, Xu Y2, Wang T2, Mei Q2. Oncol Rep. 2017 Feb 16. doi: 10.3892/or.2017.5461. [Epub ahead of print]
Increasing evidence suggests that numerous fork-head transcription factors are required to repress the mammalian cells phenotype. Among them, Foxk2 is a ubiquitously expressed family member, but the role of Foxk2 in mediating tumor metastasis in non-small cell lung cancer has not been explored. In this investigation reduced Foxk2 expression was found in lung adenocarcinoma tissues compared with the adjacent non-tumor tissues, and was associated with better overall survival. Low expression was also found in the NSCLC cell lines such as A549, NCI-H520, H1299, H358 and H460 cells. Recombinant lentivirus expressing Foxk2 constructs or ShFoxk2 were developed and transfected into A549 cells or NCI-H520 cells, immunofluorescence assay, qRT-PCR, and western blot analysis were used to measure the change of the epithelial markers, E-cadherin and α-catenin, and mesenchymal markers N-cadherin and vimentin. Wound healing assay and Transwell assay were used to measure the relative cell invasion ability. MTT assay, Edu assay, and cell cycle distribution analysis were used to confirm the effect of Foxk2 on cell proliferation. ChIP-seq, qChIP, as well as luciferase reporter gene assays were used to detect the target genes regulated by Foxk2, Bioinformatics predicated the potential miRNAs that could target Foxk2. Our study demonstrated that Foxk2 played major roles in NSCLC EMT by directly

targeting N-cadherin and Snail, we found that Foxk2 regulated NSCLC cell growth by suppressing the expression of cyclin D1 and CDK4, which suggested that Foxk2 might be a multifunctional regulator in NSCLC. The expression of Foxk2 may be regulated by miR-1271, which could serve as a promising therapeutic target for NSCLC.

[**SIRT3 is correlated with the malignancy of non-small cell lung cancer.**](#) Xiong Y1, Wang M1, Zhao J1, Wang L2, Li X1, Zhang Z1, Jia L2, Han Y1. Int J Oncol. 2017 Mar;50(3):903-910. doi: 10.3892/ijo.2017.3868. Epub 2017 Feb 2.

The mitochondrial deacetylase SIRT3 plays a pivotal role in the initiation and the progression of certain cancers acting as an oncogene. However, in others it acts anti-oncogenically. Its conflicting action is possibly due to the different key proteins it modifies depending on the context of active intracellular signaling pathways in different cancers. SIRT3 is thus a novel target for preventing and treating cancer. In the present study, we explored the function of SIRT3 in non-small cell lung cancer (NSCLC) with the aim of elucidating the underlying mechanisms. We first determined the SIRT3 expression levels by real-time PCR, western blotting and immunohistochemistry on tissue microarrays of paired samples of NSCLC tissue and adjacent normal tissue from 70 patients with associated clinicopathological data. Levels of SIRT3 protein and mRNA were significantly increased in NSCLC tissue, compared with normal tissue ($P<0.05$). Expression of SIRT3 in NSCLC positively correlated with that of malignant biomarker Ki-67 ($P<0.05$) and oncogene p-Akt ($P<0.05$). Patients with higher SIRT3 expression had a shorter overall survival duration ($P<0.05$). NSCLC tissue of squamous cell carcinoma type had higher SIRT3 expression compared with other types ($P<0.05$). Furthermore, among the clinicopathological variables examined, SIRT3 expression was correlated only with pathological type ($P<0.05$). In NSCLC cell lines, we found that downregulation of SIRT3 by siRNA decreased the activation of Akt, and that SIRT3 overexpression caused the activation of Akt. In addition, in a NSCLC cell line, SIRT3 was able to co-immunoprecipitate Akt and co-located with Akt, suggesting that SIRT3 regulates the activation of Akt through post-transcriptional modification. Our findings suggest that SIRT3 promotes the malignancy of NSCLC, showing an oncogenic preference towards squamous cell carcinoma, and that could represent a novel target for treatment.

[**Pharmacokinetic drug-drug interaction between erlotinib and paracetamol: A potential risk for clinical practice.**](#) Karbownik A1, Szałek E1, Sobańska K2, Grabowski T3, Wolc A4, Grześkowiak E1. Eur J Pharm Sci. 2017 Feb 20. pii: S0928-0987(17)30105-7. doi: 10.1016/j.ejps.2017.02.028. [Epub ahead of print]

BACKGROUND: Erlotinib is a tyrosine kinase inhibitor available for the treatment of non-small cell lung cancer. Paracetamol is an analgesic agent, commonly used in cancer patients. Because these drugs are often co-administered, there is an increasing issue of interaction between them. **OBJECTIVE:** The aim of the study was to investigate the effect of paracetamol on the pharmacokinetic parameters of erlotinib, as well as the influence of erlotinib on the pharmacokinetics of paracetamol. **METHODS:** The rabbits were divided into three groups: the rabbits receiving erlotinib (IER), the group receiving paracetamol (IIPR), and the rabbits receiving erlotinib+paracetamol (IIIER+PR). A single dose of erlotinib was administered orally (25mg) and was administered intravenously (35mg/kg). Plasma concentrations of erlotinib, its metabolite (OSI420), paracetamol and its metabolites - glucuronide and sulphate were measured with the validated method. **RESULTS:** During paracetamol co-administration we observed increased erlotinib maximum concentration (Cmax) and area under the plasma concentration-time curve from time zero to infinity (AUC0-∞) by 87.7% and 31.1%, respectively. In turn, erlotinib lead to decreased paracetamol AUC0-∞ by 35.5% and Cmax by 18.9%. The mean values of paracetamol glucuronide/paracetamol ratios for Cmax were 32.2% higher, whereas paracetamol sulphate/paracetamol ratios for Cmax and AUC0-∞ were 37.1% and 57.1% lower in the IIPR group, when

compared to the IIIER+PR group. **CONCLUSIONS:** Paracetamol had significant effect on the enhanced plasma exposure of erlotinib. Additionally, erlotinib contributed to the lower concentrations of paracetamol. Decreased glucuronidation and increased sulphation of paracetamol after co-administration of erlotinib were also observed.

SCREENING, DIAGNOSIS AND STAGING

Unique prevalence of oncogenic genetic alterations in young patients with lung adenocarcinoma.
Tanaka K1, Hida T1, Oya Y1, et al. Cancer. 2017 Feb 8. doi: 10.1002/cncr.30539. [Epub ahead of print]
BACKGROUND: Lung adenocarcinoma in the young is a rare entity, and the oncogenic genetic alterations (GAs) and clinical characteristics associated with this disease are poorly understood. Conversely, it has been demonstrated that young age at diagnosis defines unique biology in other cancers. For this report, the effects of young age on lung adenocarcinoma are reported. **METHODS:** The authors retrospectively screened 1746 consecutive patients who were diagnosed with stage I through IV adenocarcinoma between 2009 and 2015 and identified 81 who were aged 40 years or younger at diagnosis. The clinical and genetic characteristics of this younger population were analyzed. **RESULTS:** Of the 81 younger patients identified, 36 (44%) were men, 36 (44%) were never smokers, and the median age was 36 years (range, 26-40 years). Thirty-three patients (41%) harbored anaplastic lymphoma kinase (ALK) translocations, 24 (30%) had epidermal growth factor receptor (EGFR) mutations, and 2 (2%) had v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations. Rare oncogenic GAs also were studied in patients who had wild-type ALK/EGFR/KRAS adenocarcinoma, including 4 patients with HER2 mutations, 2 with Ret proto-oncogene (RET) translocations, and 2 with ROS proto-oncogene 1 receptor tyrosine kinase (ROS1) translocations. Notably, oncogenic GAs ($P < .001$), ALK ($P < .001$) and ROS1 ($P = .033$) translocations, and HER2 mutations ($P < .001$) were associated with young age, and a similar trend was observed for RET translocations ($P = .108$). Younger patients who had adenocarcinoma without GAs had a significantly worse prognosis compared with older patients without GAs (overall survival, 8.9 vs 16.4 months; $P < .001$) and patients with GAs (24.9 months; $P < .001$). **CONCLUSIONS:** Younger patients with adenocarcinoma have a distinctly unique prevalence of oncogenic GAs. Comprehensive oncogenic GA screening is especially recommended for personalized medicine strategies in this population.

PET-CT in presurgical lymph node staging in non-small cell lung cancer: the importance of false-negative and false-positive findings.
García de Castro AB1, Domínguez JF2, Bolton RD3, Pérez CF4, Martínez BC2, García-Esquinas MG2, Carreras Delgado JL5. Radiologia. 2017 Feb 23. pii: S0033-8338(17)30001-2. doi: 10.1016/j.rx.2016.12.001. [Epub ahead of print]
OBJECTIVE: To assess the importance of false-negative and false-positive findings in computed tomography (CT) and 18F-FDG positron emission tomography (PET) in mediastinal lymph node staging in patients undergoing surgery for non-small cell lung cancer (NSCLC). **MATERIAL AND METHODS:** This retrospective study included 113 consecutive patients and 120 resected NSCLCs; 22 patients received neoadjuvant treatment. We compared the findings on preoperative 18F-FDG PET-CT studies with the postoperative pathology findings. Lymph node size and primary tumor size were measured with CT, and lymph nodes and primary tumors were evaluated qualitatively and semiquantitatively (using standardized uptake values (SUVmax)) with PET. **RESULTS:** Metastatic lymph nodes were found in 26 (21.7%) of the 120 tumors and in 41 (7.7%) of the 528 lymph node stations analyzed. 18F-FDG PET-CT yielded 53.8% sensitivity, 76.6% specificity, 38.9% positive predictive value, 85.7% negative predictive value, and 71.7% diagnostic accuracy. The false-negative rate was 14.2%. Multivariable analysis found that the factors associated with false-negative findings were a moderate degree of differentiation in the primary tumor ($p = 0.005$) and an SUVmax of the primary tumor

>4 (p = 0.027). The false-positive rate was 61.1%, and the multivariable analysis found that lymph node size >1cm was associated with false-positive findings (p < 0.001). **CONCLUSIONS:** In mediastinal lymph node staging in patients with NSCLC, 18F-FDG PET-CT improves the specificity and negative predictive value and helps clinicians to select the patients that will benefit from surgery. Given the high rate of false positives, histological confirmation of positive cases is recommendable.

Early Results of Lung Cancer Screening and Radiation Dose Assessment by Low-dose CT at a Community Hospital. Jacobs CD1, Jafari ME2. Clin Lung Cancer. 2017 Feb 2. pii: S1525-7304(17)30040-2. doi: 10.1016/j.cllc.2017.01.011. [Epub ahead of print]
BACKGROUND: The National Lung Screening Trial showed a reduction in overall and cancer-specific mortality for patients screened with low-dose computed tomography (LDCT) versus chest radiograph. Some question whether this can be achieved in community healthcare settings. Our aim was to analyze lung cancer screening outcomes and administered radiation dose using LDCT scans at a community hospital. **PATIENTS AND METHODS:** We retrospectively reviewed the records of 680 patients who underwent LDCT between June 2014 and December 2015, and who met Centers for Medicare and Medicaid Services lung cancer screening criteria: asymptomatic, aged 55 to 77 years, smoked within the last 15 years, and ≥ 30 pack-year history. Effective and absorbed doses were calculated and correlated with gender and body mass index. **RESULTS:** Among the 133 patients (19.6%) with a positive screening result (Lung Imaging Reporting and Data System score of 3 or 4), 18 lung cancers were identified in 16 patients, 56.3% (9 of 16) of which were stage I non-small-cell lung cancer. The false-positive rate was 82.8% (95% confidence interval, 73.6%-89.8%). Mean estimated effective dose using dose length product and size-specific dose estimate using water equivalent diameter were 1.2 mSv and 3.7 mGy for women and 1.4 mSv and 3.9 mGy for men, respectively. All dosing metrics were strongly correlated with body mass index (P < .0001). **CONCLUSIONS:** Over half of screening patients diagnosed with non-small-cell lung cancer in our community had stage I disease, which we anticipate translating into significantly improved mortality. Patient radiation dose from LDCT scans is approximately one-fifth that from standard CT chest examinations.

Transbronchial and transesophageal fine-needle aspiration using a single ultrasound bronchoscope in the diagnosis of locoregional recurrence of surgically-treated lung cancer. Sanz-Santos J1, Serra P2,3, Andreo F2, et al. BMC Pulm Med. 2017 Feb 28;17(1):46. doi: 10.1186/s12890-017-0388-4.
BACKGROUND: The present study sought to evaluate the usefulness of EBUS-TBNA in the diagnosis of locoregional recurrence of lung cancer in a cohort of lung cancer patients who were previously treated surgically, and describe our initial experience of EUS-B-FNA in this clinical scenario. **METHODS:** We retrospectively studied the clinical records of all patients with a previous surgically-treated lung cancer who were referred to our bronchoscopy unit after suspicion of locoregional recurrence. The diagnostic sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy of EBUS-TBNA for the diagnosis of locoregional recurrence were evaluated. **RESULTS:** Seventy-three patients were included. EBUS-TBNA confirmed malignancy in 40 patients: 34 confirmed to have locoregional recurrence, six had metachronous tumours. Of the 33 patients with non-malignant EBUS-TBNA; 2 had specific non-malignant diseases, 26 underwent radiological follow up and 5 patients underwent surgery. Of the 26 patients who had radiological follow up; 18 remained stable, three presented thoracic radiological progression and 5 presented extrathoracic progression. Of the 5 patients who underwent surgery; 3 had metachronous tumours, one confirmed to be a true negative and one presented nodal invasion. Seven patients underwent EUS-B-FNA, four of them confirmed to have recurrence. The sensitivity, specificity, NPV, PPV and overall accuracy of EBUS-TBNA for the diagnosis of locoregional recurrence were 80.9, 100, 69.2, 100 and 86.6% respectively. **CONCLUSIONS:** EBUS-TBNA is an

accurate procedure for the diagnosis of locoregional recurrence of surgically-treated lung cancer. EUS-B-FNA combined with EBUS-TBNA broads the diagnostic yield of EBUS-TBNA alone.

[Preliminary evaluation of a telephone-based smoking cessation intervention in the lung cancer screening setting: A randomized clinical trial.](#) Taylor KL1, Hagerman CJ2, Luta G3, et al. Lung Cancer. 2017 Feb 14. pii: S0169-5002(17)30029-6. doi: 10.1016/j.lungcan.2017.01.020. [Epub ahead of print]

Incorporating effective smoking cessation interventions into lung cancer screening (LCS) programs will be essential to realizing the full benefit of screening. We conducted a pilot randomized trial to determine the feasibility and efficacy of a telephone-counseling (TC) smoking cessation intervention vs. usual care (UC) in the LCS setting. In collaboration with 3 geographically diverse LCS programs, we enrolled current smokers (61.5% participation rate) who were: registered to undergo LCS, 50-77 years old, and had a 20+ pack-year smoking history. Eligibility was not based on readiness to quit. Participants completed pre-LCS (T0) and post-LCS (T1) telephone assessments, were randomized to TC (N=46) vs. UC (N=46), and completed a final 3-month telephone assessment (T2). Both study arms received a list of evidence-based cessation resources. TC participants also received up to 6 brief counseling calls with a trained cessation counselor. Counseling calls incorporated motivational interviewing and utilized the screening result as a motivator for quitting. The outcome was biochemically verified 7-day point prevalence cessation at 3-months post-randomization. Participants (56.5% female) were 60.2 (SD=5.4) years old and reported 47.1 (SD=22.2) pack years; 30% were ready to stop smoking in the next 30 days. TC participants completed an average of 4.4 (SD=2.3) sessions. Using intent-to-treat analyses, biochemically verified quit rates were 17.4% (TC) vs. 4.3% (UC), p<.05. This study provides preliminary evidence that telephone-based cessation counseling is feasible and efficacious in the LCS setting. As millions of current smokers are now eligible for lung cancer screening, this setting represents an important opportunity to exert a large public health impact on cessation among smokers who are at very high risk for multiple tobacco-related diseases. If this evidence-based, brief, and scalable intervention is replicated, TC could help to improve the overall cost-effectiveness of LCS.

[Evaluations of Implementation at Early-adopting Lung Cancer Screening Programs: Lessons Learned.](#) Gesthalter YB1, Koppelman E2, Bolton R3, Slatore CG4, Yoon SH5, Cain HC6, Tanner NT7, Au DH8, Clark JA2, Wiener RS9. Chest. 2017 Feb 18. pii: S0012-3692(17)30222-2. doi: 10.1016/j.chest.2017.02.012. [Epub ahead of print]

BACKGROUND: Guidelines recommend lung cancer screening and it is currently being adopted nationwide. The American College of Chest Physicians advises inclusion of specific programmatic components to ensure high-quality screening. However, little is known about how lung cancer screening has been implemented in practice. We sought to evaluate the experience of early-adopting programs, characterize barriers faced, and identify strategies to achieve successful implementation. **METHODS:** We performed qualitative evaluations of lung cancer screening implementation at three Veterans Health Administration facilities, conducting semi-structured interviews with key staff (n=29). Guided by the Promoting Action on Research Implementation in Health Services framework, we analyzed transcripts using principals of grounded theory. **RESULTS:** Programs successfully incorporated most recommended elements of lung cancer screening, although varying in approaches to patient selection, tobacco treatment, and quality audits. Barriers to implementation included managing workload to ensure appropriate evaluation of screen-detected pulmonary nodules and difficulty obtaining primary care buy-in. To manage workload, programs employed nurse coordinators to actively maintain screening registries, held multidisciplinary conferences that generated explicit management recommendations, and rolled out implementation in a staged fashion. Successful strategies to engage primary care included educational sessions, audit and feedback of local outcomes, and assisting with and assigning clear responsibility for

nodule evaluation. Capitalizing on pre-existing relationships and including a designated program champion helped facilitate intra-disciplinary communication. **CONCLUSION:** Lung cancer screening implementation is a complex undertaking requiring coordination at many levels. The insight gained from evaluation of these early-adopting programs may inform subsequent design and implementation of lung cancer screening programs.

[Profile of the Roche cobas® EGFR mutation test v2 for non-small cell lung cancer.](#) Malapelle U1, Sirera R2,3,4, Jantus-Lewintre E2,3,4, et al. Expert Rev Mol Diagn. 2017 Mar;17(3):209-215. doi: 10.1080/14737159.2017.1288568. Epub 2017 Feb 9.

INTRODUCTION: The discovery of driver mutations in non-small cell lung cancer (NSCLC) has led to the development of genome-based personalized medicine. Fifteen to 20% of adenocarcinomas harbor an epidermal growth factor receptor (EGFR) activating mutation associated with responses to EGFR tyrosine kinase inhibitors (TKIs). Individual laboratories' expertise and the availability of appropriate equipment are valuable assets in predictive molecular pathology, although the choice of methods should be determined by the nature of the samples to be tested and whether the detection of only well-characterized EGFR mutations or rather, of all detectable mutations, is required. Areas covered: The EGFR mutation testing landscape is manifold and includes both screening and targeted methods, each with their own pros and cons. Here we review one of these companion tests, the Roche cobas® EGFR mutation test v2, from a methodological point of view, also exploring its liquid-biopsy applications. Expert commentary: The Roche cobas® EGFR mutation test v2, based on real time RT-PCR, is a reliable option for testing EGFR mutations in clinical practice, either using tissue-derived DNA or plasma-derived cfDNA. This application will be valuable for laboratories with whose purpose is purely diagnostic and lacking high-throughput technologies.

[Expression of MET in circulating tumor cells correlates with expression in tumor tissue from advanced-stage lung cancer patients.](#) Ilie M1,2, Szafer-Glusman E3, Hofman V1,2,4, et al. Oncotarget. 2017 Feb 15. doi: 10.18632/oncotarget.15345. [Epub ahead of print]

Given the difficulty in obtaining adequate tissue in NSCLC, we investigated the utility of circulating tumor cells (CTCs) for MET status assessment in NSCLC patients. We used two platforms for CTC capture, and assessed MET expression in CTCs and matched-bronchial biopsies in patients with advanced-stage III/IV lung adenocarcinoma. Baseline peripheral blood was collected from 256 advanced-stage III/IV NSCLC patients from Genentech clinical trials, and from 106 patients with advanced-stage III/IV lung adenocarcinoma treated at the Department of Pneumology, Pasteur Hospital, Nice. CTCs were enriched using CellSearch (Genentech), or ISET technologies (Pasteur Hospital). MET expression was evaluated by immunofluorescence on CellSearch, and by immunocytochemistry on ISET-enriched CTCs and on matched FFPE tissue sections (Pasteur Hospital). CTCs were detected in 83 of 256 (32%) patients evaluated on CellSearch, with 30 samples (12%) exhibiting ≥ 5 CTCs/7.5 ml blood. On ISET, CTC were observed in 80 of 106 patients (75%), and 79 patients (75%) exhibited ≥ 5 CTCs/4 ml blood. MET expression on ISET CTCs was positive in 72% of cases, and the MET expression on matched-patient tissue was positive in 65% patients using the Onartuzumab IHC scoring algorithm (93% concordance). Quantification of MET expression using H-scores showed strong correlation between MET expression in tissue and CTCs (Spearman correlation, 0.93). MET status in CTCs isolated on ISET filters from blood samples of advanced-stage NSCLC patients correlated strongly with MET status in tumor tissue, illustrating the potential for using CTCs as a non-invasive, real-time biopsy to determine MET status of patients entering clinical trials.

NSCLC - SURGERY

[Impact of PD-L1 Expression in Patients with Surgically Resected Non-Small-Cell Lung Cancer.](#)
Igawa S1, Sato Y, Ryuge S, et al. Oncology. 2017 Feb 22. doi: 10.1159/000458412. [Epub ahead of print]
BACKGROUND: Immunotherapy can become a crucial therapeutic option to improve the prognosis of patients with non-small-cell lung cancer (NSCLC). Here, we evaluated the impact of programmed cell death ligand-1 (PD-L1) expression in surgically resected NSCLCs. **METHODS:** We estimated PD-L1 expression in 229 consecutive NSCLC specimens using rabbit polyclonal antibodies to human PD-L1 in a SP263 immunohistochemical assay and evaluated PD-L1 expression for potential associations with clinicopathological parameters and survival time. **RESULTS:** PD-L1 expression was significantly higher in tumors from men or current smokers. Squamous cell carcinoma histology was independently associated with high PD-L1 expression according to multivariate analysis ($p = 0.015$). The 5-year survival rate of patients was 70%, and the difference in the 5-year survival rate according to PD-L1 expression was not statistically significant (high expression group [67%] vs. low expression group [68%]); however, the squamous cell carcinoma group exhibited significantly lower 5-year survival rates as compared to the non-squamous cell carcinoma group (53 and 71%, respectively; $p = 0.026$). **CONCLUSION:** Here, we revealed high PD-L1 expression and poor prognosis observed in patients with surgically resected squamous NSCLC as compared with non-squamous NSCLC. Our results support the identification of patient subsets that most likely respond to anti-PD-1 therapy as the first step in precision medicine.

[Surgical treatment in non-small cell lung cancer with pulmonary oligometastasis.](#) He J1, Li Y1, An J1, Hu L1, Zhang J2. World J Surg Oncol. 2017 Feb 2;15(1):36. doi: 10.1186/s12957-017-1105-8.
BACKGROUND: Previous studies have demonstrated survival benefits for local treatment in solitary metastatic non-small cell lung cancer (NSCLC).This study aimed to investigate the effect of local surgery for NSCLC with pulmonary oligometastasis. **METHODS:** This study included 21 patients of NSCLC with pulmonary oligometastasis between January 2003 and December 2013, which were divided into two groups, group A (11 cases) for local surgery and group B (10 cases) for systematic chemotherapy, compared the median survival time (MST) and 5-year survival rate between the two groups, and analyzed the impact of the pathological types, the TNM and pN stage of primary tumor, the site, and the mode and number of oligometastatic nodule on group A. **RESULTS:** The MST of group A and B were 37 and 11.6 months respectively, 5-year survival rates were 18.2 and 9.1% respectively ($p < 0.05$). Patients with single nodule, oligo-recurrence, primary tumor of pN0, TNM stage I or II obtained higher survival rate than those with multiple nodules, sync-oligometastases, pN1-2, stage III or IV in group A ($p < 0.05$). There was no significant survival time difference among pathological types of primary tumor and oligometastatic site ($p > 0.05$). **CONCLUSION:** Local surgery significantly prolonged the overall survival time and 5-year survival rate of primary NSCLC with pulmonary oligometastasis.

[Salvage surgery for primary lung cancer after chemotherapy in octogenarians.](#)
Hino H1, Nishimura T1, Usuki C2, Sazuka M2, Ito T1, Seki A3, Nitadori JI1,4, Yamada H2, Arai T3, Yamamoto H3, Nakajima J1,4. Thorac Cancer. 2017 Feb 27. doi: 10.1111/1759-7714.12423. [Epub ahead of print]
An 81-year-old female patient was admitted to our institute because of abnormal X-ray results. Chest computed tomography showed a 7.7 × 5.3 cm mass located in the left lower lobe and multiple swollen lymph nodes. 18F-fluorodeoxyglucose-positron emission tomography indicated high standard uptake values in the mass and swollen lymph nodes. The patient was diagnosed with stage cT3N2M0-IIIA squamous cell carcinoma. Although the patient had multiple lymph node metastases and severe

obstructive pulmonary function, four cycles of platinum doublet chemotherapy were initially performed and no side effect greater than grade 3 was experienced. As the lung cancer was downstaged to ycT2aN0M0-IB and pulmonary function had improved, a bronchodilating preparation, an uneventful left lower lobectomy, and a lymphadenectomy were performed. The patient was discharged 39 days after surgery and exhibited good health for a year at pathological stage ypT1aN0M0-IA (Ef2).

[Long-term Survival Based on the Surgical Approach to Lobectomy For Clinical Stage I Nonsmall Cell Lung Cancer: Comparison of Robotic, Video-assisted Thoracic Surgery, and Thoracotomy Lobectomy.](#) Yang HX1, Woo KM, Sima CS, Bains MS, Adusumilli PS, Huang J, Finley DJ, Rizk NP, Rusch VW, Jones DR, Park BJ. Ann Surg. 2017 Feb;265(2):431-437. doi: 10.1097/SLA.0000000000001708.

OBJECTIVE: To compare the long-term outcomes among robotic, video-assisted thoracic surgery (VATS), and open lobectomy in stage I nonsmall cell lung cancer (NSCLC). **BACKGROUND:** Survival comparisons between robotic, VATS, and open lobectomy in NSCLC have not yet been reported. Some studies have suggested that survival after VATS is superior, for unclear reasons. **METHODS:** Three cohorts (robotic, VATS, and open) of clinical stage I NSCLC patients were matched by propensity score and compared to assess overall survival (OS) and disease-free survival (DFS). Univariate and multivariate analyses were performed to identify factors associated with the outcomes. **RESULTS:** From January 2002 to December 2012, 470 unique patients (172 robotic, 141 VATS, and 157 open) were included in the analysis. The robotic approach harvested a higher number of median stations of lymph nodes (5 for robotic vs 3 for VATS vs 4 for open; $P < 0.001$). Patients undergoing minimally invasive approaches had shorter median length of hospital stay (4 d for robotic vs 4 d for VATS vs 5 d for open; $P < 0.001$). The 5-year OS for the robotic, VATS, and open matched groups were 77.6%, 73.5%, and 77.9%, respectively, without a statistically significant difference; corresponding 5-year DFS were 72.7%, 65.5%, and 69.0%, respectively, with a statistically significant difference between the robotic and VATS groups ($P = 0.047$). However, multivariate analysis found that surgical approach was not independently associated with shorter OS and DFS. **CONCLUSIONS:** Minimally invasive approaches to lobectomy for clinical stage I NSCLC result in similar long-term survival as thoracotomy. Use of VATS and robotics is associated with shorter length of stay, and the robotic approach resulted in greater lymph node assessment.

[The Preoperative Controlling Nutritional Status Score Predicts Survival After Curative Surgery in Patients with Pathological Stage I Non-small Cell Lung Cancer.](#) Shoji F1, Haratake N2, Akamine T2, et al. Anticancer Res. 2017 Feb;37(2):741-747.

BACKGROUND: The prognostic Controlling Nutritional Status (CONUT) score is used to evaluate immuno-nutritional conditions and is a predictive factor of postoperative survival in patients with digestive tract cancer. We retrospectively analyzed clinicopathological features of patients with pathological stage I non-small cell lung cancer (NSCLC) to identify predictors or prognostic factors of postoperative survival and to investigate the role of preoperative CONUT score in predicting survival. **PATIENTS AND METHODS:** We selected 138 consecutive patients with pathological stage I NSCLC treated from August 2005 to August 2010. We measured their preoperative CONUT score in uni- and multivariate Cox regression analyses of postoperative survival. **RESULTS:** A high CONUT score was positively associated with preoperative serum carcinoembryonic antigen level (p=0.0100) and postoperative recurrence (p=0.0767). In multivariate analysis, the preoperative CONUT score [relative risk (RR)=6.058; 95% confidence interval (CI)=1.068-113.941; p=0.0407), increasing age (RR=7.858; 95% CI=2.034-36.185; p=0.0029), and pleural invasion (RR=36.615; 95% CI=5.900-362.620; p<0.0001) were independent prognostic factors. In Kaplan-Meier analysis of recurrence-free survival (RFS), cancer-specific survival (CS), and overall survival (OS), the group with high CONUT score had a significantly shorter RFS, CS, and OS than did the low-CONUT score group by log-rank test (p=0.0458, p=0.0104 and

p=0.0096, respectively). **CONCLUSION:** The preoperative CONUT score is both a predictive and prognostic factor in patients with pathological stage I NSCLC. This immuno-nutritional score can indicate patients at high risk of postoperative recurrence and death.

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

Combination immunotherapy: a road map. Ott PA1, Hodi FS1, Kaufman HL2, Wigginton JM3, Wolchok JD4. J Immunother Cancer. 2017 Feb 21;5:16. doi: 10.1186/s40425-017-0218-5. eCollection 2017.
Cancer immunotherapy and in particular monoclonal antibodies blocking the inhibitory programed cell death 1 pathway (PD-1/PD-L1) have made a significant impact on the treatment of cancer patients in recent years. However, despite the remarkable clinical efficacy of these agents in a number of malignancies, it has become clear that they are not sufficiently active for many patients. Initial evidence, for example with combined inhibition of PD-1 and CTLA-4 in melanoma and non-small cell lung cancer (NSCLC), has highlighted the potential to further enhance the clinical benefits of monotherapies by combining agents with synergistic mechanisms of action. In order to address the current progress and consider challenges associated with these novel approaches, the Society for Immunotherapy of Cancer (SITC) convened a Combination Immunotherapy Task Force. This Task Force was charged with identifying and prioritizing the most promising prospects for combinatorial approaches as well as addressing the challenges associated with developing these strategies. As a result of the extensive clinical benefit and tolerable side effects demonstrated with agents inhibiting the PD-1 pathway, an overview of current evidence to support its promising potential for use as a backbone in combination strategies is presented. In addition, key issues in the development of these strategies including preclinical modeling, patient safety and toxicity considerations, clinical trial design, and endpoints are also discussed. Overall, the goal of this manuscript is to provide a summary of the current status and potential challenges associated with the development and clinical implementation of these strategies.

Treatment Patterns and Overall Survival Associated with First-Line Systemic Therapy for Patients with Advanced Non-Small Cell Lung Cancer. Spence MM1, Hui RL2, Chang JT3, Schottinger JE4, Millares M5, Rashid N1. J Manag Care Spec Pharm. 2017 Feb;23(2):195-205. doi: 10.18553/jmcp.2017.23.2.195.
BACKGROUND: A variety of regimens are used as first-line treatment in patients with advanced non-small cell lung cancer (NSCLC), which may include combination regimens and single agents, depending on histology, molecular profile, and performance status. **OBJECTIVE:** To describe the types of first-line therapies and compare overall survival between therapies used for patients with advanced NSCLC in an integrated health care system. **METHODS:** This retrospective cohort study included patients aged 18 years or older from Kaiser Permanente California with a diagnosis of stage IIIB/IV NSCLC. First systemic treatment date occurred from January 1, 2008, through September 30, 2013. Overall survival was measured as the number of months from initial treatment until death, end of enrollment, or September 30, 2014. Treatment regimens were categorized into 6 mutually exclusive groups: platinum doublets; pemetrexed-based, bevacizumab-based, and pemetrexed + bevacizumab-based combinations; singlets; and tyrosine-kinase inhibitors (TKIs). Survival was compared using Kaplan-Meier curves and adjusted Cox proportional hazard models. Subgroup analyses were performed by age group and by nonsquamous histology. **RESULTS:** Of 2,081 patients, approximately half (52.3%) received platinum doublets, followed by TKIs (19.0%), pemetrexed-based regimens (13.4%), bevacizumab-regimens (8.0%), singlets (5.5%), and pemetrexed + bevacizumab-based combinations (1.8%). Median survival was longest for pemetrexed + bevacizumab-based combinations (18.5 months), followed by bevacizumab-based regimens (14.5), TKIs (12.7), pemetrexed-based regimens (10.4), doublets (9.2), and singlets (5.3). There was a

significantly reduced risk of mortality for pemetrexed + bevacizumab-based combinations (HR = 0.64; 95% CI = 0.42-0.94) and TKIs (HR = 0.83; 95% CI = 0.73-0.94) compared with doublets. Singlets were associated with an increased risk of mortality (HR = 1.50; 95% CI = 1.22-1.84). Subgroup analysis among patients aged 65 years and over found no significant differences among treatment groups, with the exception of singlets, which were associated with an increased risk of mortality compared with doublets (HR = 1.51; 95% CI = 1.20-1.90). Among patients under aged 65 years, pemetrexed + bevacizumab-based combinations (HR = 0.36; 95% CI = 0.21-0.64) and TKIs (HR = 0.76; 95% CI = 0.59-0.97) were associated with a reduced risk of mortality, and singlets were associated with an increased risk (HR = 1.85; 95% CI = 1.17-2.92). **CONCLUSIONS:** In this cohort of patients with advanced NSCLC, patients received a platinum agent with or without bevacizumab or pemetrexed, a TKI, or a single agent. Younger patients (aged < 65 years) receiving bevacizumab + pemetrexed-based combinations had a survival advantage over those receiving platinum doublets, and this finding merits further investigation. Younger patients receiving TKIs also had longer survival. Compared with platinum doublets, we found no survival advantage for older patients receiving bevacizumab or pemetrexed, which suggests that combination therapy of a platinum agent and taxane, such as carboplatin and paclitaxel, could be a reasonable option for older patients who are not candidates for targeted therapy. **DISCLOSURES:** No outside funding supported this study. Rashid has received past funding from Bristol-Myers Squibb, Astellas, Novartis, and Pfizer. No other authors report any potential financial conflicts of interest. Study concept and design were primarily contributed by Spence and Hui, with input from the other authors. Hui, Spence, and Rashid took the lead in data collection, and data interpretation was performed by Schottinger, Millares, and Spence, assisted by the other authors. The manuscript was written primarily by Spence, along with Chang, and revised by Spence, with input from the other authors.

[**Maintenance Sunitinib following Initial Platinum-Based Combination Chemotherapy in Advanced Stage IIIB/IV Non-small cell Lung Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase III Study - CALGB 30607 (Alliance).**](#) Baggstrom MQ1, Socinski MA2, Wang XF3, et al. J Thorac Oncol. 2017 Feb 1. pii: S1556-0864(17)30089-8. doi: 10.1016/j.jtho.2017.01.022. [Epub ahead of print]

INTRODUCTION: To evaluate efficacy of maintenance sunitinib after first-line chemotherapy for stage IIIB/IV non-small cell lung cancer (NSCLC). **METHODS:** Cancer and Leukemia Group B (CALGB) 30607 trial was a randomized, double-blind, placebo-controlled, phase III study that enrolled patients without progression after four cycles of first-line platinum-based doublet chemotherapy with or without bevacizumab. Bevacizumab was only allowed during the four cycles of chemotherapy. Patients were randomized to sunitinib 37.5 mg per day or placebo and were treated until unacceptable adverse event(s), progression, or death. Primary endpoint was progression-free survival (PFS). **RESULTS:** Two hundred ten patients were enrolled, randomized, and were included in the intent-to-treat (ITT) analysis. Ten patients did not receive maintenance therapy (4 on placebo and 6 on sunitinib). Grade 3/4 adverse events affecting more than 5% of the patients were fatigue (25%), thrombocytopenia (12%), hypertension (12%), rash (11%), mucositis (11%), neutropenia (7%), and anemia (6%) for sunitinib and none for placebo. There were three grade 5 events on sunitinib (1 pulmonary hemorrhage, 1 other pulmonary, and 1 death not associated with a CTCAE term) and two grade 5 events on placebo (1 pulmonary other and 1 thromboembolism). Median PFS was 4.3 months for sunitinib and 2.6 months for placebo (HR, 0.62; 95% CI, 0.47 - 0.82, P=0.0006). Median overall survival (OS) was 11.7 months for sunitinib versus 12.1 months for placebo versus (HR, 0.98, 95% CI, 0.73-1.31; P=0.89). **CONCLUSION:** Maintenance sunitinib was safe and improved PFS as maintenance therapy in stage IIIB/IV NSCLC but had no impact on overall survival. There is no room for future investigations of sunitinib in this setting.
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[Carboplatin plus Weekly Paclitaxel Combined with Bevacizumab as First-line Treatment for Non-small Cell Lung Cancer.](#) Yamasaki M1, Murakami I2, Nakano K3, Doi M4, Kitaguchi S5, Kondo T6, Sakurai J7, Hattori N8, Arita KI9. Anticancer Res. 2017 Feb;37(2):923-928.
AIM: We aimed to evaluate the efficacy and safety of carboplatin plus weekly paclitaxel with bevacizumab in patients with advanced non-squamous non-small cell lung cancer (NSCLC). **PATIENTS AND METHODS:** Patients with stage IIIB/IV or postoperative recurrent NSCLC (n=33) were treated with carboplatin (area under the curve of 6) on day 1; paclitaxel (80 mg/m2) on days 1, 8, and 15; and bevacizumab (15 mg/kg) on day 1 repeated every 4 weeks, for four to six cycles; followed by maintenance bevacizumab (15 mg/kg) every 3 weeks. **RESULTS:** The overall response rate was 76%. The median progression-free survival and overall survival were 8.4 months and 22.2 months, respectively. Grade 3-4 toxicities included neutropenia in 55% of patients, anemia in 18%, febrile neutropenia in 12%, and anorexia in 9%. No treatment-related deaths were observed. **CONCLUSION:** Carboplatin plus weekly paclitaxel with bevacizumab was effective and well tolerated by patients with advanced NSCLC.

[Retrospective Analysis of Different Treatment Schemes After Gefitinib Resistance in Advanced Non-Small Cell Lung Cancer.](#) Wang H1, Zhang M1, Li P1, Zhang G1, Yan X1, Ma Z2. Clin Ther. 2017 Feb 9. pii: S0149-2918(17)30073-5. doi: 10.1016/j.clinthera.2017.01.027. [Epub ahead of print]
PURPOSE: The goal of this study was to assess the survival of patients with acquired resistance to gefitinib who underwent different subsequent treatments. **METHODS:** From September 2007 to July 2014, a total of 103 patients with pathologically confirmed advanced non-small cell lung cancer and acquired resistance to gefitinib were retrospectively analyzed. Fifty-eight (56%) patients received chemotherapy; 36 were treated with chemotherapy and gefitinib continuation (CT + G), and 22 patients received chemotherapy (CT) alone. Twenty-two patients (22%) received continued gefitinib medication and local therapy (LT + G), and 23 (22%) received best supportive care (BSC). **FINDINGS:** The median age of the patients was 62 years and 99 (96%) were diagnosed with adeno-carcinoma and 93 (90%) were stage IV cases. In the chemotherapy groups, patients had high objective response rates and disease control rates (CT + G, 16.7% and 42.7%; CT, 9.1% and 40.9%, respectively). The median progression-free survival times from the beginning of gefitinib resistance was 5.3 months in the CT + G group, 3.6 months in the CT group, 3.1 months in the LT + G group, and 1.4 months in the BSC group (P < 0.005). Moreover, the median overall survival time after gefitinib resistance in the CT + G group was 11.6 months, which was significantly longer than for CT (9.6 months), LT + G (8.1 months), and BSC (3.7 months) patients (P < 0.001). **IMPLICATIONS:** Subsequent chemotherapy after acquired gefitinib resistance led to better survival rates, particularly when combined with continued gefitinib treatment. Local treatment combined with continued gefitinib is an alternative therapy when local progression has occurred. However, larger sample size studies in similar or other population groups are necessary to validate these findings.

[PD-1 and PD-L1 antibodies in cancer: current status and future directions.](#) Balar AV1, Weber JS2. Cancer Immunol Immunother. 2017 Feb 17. doi: 10.1007/s00262-017-1954-6. [Epub ahead of print]
Immunotherapy has moved to the center stage of cancer treatment with the recent success of trials in solid tumors with PD-1/PD-L1 axis blockade. Programmed death-1 or PD-1 is a checkpoint molecule on T cells that plays a vital role in limiting adaptive immune responses and preventing autoimmune and auto-inflammatory reactivity in the normal host. In cancer patients, PD-1 expression is very high on T cells in the tumor microenvironment, and PD-L1, its primary ligand, is variably expressed on tumor cells and antigen-presenting cells within tumors, providing a potent inhibitory influence within the tumor microenvironment. While PD-L1 expression on tumors is often regarded as a negative prognostic factor, it is clearly associated with a positive outcome for treatment with PD-1/PD-L1 blocking antibodies, and has been used to select patients for this therapy. Responses of long duration, a minority of patients with

atypical responses in which progression may precede tumor shrinkage, and a pattern of autoimmune side effects often seen with this class of drugs characterize therapy with PD-1/PD-L1 blocking drugs. While excellent efficacy has been seen with a limited number of tumor types, most epithelial cancers do not show responses of long duration with these agents. In the current review, we will briefly summarize the scientific background data supporting the development of PD-1/PD-L1 blockade, and then describe the track record of these antibodies in multiple different histologies ranging from melanoma and lung cancer to less common tumor types as well as discuss biomarkers that may assist in patient selection.

NSCLC - RADIOTHERAPY

Analysis of components of variance determining probability of setup errors in CBCT-guided stereotactic radiotherapy of lung tumors. Cuijpers JP1, Dahele M1, Jonker M2, Kraan B1, Senan S1, Slotman B1, Verbakel WF1. Med Phys. 2017 Feb;44(2):382-388. doi: 10.1002/mp.12074. Epub 2017 Feb 2.
PURPOSE: Online tumor matching for SABR lung setup requires margins for inaccuracies due to intra-fraction variability of breathing-averaged tumor position (BATP) and CBCT image guidance. We studied intra-fraction variability during SABR delivery using VMAT, corrected these for measurement inaccuracies, and quantified the CBCT image-guidance uncertainties. **MATERIALS AND METHODS:** For 193 fractions in 38 patients positioned without immobilization devices, CBCT scans were acquired before and after 2 arcs of a RapidArc treatment. A hidden marker test was performed to determine the accuracy of the CBCT system and an inter-observer test was performed to measure registration accuracy. Intra-fraction variability was calculated after correction for these components of variance, and the prediction interval for setup inaccuracies was determined. **RESULTS:** Correction for measurement inaccuracies reduced the intra-fraction variability of the BATP from 1.9 to 1.6 mm in AP, from 1.7 to 1.4 mm in SI and from 1.5 to 1.1 mm in LR direction (1 SD). Intra-fraction variability in bony anatomy after correction was ≤ 1 mm (1 SD). The 95% prediction interval to account for CBCT image-guidance uncertainties and intra-fraction variability was determined, and was found to be within our institutional PTV margins of 5 mm. **CONCLUSIONS:** Our findings show that it is essential to account for measurement and system inaccuracies when obtaining data for validating PTV margins from online CBCT image guidance.

Theoretical effectiveness of cell survival in fractionated radiotherapy with hypoxia-targeted dose escalation. Chvetsov AV1, Rajendran JG2, Zeng J1, Shilpen PA1, Bowen SR3, Kim EY1. Med Phys. 2017 Feb 25. doi: 10.1002/mp.12177. [Epub ahead of print]
PURPOSE: The goal of this article is to compute the cell survival during fractionated radiotherapy with non-uniform hypoxia-targeted dose distribution relative to cell survival for a uniform dose distribution with equal integral tumor dose. The analysis is performed for different parameters of radiotherapy with conventional and hypofractionated dose regimens. **METHODS:** Our analysis is done using a parsimonious tumor response model that describes the major components of tumor response to radiotherapy such as radiosensitivity, cell proliferation and hypoxia using as few variables as possible. Two levels of oxygenated and hypoxic cells with the survival curves described by the Linear Quadratic (LQ) model are implemented in the model. The model allows for analytical solutions for relative cell survival in a single fraction simulation which can be used for additional validation of our numerical simulations. The relative cell survival was computed for conventional and hypofractionated dose regimens in a model problem with radiobiological parameters for the non-small cell lung cancer. Sensitivity of cell survival to different parameters of radiotherapy such as the relative volume of hypoxic fraction, boost dose ratio, re-oxygenation rate and delivery errors was investigated. **RESULTS:** Our computational and analytical results show that relative cell survival for non-uniform and uniform dose

distributions is larger than 1.0 during the first few fractions of radiotherapy with conventional fractionation. This indicates that the uniform dose distribution produces a higher cell killing effect for the equal integral dose. This may stem from domination of linear contribution to the cell killing effect seen in the dose range of 1-2 Gy and a steeper slope of survival curve in the oxygenated tumor region. This effect can only happen if the distribution of clonogens is nearly uniform; therefore, after the first few fractions, the non-uniform dose distributions outperform the uniform dose distribution and relative cell survival becomes less than 1.0. However, re-oxygenation and delivery errors can also reduce effectiveness of hypoxia-targeted non-uniform dose distributions toward the end of treatment. For hypofractionated radiotherapy with fractional dose > 3 Gy, the relative cell survival was always below 1.0, which means the non-uniform dose distributions produced higher cell killing effect than the uniform dose distribution during the entire treatment. **CONCLUSIONS:** The data obtained in this work suggests that non-uniform hypoxia-targeted dose distributions are less effective at cell killing than uniform dose distributions at the beginning of radiotherapy with conventional fractionation. However; non-uniform dose distributions can outperform uniform dose distribution by the end of the treatment if the effects of re-exygenation and delivery errors are reduced. In hypofractionated radiotherapy, non-uniform hypoxia-targeted dose distributions are more efficient than uniform dose distributions during the entire treatment.

[Radical hypo-fractionated radiotherapy with volumetric modulated arc therapy in lung cancer : A retrospective study of elderly patients with stage III disease.](#) Franceschini D1,2, De Rose F3, Cozzi L4,5, et al. Strahlenther Onkol. 2017 Feb 6. doi: 10.1007/s00066-017-1103-3. [Epub ahead of print]
BACKGROUND: This study aimed to analyse the feasibility and acute toxicity of radical hypo-fractionated radiotherapy (RT) for elderly patients with non-small-cell lung cancer (NSCLC).
PATIENTS AND METHODS: We conducted a retrospective evaluation of treatment with volumetric modulated arc therapy (VMAT) of elderly patients affected by stage III inoperable NSCLC. The dose prescription was 56 Gy in 20 fractions, 55 Gy in 22 fractions, or 50 Gy in 20 fractions. Target volume included only the primary lesion and the infiltrated lymph nodes. The primary end point was acute and late toxicity, while secondary end points were progression-free survival (PFS), and overall survival (OS).
RESULTS: In all, 41 patients were included in this analysis. The mean age of the patients was 78.6 years, and 22 patients had staged IIIA while 19 patients had stage IIIB disease. All but one patient had pathological nodal involvement; 15 patients received chemotherapy before RT. Acute grade 1-2 toxicity was recorded in 25 (61%) patients. Late toxicity was recorded in 13 (32%) patients. No cases of G3 or G4 toxicity were recorded. Complete response was obtained in two (5%) patients, 26 (63%) showed a partial response, and two (5%) experience disease progression. At a mean follow-up of 9.9 months (range, 1.1-25.4), 17 patients had died from disease progression, one died from other causes, and 23 were alive. Median OS was 13.7 ± 1.5 months (95% CI: 10.7-16.7), OS at 12 and 18 months was $51.3 \pm 9.5\%$ and $35.1 \pm 10.1\%$, respectively. Median PFS was 13.7 ± 2.3 months (95% CI: 9.1-18.2), and PFS at 12 and 18 months was $50.1 \pm 9.9\%$ and $38.9 \pm 10.4\%$, respectively. **CONCLUSION:** Radical hypo-fractionated VMAT is a promising treatment for locally advanced NSCLC in the elderly. The use of hypo-fractionated radiotherapy for lung cancer in older patients can be considered a valuable approach, particularly for patients with poor performance status or refusing other treatment approaches.

[Lower Incidence of Esophagitis in the Elderly Undergoing Definitive Radiation Therapy for Lung Cancer.](#) Soni PD1, Boonstra PS2, Schipper MJ3, et al. [J Thorac Oncol.](#) 2017 Mar;12(3):539-546. doi: 10.1016/j.jtho.2016.11.2227. Epub 2017 Feb 1.
INTRODUCTION: Most patients with lung cancer are elderly and poorly represented in randomized clinical trials. They are often undertreated because of concerns about their ability to tolerate aggressive treatment. We tested the hypothesis that elderly patients undergoing definitive lung radiation might

tolerate treatment differently than younger patients. **METHODS:** A total of 125 patients who underwent definitive lung radiotherapy were identified from a prospective institutional database (University of Michigan cohort). Logistic regression modeling was performed to assess the impact of age on esophagitis grade 2 or higher or grade 2 or higher and pneumonitis grade 3 or higher or grade 2 or higher, with adjustment for esophageal and lung dose, respectively, as well as for chemotherapy utilization, smoking status, and performance status. The analysis was validated in a large cohort of 691 patients from the Michigan Radiation Oncology Quality Consortium registry, an independent statewide prospective database. **RESULTS:** In the University of Michigan cohort, multivariable regression models revealed a significant inverse correlation between age and rate of esophagitis for both toxicity levels, (adjusted OR = 0.93 for both models and 95% confidence intervals of 0.88-0.98 and 0.87-0.99), with areas under the curve of 0.747 and 0.721, respectively, demonstrating good fit. This same association was noted in the Michigan Radiation Oncology Quality Consortium cohort. There was no significant association between age and pneumonitis. **CONCLUSIONS:** There is a lower incidence of esophagitis with increasing age even after adjustment for use of chemotherapy. This is a novel finding in thoracic oncology. No age dependence was noted for pulmonary toxicity. The elderly are able to tolerate definitive thoracic radiation well and should be offered this option when clinically warranted.

SMALL CELL LUNG CANCER - SCLC

High PD-L1 expression is associated with stage IV disease and poorer overall survival in 186 cases of small cell lung cancers. Chang YL1,2, Yang CY3,2, Huang YL1, Wu CT1,2, Yang PC3,2,4. Oncotarget. 2017 Feb 1. doi: 10.18632/oncotarget.14935. [Epub ahead of print]
BACKGROUND: Small cell lung cancer (SCLC) is an aggressive malignancy with a distinct natural history and dismal prognosis. SCLC is characterized as a recalcitrant neoplasm with limited therapeutic options and platinum-based chemotherapy is the treatment of choice. Programmed cell death-ligand 1(PD-L1)-mediated immune escape may be a suitable target for specific therapy, but its role in SCLC is unclear. **MATERIALS AND METHODS:** In total, 186 SCLC cases were investigated. Paraffin-embedded tumor sections were stained with a PD-L1 antibody. PD-L1 overexpression was denoted by moderate-to-strong PD-L1 membrane staining in ≥ 5% of tumor cells. Tumor cells and infiltrating lymphocytes were scored separately. **RESULTS:** The overall frequency of PD-L1 overexpression, in tumor cells and tumor infiltrating lymphocytes (TILs) was 78.0% and 54.3%, respectively. High tumor PD-L1 expression was significantly correlated with high TIL PD-L1 expression (P=0.001) and stage IV disease (P=0.048). Multivariate analysis revealed that high tumor PD-L1 expression and stage IV disease were two independent risk factors for poor overall survival. **CONCLUSIONS:** High PD-L1 expression was observed in SCLCs compared with their expression in conventional NSCLCs. The aggressive behavior of SCLC could be partially related to PD-L1-mediated immune escape. High PD-L1 expression correlated with poor prognosis and may provide a rationale for immunotherapy for high-grade SCLC.

Radiological Features of the Surgically Resected Small-sized Small-cell Lung Cancer on Computed Tomography. Toyokawa G1, Kozuma Y2, Matsubara T2, et al. Anticancer Res. 2017 Feb;37(2):877-881.
BACKGROUND/AIM: Surgical resection can be applied in cases of early-stage small-cell lung cancer (SCLC). Predicting the histology of SCLC and discriminating SCLC from other histologies would be useful for determining the optimal treatment strategies for small pulmonary nodules that have not been preoperatively diagnosed. **MATERIALS AND METHODS:** The study population included 17 patients with resected SCLC and 296 patients with adenocarcinoma (ADC) whose preoperative CT were available. The tumors of all patients were smaller than 3.0 cm. **RESULTS:** Univariate and multivariate analyses demonstrated that SCLC was significantly associated with the presence of notching and the absence of surrounding ground glass opacity, air bronchogram, pleural indentation, and spiculation in comparison to

ADC. **CONCLUSION:** The CT scans of patients with SCLC of less than 3.0 cm in size showed notching more frequently than those of patients with ADC, whereas surrounding GGO, air bronchogram, pleural indentation and spiculation were observed less frequently compared to ADC.

Potential effect of spliceosome inhibition in small cell lung cancer irrespective of the MYC status.
Suda K1,2, Rozeboom L1, Yu H1, Ellison K1, Rivard CJ1, Mitsudomi T2, Hirsch FR1. PLoS One. 2017 Feb 13;12(2):e0172209. doi: 10.1371/journal.pone.0172209. eCollection 2017.
Small cell lung cancer (SCLC) is a highly aggressive malignancy with few therapeutic advances in the treatment in recent decades. Based on a recent study that identified the spliceosome as a therapeutic vulnerability in MYC-driven breast cancers, we evaluated the efficacy of a spliceosome inhibitor in SCLC cell lines and analyzed the correlation with MYC status. Among 23 SCLC cell lines examined, eight showed high MYC protein expression (> 80% positive cells) by immunohistochemistry (IHC), while 10 cell lines demonstrated no staining for MYC. The remaining five cell lines showed weak staining (< 40% positive cells). All four cell lines that were previously demonstrated to have MYC gene amplification were positive for MYC by IHC. Four cell lines with high MYC expression and four with low MYC expression were used in further analysis. A spliceosome inhibitor, pladienolide B, showed high efficacy (IC50 < 12nM) in all eight cell lines tested, irrespective of the MYC IHC or MYC gene amplification status. We observed that the four cell lines with higher sensitivity to the spliceosome inhibitor were established from patients with prior chemotherapy. Therefore we chronically treated H1048 cells, that were established from a treatment-naïve patient, with cisplatin for 4 weeks, and found that H1048-cisplatin treated cells became more sensitive to pladienolide B. In conclusion, our in vitro results indicate that spliceosome inhibitors would be promising molecular target drugs in SCLC irrespective of the MYC status, especially in the second-line settings after an effective front-line chemotherapy.

Heterogeneity in immune marker expression after acquisition of resistance to EGFR kinase inhibitors: analysis of a case with small cell lung cancer transformation. Suda K1, Murakami I2, Yu H3, Kim J3, Ellison K3, Rivard CJ3, Mitsudomi T4, Hirsch FR5. J Thorac Oncol. 2017 Feb 10. pii: S1556-0864(17)30098-9. doi: 10.1016/j.jtho.2017.02.002. [Epub ahead of print]
INTRODUCTION: Expression of immune-markers is of scientific interest due to their potential roles as predictive biomarkers for immunotherapy. Although the microenvironment of metastatic tumors and/or therapy-inducible histological transformation may affect the expression of these immune-markers, there is little data regarding this context. **METHODS:** A 76-year-old never-smoking female with epidermal growth factor receptor (EGFR) mutated lung adenocarcinoma (AC) acquired resistance to gefitinib. After death, autopsy revealed small-cell lung cancer (SCLC) transformation and EGFR T790M secondary mutation (T790M) as mutually exclusive resistance mechanisms occurring differently in different metastases; two liver metastases (SCLC vs. AC with T790M) and two lymph node metastases (SCLC vs. AC with T790M) were analyzed to compare the expression status of immune-markers by immunohistochemistry and by an immune-oncology gene expression panel. **RESULTS:** Programmed death ligand 1 (PD-L1) protein was partially expressed in tumor cells with AC histology (T790M) but not in tumor cells with SCLC transformation. The liver metastasis with SCLC transformation showed no stromal PD-L1 expression and scant tumor infiltrating lymphocytes, while the other lesions demonstrated stromal PD-L1 staining and infiltration of CD8-positive T cells. Data generated using an immuno-oncology gene expression panel indicated higher level of T cell co-stimulatory molecules, and lower expression of type I interferon regulated genes in lesions with SCLC transformation. **CONCLUSION:** These data highlight the heterogeneity of expression of immune-markers depending on the metastatic sites and histological transformation, and indicate that biopsy from one lesion may not be representative of immune-markers status for all lesions.

Clinical significance of circulating tumor cells in patients with small-cell lung cancer. Wang YL1, Liu CH2, Li J3, Ma XP3, Gong P3. Tumori. 2017 Feb 15:0. doi: 10.5301/tj.5000601. [Epub ahead of print]

BACKGROUND: This study investigated the correlation of the presence of circulating tumor cells (CTCs) with clinical characteristics, and the predictive value of CTCs for progression-free survival (PFS) in patients with small-cell lung cancer (SCLC). **METHODS:** Samples were obtained from 42 patients with SCLC before and after the first cycle of chemotherapy. CTCs were quantitated by negative immunomagnetic enrichment and immunocytochemistry using anti-CD45 and anti-pancytokeratin antibodies. **RESULTS:** CTCs were positive (≥2) in 76.19% of patients with SCLC and negative in the control group. The presence of CTCs was positively correlated with 6 clinical characteristics. PFS was 6.055 and 10.670 months for patients with ≥2 and >2 CTCs/7.5 mL of blood before chemotherapy; after chemotherapy PFS was 4.862 and 10.535 months, respectively. **CONCLUSIONS:** This study showed that both baseline CTC numbers and the change in CTC numbers after 1 cycle of chemotherapy are significant prognostic factors of PFS for SCLC.

Risk factors for brain metastases after prophylactic cranial irradiation in small cell lung cancer.
Zeng H1,2, Xie P2,3, Meng X2,3, et al. Sci Rep. 2017 Feb 16;7:42743. doi: 10.1038/srep42743.
Despite administration of prophylactic cranial irradiation (PCI), some small cell lung cancer (SCLC) patients still suffer from brain metastases (BM) with unknown risk factors. We conducted this study to identify patients with higher BM risk after PCI and improve their outcome. The characteristics and survival of all the SCLC patients underwent PCI in our institute from 2003 to 2014 were analyzed. Kaplan-Meier method was applied to estimate BM free survival (BMFS) and overall survival (OS). Cox regression analyses were performed to explore risk factors for BM. A total of 175 patients with the median age of 55 years (range, 29-76) were eligible, among whom 36 (20.6%) developed BM with median follow-up of 42 months. Both univariate and multivariate analyses showed HART and TNM classification (p < 0.05) were associated with BM. Two-stage system was not related with BMFS or OS (p > 0.05). Stage IIIB-IV and HART were independent risk factors for BM after PCI in SCLC. TNM classification was more valuable on prognosis than two-stage system. Further large-scale studies are needed to confirm our findings.

The Pulmonary Fibrosis Associated MUC5B Promoter Polymorphism Is Prognostic of the Overall Survival in Patients with Non-Small Cell Lung Cancer (NSCLC) Receiving Definitive Radiotherapy. Yang J1, Xu T2, Gomez DR3, Jeter M4, Levy LB5, Song Y6, Hahn S7, Liao Z8, Yuan X9. Transl Oncol. 2017 Feb 8;10(2):197-202. doi: 10.1016/j.tranon.2016.12.009. [Epub ahead of print]
BACKGROUND: MUC5B is glycoprotein secreted by bronchial glands. A promoter variant in MUC5B, rs35705950, was previously found to be strongly associated with the incidence of idiopathic pulmonary fibrosis (IPF) and also the overall survival (OS) of such patients. Patients with IPF and patients with radiation pneumonitis (RP) have the similar pathologic process and clinical symptoms. However, the role of rs35705950 in patients receiving thoracic radiotherapy remains unclear. **PATIENTS AND METHODS:** In total, 664 patients with NSCLC receiving definitive radiotherapy (total dose ≥60 Gy) were included in our study. RP was scored via the Common Terminology Criteria for Adverse Events v3.0. OS was the second end point. MUC5B rs35705950 was genotyped, and Kaplan-Meier and Cox regression analyses were used to evaluate associations between MUC5B rs35705950 and the risk of RP or OS. **RESULTS:** The median patient age was 66 years (range 35-88); most (488 [73.2%]) had stage III of the disease. Until the last follow-up, 250 patients developed grade≥2 RP, 82 patients developed grade≥3 RP, and 440 patients died. The median mean lung dose was 17.9 Gy (range 0.15-32.74). No statistically significant associations were observed between genotypes of MUC5B rs35705950 and the incidence of RP≥grade 2 either in univariate analysis (hazard ratio [HR] 1.009, 95% confidence interval [CI] 0.728-

1.399, P=.958) or in multivariate analysis (HR 0.921, 95% CI 0.645-1.315, P=.65). Similar results were also observed for RP≥grade 3, while TT/GT genotypes in MUC5B were significantly associated with poor OS in both univariate analysis (HR 1.287, 95% CI 1.009-1.640, P=.042) and multivariate analysis (HR 1.561, 95% CI 1.193-2.042, P=.001). **CONCLUSION:** MUC5B promoter polymorphism could be prognostic of the OS among NSCLC patients receiving definitive radiotherapy, although no significant associations were found with the risk of RP.

[Pretreatment metabolic parameters measured by 18F-FDG-PET to predict the outcome of first-line chemotherapy in extensive-stage small-cell lung cancer.](#) Yu X1, Zhu Y, Wang J, Song X, Zhu L, Men X, Li X, Dai D, Xu W. Nucl Med Commun. 2017 Feb;38(2):193-200. doi: 10.1097/MNM.0000000000000637.
OBJECTIVE: Patients' pretreatment metabolic burden, as measured by radiotracer fluorine-18 fluorodeoxyglucose (F-FDG) PET/computed tomography (CT), has been shown to predict treatment outcome in various malignancies. However, its predictive role in extensive-stage small cell lung cancer (SCLC) has not been definitively determined. This retrospective study investigated the viability of using common pretreatment metabolic parameters, obtained through F-FDG-PET/CT, to predict outcomes of first-line chemotherapy in extensive-stage SCLC. **PARTICIPANTS AND METHODS:** The study population comprised 154 consecutive patients with extensive-stage SCLC who underwent a pretreatment F-FDG-PET/CT scan and received standard first-line chemotherapy between January 2011 and December 2015. **RESULTS:** Ten (6.5%) and 66 (42.9%) patients achieved a complete or a partial response, respectively (considered an objective response); 35 (22.7%) and 43 (27.9%) experienced stable or progressive disease. The metabolic tumor volume (MTV) was a significant factor for predicting an objective response. For predicting disease control (objective response or stable disease), MTV and total lesion glycolysis (TLG) were nonindependent factors. **CONCLUSION:** Greater MTV and TLG could indicate a poorer response to first-line chemotherapy for patients with extensive-stage SCLC, but the predictive efficiency was not high enough for routine reliance. For patients who are not suitable to receive first-line chemotherapy, MTV and TLG may help guide clinical decisions.

PALLIATIVE AND SUPPORTIVE CARE

[A Multimedia Self-management Intervention to Prepare Cancer Patients and Family Caregivers for Lung Surgery and Postoperative Recovery.](#) Sun V1, Raz DJ2, Ruel N3, et al. Clin Lung Cancer. 2017 Feb 2. pii: S1525-7304(17)30039-6. doi: 10.1016/j.cllc.2017.01.010. [Epub ahead of print]
BACKGROUND: The purpose of this study was to evaluate the feasibility and acceptability of a multimedia self-management (MSM) intervention to prepare patients and family caregivers for lung surgery. **PATIENTS AND METHODS:** This is a quasi-experimental, 2-group, sequential enrollment pilot study of a 4-session multimedia intervention (audio/visual + print) to enhance self-management and quality of life (QOL) for patients and family caregivers. The intervention, Preparing for Lung Surgery, begins before surgery, and continues through hospitalization and discharge, with 2 telephone support sessions after discharge. Outcomes were assessed before surgery (preintervention), at discharge, and 2 to 4 weeks postdischarge (postintervention). Patient outcomes were assessed using the Functional Assessment of Cancer Therapy-General (QOL), MD Anderson Symptom Inventory and Functional Assessment of Cancer Therapy-Pulmonary Symptom Index (symptoms), self-efficacy, surgery-related knowledge, and patient activation. Family caregiver outcomes included City of Hope-QOL-Family (QOL), Caregiver Burden Scale, and knowledge. Paired t tests were used for exploratory evaluations of score changes from pre- to postintervention. **RESULTS:** Sixty participants (38 patients, 22 family caregivers) enrolled in the study (70% accrual). Postintervention scores were significantly improved for patients' emotional QOL (P = .001). Trends for improvements were observed for patient self-efficacy,

surgery-related knowledge, and activation. Family caregivers' surgery-related knowledge was significantly improved (P = .02). Overall, participants were highly satisfied with the acceptability/usability of the intervention (3.6-3.7 of 4.0). **CONCLUSION:** A standardized MSM intervention was feasible and acceptable in supporting readiness and preparedness for lung surgery and postoperative recovery. A larger randomized trial is needed to verify the impact of the MSM intervention on patient/family caregiver outcomes and health care resource use.

[**Predictors of the multidimensional symptom experience of lung cancer patients receiving chemotherapy.**](#) Wong ML1, Paul SM2, Cooper BA3, et al. Support Care Cancer. 2017 Feb 3. doi: 10.1007/s00520-017-3593-z. [Epub ahead of print]

PURPOSE: Few studies have examined interindividual variability in the symptom experience of lung cancer patients. We aimed to identify the most prevalent, severe, and distressing symptoms, and risk factors associated with increased symptom burden. **METHODS:** Lung cancer patients (n = 145) reported occurrence, severity, and distress for 38 symptoms on the Memorial Symptom Assessment Scale 1 week after chemotherapy. Using multidimensional subscales, risk factors for higher global distress, physical, and psychological symptoms were evaluated using simultaneous linear regression. **RESULTS:** Mean age was 64.0 years and 56.6% were female. Mean Karnofsky Performance Status score was 79.1 (SD 14.6) and mean Self-Administered Comorbidity Questionnaire score was 7.3 (SD 3.9). The most distressing and prevalent symptom was fatigue. Problems with sexual interest/activity had the highest mean severity rating. Patients with lower functional status (p = 0.001) and higher comorbidity (p = 0.02) reported higher global distress. Similarly, lower functional status (p = 0.003) and higher comorbidity (p = 0.04) were associated with a higher physical symptom burden along with lower body mass index (p = 0.02). Higher psychology symptom burden was associated with lower functional status (p = 0.01), younger age (p = 0.02), non-metastatic disease (p = 0.03), higher number of prior treatments (p = 0.04), and income (p = 0.03). **CONCLUSIONS:** Fatigue was the most distressing and prevalent symptom among lung cancer patients receiving chemotherapy. Lower functional status was associated with a higher burden of global distress, physical, and psychological symptoms. Younger age and non-metastatic disease were additional risk factors for increased psychological symptoms. Together, these risk factors can help clinicians identify lung cancer patients at increased need for aggressive symptom management.

[**Interventional Analgesic Management of Lung Cancer Pain.**](#) Hochberg U1, Elgueta MF2, Perez J3. Front Oncol. 2017 Feb 14;7:17. doi: 10.3389/fonc.2017.00017. eCollection 2017.

Lung cancer is one of the four most prevalent cancers worldwide. Comprehensive patient care includes not only adherence to clinical guidelines to control and when possible cure the disease but also appropriate symptom control. Pain is one of the most prevalent symptoms in patients diagnosed with lung cancer; it can arise from local invasion of chest structures or metastatic disease invading bones, nerves, or other anatomical structures potentially painful. Pain can also be a consequence of therapeutic approaches like surgery, chemotherapy, or radiotherapy. Conventional medical management of cancer pain includes prescription of opioids and coadjuvants at doses sufficient to control the symptoms without causing severe drug effects. When an adequate pharmacological medical management fails to provide satisfactory analgesia or when it causes limiting side effects, interventional cancer pain techniques may be considered. Interventional pain management is devoted to the use of invasive techniques such as joint injections, nerve blocks and/or neurolysis, neuromodulation, and cement augmentation techniques to provide diagnosis and treatment of pain syndromes resistant to conventional medical management. Advantages of interventional approaches include better analgesic outcomes without experiencing drug-related side effects and potential for opioid reduction thus avoiding central side effects. This review will describe various pain syndromes frequently described in lung cancer patients and those interventional techniques potentially indicated for those cases.

Physical activity (PA) levels are low in patients with lung cancer. Emerging evidence supports the use of interventions to increase PA in this population. We aimed to (1) identify and synthesize outcome measures which assess PA levels in patients with lung cancer and (2) to evaluate, synthesize and compare the psychometric properties of these measures. A systematic review of articles from searches was conducted of five electronic databases and personal records. Eligible studies were those which assessed PA using either performance-based or patient-reported measures. For aim 2, studies identified in aim 1 reporting on at least one psychometric property (validity, reliability, responsiveness or measurement error) were included. Two independent reviewers assessed eligibility and risk of bias with the COnsensus-based Standards for the selection of health status Measurement INstruments. Thirty-four studies using 21 different measures of PA were identified. Seventeen studies used performance-based measures. The Godin Leisure Time Exercise Questionnaire (GLTEQ) was the most frequently used patient-reported measure. Psychometric properties were reported for 13 of these measures and most frequently for movement sensors. Two studies reported on properties of the GLTEQ. Quality ratings for risk of bias were low. There is significant heterogeneity amongst studies regarding method of PA measurement along the lung cancer continuum. Greater consensus could be achieved by using a consensus approach such as a Delphi process. Future studies should include assessment of psychometric properties of the measurement tool being used. Currently, it is recommended where feasible, both performance-based and patient-reported measurements of PA should be undertaken.

PURPOSE: Pain commonly occurs in cancer patients, and has been associated with shorter survival. However, the importance of pain is less clear when analyzed with other known prognostic variables. This systematic review was performed to better understand how pain impacts overall survival (OS) in common cancers when key clinical variables are included in multivariate analysis. **METHODS:** A Medline search was completed to find studies examining the relationship between pain, clinical variables, and OS in patients with breast, colorectal, lung, or prostate cancer. Multivariate analysis included known prognostic variables including age, performance status, disease burden, and laboratory parameters. **RESULTS:** Fifty studies met inclusion criteria. In patients with breast, colorectal, and lung cancer, pain was not a significant prognostic factor for OS on multivariate analysis in most studies. In contrast, several studies suggest that pain is an independent prognostic factor for OS in advanced prostate cancer, even when relevant clinical prognostic variables are included. However, analgesic use was often used as a surrogate for prostate cancer pain, making it difficult to determine whether pain or opioid exposure was more important in influencing survival. **CONCLUSIONS:** Pain may be associated with shorter survival in patients with cancer, but the mechanism for this relationship is unknown. The available evidence is insufficient to definitively determine if pain independently influences survival in patients with breast, colorectal, or lung cancer. The majority of studies in prostate cancer show pain to be an independent prognostic factor for OS, and often also incorporate opioid analgesic use in multivariate analysis. Prospective studies are needed to better understand how opioid utilization and pain may affect cancer progression and survival in diverse malignancies.

[**The prognostic value of pre-diagnosis health-related quality of life on survival: a prospective cohort study of older Americans with lung cancer.**](#) Pinheiro LC1, Zagar TM2, Reeve BB3,4. Qual Life Res. 2017 Feb 14. doi: 10.1007/s11136-017-1515-7. [Epub ahead of print]

PURPOSE: Health-related quality of life (HRQOL) after cancer diagnosis is prognostic for overall survival (OS). However, no studies have assessed if HRQOL before diagnosis is predictive for OS. The objective of this study was to determine the association between pre-lung cancer diagnosis HRQOL and OS. **METHODS:** Our prospective cohort study used surveillance, epidemiology, and end results linked to the Medicare Health Outcomes Survey. We included 6290 individuals 65 years or older diagnosed with incident lung cancer from 1998 to 2013. We assessed the prognostic value of (1) short-form 36 summary component and domain-specific scores, (2) activities of daily living (ADL), and (3) two global HRQOL questions. Cox-proportional hazards models were used to examine associations between HRQOL and OS, adjusting for demographics, comorbid conditions, and clinical characteristics. **RESULTS:** Worse pre-diagnosis HRQOL was significantly associated with greater risk of death across HRQOL measures. An above average physical or mental component summary score was associated with 16 and 24% decreases in the hazard of death, respectively ($p < 0.0001$). Being unable to perform ADLs, such as bathing oneself, was associated with an 89% increased hazard of death ($p < 0.0001$). Reporting "poor" versus "excellent" health was associated with a 74% increase in the hazard of death ($p < 0.0001$). **CONCLUSION:** This population-based study reinforces the importance of self-reported health status as a predictor for OS. Routine HRQOL screening may identify patients who could benefit from early interventions to improve HRQOL. Future studies should explore associations between changes in HRQOL before and after cancer diagnosis and OS.

COMPLEMENTARY & ALTERNATIVE THERAPY

[**Antitumor Effects of Laminaria Extract Fucoxanthin on Lung Cancer.**](#) Mei C1, Zhou S2, Zhu L3, Ming J4, Zeng F5, Xu R6. Mar Drugs. 2017 Feb 15;15(2). pii: E39. doi: 10.3390/md15020039.

Lung cancer is the leading cause of cancer mortality worldwide and non-small-cell lung cancer (NSCLC) is the most common type. Marine plants provide rich resources for anticancer drug discovery. Fucoxanthin (FX), a Laminaria japonica extract, has attracted great research interest for its antitumor activities. Accumulating evidence suggests anti-proliferative effects of FX on many cancer cell lines including NSCLCs, but the detailed mechanisms remain unclear. In the present investigation, we confirmed molecular mechanisms and in vivo anti-lung cancer effect of FX at the first time. Flow cytometry, real-time PCR, western blotting and immunohistochemistry revealed that FX arrested cell cycle and induced apoptosis by modulating expression of p53, p21, Fas, PUMA, Bcl-2 and caspase-3/8. These results show that FX is a potent marine drug for human non-small-cell lung cancer treatment.

[**Stephania Tetrandra and Ginseng-Containing Chinese Herbal Formulation NSENL Reverses Cisplatin Resistance in Lung Cancer Xenografts.**](#) Jin L1,2, Xu M1, Luo XH2, Zhu XF2. Am J Chin Med. 2017 Feb 23:1-17. doi: 10.1142/S0192415X17500240. [Epub ahead of print]

Chinese Herbal Formulation, supplement energy and nourish lung (SENL), effectively enhances chemotherapeutic efficacy in lung cancer treatment and reverses multi-drug resistance (MDR) in lung cancer cells in vitro. The present study is designed to assess the effect of a New SENL (NSENL, modification of SENL) formulation on resistance to chemotherapy of cisplatin (DDP)-resistant human lung cancer cell line (A549/DDP) xenografts in nude mice. We assessed six constituents in NSENL by high performance liquid chromatography (HPLC). BALB/c nude mice harboring A549/DDP cell xenografts were established to assess the antitumor effect of NSENL and its impact on the expression of MDR related genes. The six constituents in NSENL, including ginsenoside Rg1, ginsenoside Rb1, ginsenoside Rg3, astragaloside IV, ophiopogonin D and tetrandrine were quantitated simultaneously by

HPLC. The combination of NSENL with DDP significantly inhibited tumor growth at a rate of up to 66.8% ([Formula: see text]). In addition, NSENL as monotherapy or combined with DDP downregulated multidrug resistance-associated protein 1 (MRP1), basic fibroblast growth factor (bFGF) and fibroblast growth factor receptor 1 (FGFR1) at both the mRNA and protein levels ([Formula: see text]), reduced glutathione S-transferase π (GST-π) protein expression and tumor microvascular density as well as decreased phosphorylation of protein kinase B (Akt) and mammalian target of rapamycin (mTOR) ([Formula: see text]). These findings demonstrated that NSENL can reverse MDR in A549/DDP cells in vivo, an effect possibly associated with downregulation of MDR-associated genes as well as inhibition of bFGF/FGFR and phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR signaling pathways.

MISCELLANEOUS WORKS

Variation in CYP2A6 and nicotine metabolism among two American Indian tribal groups differing in smoking patterns and risk for tobacco-related cancer.

Tanner JA1, Henderson JA, Buchwald D, Howard BV, Nez Henderson P, Tyndale RF. Pharmacogenet Genomics. 2017 Feb 8. doi: 10.1097/FPC.0000000000000271. [Epub ahead of print]

OBJECTIVE: The Northern Plains (NP) and Southwest (SW) American Indian populations differ in their smoking patterns and lung cancer incidence. We aimed to compare CYP2A6 genetic variation and CYP2A6 enzyme activity (representative of the rate of nicotine metabolism) between the two tribal populations as these have previously been associated with differences in smoking, quitting, and lung cancer risk. **PARTICIPANTS AND METHODS:** American Indians (N=636) were recruited from two different tribal populations (NP in South Dakota, SW in Arizona) as part of a study carried out as part of the Collaborative to Improve Native Cancer Outcomes P50 Project. A questionnaire assessed smoking-related traits and demographics. Participants were genotyped for CYP2A6 genetic variants *1B, *2, *4, *7, *9, *12, *17, and *35. Plasma and/or saliva samples were used to measure nicotine's metabolites cotinine and 3'-hydroxycotinine and determine CYP2A6 activity (3'-hydroxycotinine/cotinine, i.e. the nicotine metabolite ratio, NMR). **RESULTS:** The overall frequency of genetically reduced nicotine metabolizers, those with CYP2A6 decrease-of-function or loss-of-function alleles, was lower in the NP compared with the SW (P=0.0006). The CYP2A6 genotype was associated with NMR in both tribal groups (NP, P<0.0001; SW, P=0.04). Notably, the rate of nicotine metabolism was higher in NP compared with SW smokers (P=0.03), and in comparison with other ethnic groups in the USA. Of the variables studied, the CYP2A6 genotype was the only variable to significantly independently influence NMR among smokers in both tribal populations (NP, P<0.001; SW, P=0.05). **CONCLUSION:** Unique CYP2A6 allelic patterns and rates of nicotine metabolism among these American Indian populations suggest different risks for smoking, and tobacco-related disease.

Case-control study of cumulative cigarette tar exposure and lung and upper aerodigestive tract cancers.
Meyers TJ1, Chang SC1,2, Chang PY3, et al. Int J Cancer. 2017 Feb 6. doi: 10.1002/ijc.30632. [Epub ahead of print]

The development of comprehensive measures for tobacco exposure is crucial to specify effects on disease and inform public health policy. In this population-based case-control study, we evaluated the associations between cumulative lifetime cigarette tar exposure and cancers of the lung and upper aerodigestive tract (UADT). The study included 611 incident cases of lung cancer; 601 cases of UADT cancers (oropharyngeal, laryngeal and esophageal cancers); and 1,040 cancer-free controls. We estimated lifetime exposure to cigarette tar based on tar concentrations abstracted from government cigarette records and self-reported smoking histories derived from a standardized questionnaire. We analyzed the associations for cumulative tar exposure with lung and UADT cancer, overall and according to histological subtype. Cumulative tar exposure was highly correlated with pack-years among ever smoking

controls (Pearson coefficient = 0.90). The adjusted odds ratio (95% confidence limits) for the estimated effect of about 1 kg increase in tar exposure (approximately the interquartile range in all controls) was 1.61 (1.50, 1.73) for lung cancer and 1.21 (1.13, 1.29) for UADT cancers. In general, tar exposure was more highly associated with small, squamous and large cell lung cancer than adenocarcinoma. With additional adjustment for pack-years, positive associations between tar and lung cancer were evident, particularly for small cell and large cell subtypes. Therefore, incorporating the composition of tobacco carcinogens in lifetime smoking exposure may improve lung cancer risk estimation. This study does not support the claim of a null or inverse association between "low exposure" to tobacco smoke and risk of these cancer types.

Survival Gains from First-Line Systemic Therapy in Metastatic Non-Small Cell Lung Cancer in the U.S., 1990-2015: Progress and Opportunities. Roth JA1,2, Goulart BH3,2, Ravelo A4, Kolkey H4, Ramsey SD3,2. Oncologist. 2017 Feb 27. pii: theoncologist.2016-0253. doi: 10.1634/theoncologist.2016-0253. [Epub ahead of print]

BACKGROUND: Approximately 190,000 Americans are diagnosed with non-small cell lung cancer (NSCLC) annually, and about half have metastatic (Stage IV) disease. These patients have historically had poor survival prognosis, but several new therapies introduced since 2000 provide options for improved outcomes. The objectives of this study were to quantify survival gains from 1990, when best supportive care (BSC) only was standard, to 2015 and to estimate the impact of expanded use of systemic therapies in clinically appropriate patients. **MATERIALS AND METHODS:** We developed a simulation model to estimate survival gains for patients with metastatic NSCLC from 1990-2015. Survival estimates were derived from major clinical trials and extrapolated to a lifetime horizon. Proportions of patients receiving available therapies were derived from the Surveillance, Epidemiology, and End Results database and a commercial treatment registry. We also estimated gains in overall survival (OS) in scenarios in which systemic therapy use increased by 10% and 30% relative to current use. **RESULTS:** From 1990-2015, one-year survival proportion increased by 14.1% and mean per-patient survival improved by 4.2 months (32,700 population life years). Increasing treated patients by 10% or 30% increased OS by 5.1 months (39,700 population life years) and 6.9 months (53,800 population life years), respectively. **CONCLUSION:** Although survival remains poor in metastatic NSCLC relative to other common cancers, meaningful progress in per-patient and population-level outcomes has been realized over the past 25 years. These advances can be improved even further by increasing use of systemic therapies in the substantial proportion of patients who are suitable for treatment yet who currently receive BSC only. The Oncologist 2017;22:1-7Implications for Practice: Approximately 93,500 Americans are diagnosed with metastatic non-small cell lung cancer (NSCLC) annually. Historically, these patients have had poor survival prognosis, but newer therapies provide options for improved outcomes. This simulation modeling study quantified metastatic NSCLC survival gains from 1990-2015. Over this period, the one-year survival proportion and mean per-patient survival increased by 14.1% and 4.2 months, respectively. Though metastatic NSCLC survival remains poor, the past 25 years have brought meaningful gains. Additional gains could be realized by increasing systemic therapy use in the substantial proportion of patients who are suitable for treatment, yet currently receive only supportive care.