Caring Ambassadors Lung Cancer Program
Literature Review, August 2016

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Prognostic significance of circulating laminin gamma2 for early-stage non-small-cell lung cancer.
Teng Y1, Wang Z2, Ma L1, et al. Onco Targets Ther. 2016 Jul 7;9:4151-62. doi: 10.2147/OTT.S105732. eCollection 2016.
BACKGROUND: Laminin gamma2 (Ln-γ2) chain, a distinctive subunit of heterotrimeric laminin-332, is frequently upregulated in carcinomas and is of great importance in cell migration and invasion. Despite this, the status of circulating Ln-γ2 in lung cancer patients is still uncertain. **PATIENTS AND METHODS:** In this retrospective study, serum samples from 538 all-stage (stages I-IV) patients with non-small-cell lung cancer (NSCLC) and 94 age-matched healthy volunteers were investigated by enzyme-linked immunosorbent assay. Data were statistically analyzed in combination with clinicopathological information. **RESULTS:** Circulating Ln-γ2 was markedly increased in NSCLC, even in stage I cases (P<0.01), reflecting the progression of lung cancer. Survival analysis on 370 eligible patients indicated that serum Ln-γ2-negative patients survived much longer compared with Ln-γ2-positive individuals (P=0.028), and it was especially the case for stage I (P<0.001), stage T1 (P=0.001), and stage N0 patients (P=0.038), all of whom represented early-stage cases. For the advanced patients, however, overall survivals were not significantly different among stages II-IV (P=0.830), stages T2-T4 (P=0.575), stages N1-N3 (P=0.669), and stage M1 (P=0.849). Cox analysis subsequently defined serum Ln-γ2 as an independent prognostic indicator of NSCLC, particularly for early-stage patients. Furthermore, we demonstrated the association of serum Ln-γ2 with smoking behavior, but its association with tumor progression and early prognostic significance were not altered in the nonsmoking cohort.
CONCLUSION: Our study demonstrated that elevation of circulating Ln-γ2 was an early-emerging event in NSCLC and was significantly associated with poor prognosis in NSCLC, especially for early-stage cases.

Differential expression and significance of PD-L1, IDO-1 and B7-H4 in human lung cancer.
Schalper KA1, Carvajal-Hausdorf D2, McLaughlin J3, Altan M4, Velcheti V5, Gaule P2, Sanmamed MF6, Chen L7, Herbst RS8, Rimm DL2. Clin Cancer Res. 2016 Jul 20. pii: clincanres.0150.2016. [Epub ahead of print]

PURPOSE: To determine the expression level, associations and biological role of PD-L1, IDO-1 and B7-H4 in non-small cell lung cancer (NSCLC). **EXPERIMENTAL DESIGN:** Using multiplexed quantitative immunofluorescence (QIF), we measured the levels of PD-L1, IDO-1, B7-H4 and different tumor infiltrating lymphoycte (TIL) subsets in 552 stages I-IV lung carcinomas from 2 independent populations. Associations between the marker levels, TILs and major clinico-pathological variables were determined. Validation of findings was performed using mRNA expression data from The Cancer Genome Atlas (TCGA) and in vitro stimulation of lung adenocarcinoma A549 cells with IFN-γ and IL-10. **RESULTS:** PD-L1 was detected in 16.9% and 21.8% of cases in each population. IDO-1 was expressed in 42.6% and 49.8%; and B7-H4 in 12.8% and 22.6% of cases, respectively. Elevated PD-L1 and IDO-1 were consistently associated with prominent B and T-cell infiltrates, but B7-H4 was not. Co-expression of the 3 protein markers was infrequent and comparable results were seen in the lung cancer TCGA dataset. Levels of PD-L1 and IDO-1 (but not B7-H4) were increased by IFN-γ stimulation in A549 cells. Treatment with IL-10 upregulated B7-H4, but did not affect PD-L1 and IDO-1 levels. **CONCLUSIONS:** PD-L1, IDO-1 and B7-H4 are differentially expressed in human lung carcinomas and show limited co-expression. While PD-L1 and IDO-1 are associated with increased TILs and IFN-γ stimulation, B7-H4 is not. The preferential expression of discrete immune evasion pathways in lung cancer could participate in therapeutic resistance and support design of optimal clinical trials.

[High Specificity in Circulating Tumor Cell Identification Is Required for Accurate Evaluation of Programmed Death-Ligand 1.](#) Schehr JL1, Schultz ZD1, Warrick JW2, et al. PLoS One. 2016 Jul 26;11(7):e0159397. doi: 10.1371/journal.pone.0159397. eCollection 2016.

BACKGROUND: Expression of programmed-death ligand 1 (PD-L1) in non-small cell lung cancer (NSCLC) is typically evaluated through invasive biopsies; however, recent advances in the identification of circulating tumor cells (CTCs) may be a less invasive method to assay tumor cells for these purposes. These liquid biopsies rely on accurate identification of CTCs from the diverse populations in the blood, where some tumor cells share characteristics with normal blood cells. While many blood cells can be excluded by their high expression of CD45, neutrophils and other immature myeloid subsets have low to absent expression of CD45 and also express PD-L1. Furthermore, cytokeratin is typically used to identify CTCs, but neutrophils may stain non-specifically for intracellular antibodies, including cytokeratin, thus preventing accurate evaluation of PD-L1 expression on tumor cells. This holds even greater significance when evaluating PD-L1 in epithelial cell adhesion molecule (EpCAM) positive and EpCAM negative CTCs (as in epithelial-mesenchymal transition (EMT)). **METHODS:** To evaluate the impact of CTC misidentification on PD-L1 evaluation, we utilized CD11b to identify myeloid cells. CTCs were isolated from patients with metastatic NSCLC using EpCAM, MUC1 or Vimentin capture antibodies and exclusion-based sample preparation (ESP) technology. **RESULTS:** Large populations of CD11b+CD45lo cells were identified in buffy coats and stained non-specifically for intracellular antibodies including cytokeratin. The amount of CD11b+ cells misidentified as CTCs varied among patients; accounting for 33-100% of traditionally identified CTCs. Cells captured with vimentin had a higher frequency of CD11b+ cells at 41%, compared to 20% and 18% with MUC1 or EpCAM, respectively. Cells misidentified as CTCs ultimately skewed PD-L1 expression to varying degrees across patient samples. **CONCLUSIONS:** Interfering myeloid populations can be differentiated from true CTCs with additional staining criteria, thus improving the specificity of CTC identification and the accuracy of biomarker evaluation.

Glypican-5 is a tumor suppressor in non-small cell lung cancer cells. Guo L1, Wang J1, Zhang T1, Yang Y2. Biochem Biophys Rep. 2016 Jul;6:108-112.

Glypican-5 (GPC5) belongs to the glypican family of proteoglycans that have been implicated in a variety of physiological processes, ranging from cell proliferation to morphogenesis. However, the role of GPC5 in human cancer remains poorly understood. We report that knockdown of GPC5 in bronchial epithelial cells promoted, and forced expression of GPC5 in non-small lung cancer (NSCLC) cells suppressed, the anchorage-independent cell growth. In vivo, expression of GPC5 inhibited xenograft tumor growth of NSCLC cells. Furthermore, we found that GPC5 was expressed predominantly as a membrane protein, and its expression led to diminished phosphorylation of several oncogenic receptor tyrosine kinases, including the ERBB family members ERBB2 and ERBB3, which play critical roles in lung tumorigenesis. Collectively, our results suggest that GPC5 may act as a tumor suppressor, and reagents that activate GPC5 may be useful for treating NSCLC.

SCREENING, DIAGNOSIS AND STAGING

Factors Associated with a Positive Baseline Screening Exam Result in the National Lung Screening Trial. Balekian AA1, Tanner NT2,3, Fisher JM4, Silvestri GA5, Gould MK6. Ann Am Thorac Soc. 2016 Jul 7. [Epub ahead of print]

RATIONALE: Lung cancer screening with low-dose computed tomography (LDCT) has been shown to decrease mortality in eligible high-risk patients. However, this mortality benefit comes with a high rate of false positive findings, which require further evaluation. **OBJECTIVES:** To identify patient- and center-specific factors associated with having a pulmonary nodule on baseline LDCT, and to develop a prediction rule to help in shared decision-making. **METHODS:** We identified individuals who underwent baseline LDCT screening as part of the National Lung Screening Trial (NLST). A positive screen was defined as a nodule 4mm or greater in largest dimension. Using multiple logistic regression, we identified variables independently associated with having a positive screen. **MEASUREMENTS AND MAIN RESULTS:** Among the 26,004 patients with complete data who underwent baseline LDCT, 7,123 patients (27%) had a positive screen. In a multivariate analysis, older age (OR 1.03 per 1-year increase, 95%CI[1.03-1.04]), female sex (OR 1.08, 95%CI[1.01-1.14]), white race (OR 1.39, 95%CI[1.25-1.55]), heavier smoking history (OR 1.02 per 5-pack years smoked over 30, 95%CI[1.00-1.04]), history of COPD (OR 1.08, 95%CI[1.01-1.17]), being married (OR 1.08, 95%CI[1.02-1.15]), hard rock mining (OR 1.40, 95%CI[1.04-1.89]), and farm work (OR 1.13, 95%CI[1.03-1.23]) were independently associated with having a positive screen, while having a college degree (OR 0.94, 95%CI[0.86-1.00]) and abstinence from smoking (OR 0.98 per year, 95%CI[0.98-0.99]) were associated with not having a positive screen. Patients enrolled at a site in an area highly endemic for histoplasma were 30% more likely to have a positive baseline LDCT screen (OR 1.30, 95%CI[1.21-1.40]). The area under the ROC curve for the full model was 0.57 (0.56-0.58); including enrollment center as a random effect increased the AU-ROC to 0.65. **CONCLUSIONS:** In the NLST, both patient- and center-specific factors were associated with having a positive baseline screen. Although the model does not have sufficient accuracy to provide personalized risk estimates to guide shared decision-making on an individual basis, it can nonetheless inform screening centers of the likelihood of further follow-up testing for their populations at large when allocating resources. Data collected from centers as broad based screening is implemented can be used to improve model accuracy further.

Does Lymph Node Count Influence Survival in Surgically Resected Non-Small Cell Lung Cancer? David EA1, Cooke DT2, Chen Y3, Nijar K4, Canter RJ5, Cress RD6. Ann Thorac Surg. 2016 Jul 25. pii: S0003-4975(16)30500-8. doi: 10.1016/j.athoracsur.2016.05.018. [Epub ahead of print]

BACKGROUND: The prognostic significance of the number of lymph nodes sampled (NLNS) during resection for non-small cell lung cancer (NSCLC) is unclear. The NLNS is influenced by many factors, and some have argued that it should be a surrogate for quality. We sought to determine the influence of the NLNS on overall survival and cancer-specific survival for surgically resected NSCLC. **METHODS:** The California Cancer Registry was queried from 2004 to 2011 for cases of stage I to III NSCLC treated with surgical resection, identifying 16,393 patients. Kaplan-Meier and Cox proportional hazards modeling were used to determine the influence of NLNS on overall survival and cancer-specific survival. **RESULTS:** In all, 15,195 patients had information regarding nodal sampling. Eighty percent (13,167 of 15,195) were treated with lobectomy. Patients who were younger, male, non-Hispanic white, highest socioeconomic status, higher stage, or larger size tumor had more nodes removed. Sampling fewer than 10 nodes was associated with poorer overall survival when compared with sampling 10 or more nodes after adjustment for demographic and clinical factors for stage I: overall survival hazard ratio 1.78 (95% confidence interval: 1.54 to 2.05, $p < 0.0001$), hazard ratio 1.43 (95% confidence interval: 1.27 to 1.59, $p < 0.0001$), and hazard ratio 1.16 (95% confidence interval: 1.05 to 1.28, $p = 0.004$), for 0, 1 to 3, and 4 to 10 nodes, respectively. Of patients who underwent sublobar resection, 43.8% had no nodes sampled. **CONCLUSIONS:** For NSCLC, the NLNS influenced both overall survival and cancer-specific survival, but the influence is dependent on stage. Surgeons should perform mediastinal lymphadenectomy to maximize patient survival, but the optimal NLNS remains unclear.

[**Limits and potential of targeted sequencing analysis of liquid biopsy in patients with lung and colon carcinoma.**](#) Rachiglio AM1, Abate RE1, Sacco A1, et al. Oncotarget. 2016 Jul 19. doi: 10.18632/oncotarget.10704. [Epub ahead of print]
The circulating free tumor DNA (ctDNA) represents an alternative, minimally invasive source of tumor DNA for molecular profiling. Targeted sequencing with next generation sequencing (NGS) can assess hundred mutations starting from a low DNA input. We performed NGS analysis of ctDNA from 44 patients with metastatic non-small-cell lung carcinoma (NSCLC) and 35 patients with metastatic colorectal carcinoma (CRC). NGS detected EGFR mutations in 17/22 plasma samples from EGFR-mutant NSCLC patients (sensitivity 77.3%). The concordance rate between tissue and plasma in NSCLC was much lower for other mutations such as KRAS that, based on the allelic frequency and the fraction of neoplastic cells, were likely to be sub-clonal. NGS also identified EGFR mutations in plasma samples from two patients with EGFR wild type tumor tissue. Both mutations were confirmed by droplet digital PCR (ddPCR) in both plasma and tissue samples. In CRC, the sensitivity of the NGS plasma analysis for RAS mutations was 100% (6/6) in patients that had not resection of the primary tumor before blood drawing, and 46.2% (6/13) in patients with primary tumor resected before enrollment. Our study showed that NGS is a suitable method for plasma testing. However, its clinical sensitivity is significantly affected by the presence of the primary tumor and by the heterogeneity of driver mutations.

[**PET/CT-guided percutaneous biopsy of FDG-avid metastatic bone lesions in patients with advanced lung cancer: a safe and effective technique.**](#) Guo W1, Hao B1, Chen HJ1, Zhao L1, Luo ZM1, Wu H1, Sun L2. Eur J Nucl Med Mol Imaging. 2016 Jul 22. [Epub ahead of print]
PURPOSE: 18F-FDG PET/CT should be performed before a diagnostic biopsy site is chosen in patients with a high clinical suspicion of aggressive, advanced tumour. The aim of this study was to evaluate the safety and efficacy of 18F-FDG PET/CT in guiding biopsy of bone metastases in patients with advanced lung cancer. **METHODS:** PET/CT-guided percutaneous core biopsies were performed in 51 consecutive patients with suspected lung cancer and 18F-FDG-avid bone lesions after whole-body 18F-FDG PET/CT scans. Generally, one tissue sample was obtained from each patient. The final diagnoses were established on the basis of the histology results. The histopathological and molecular testing results were systematically evaluated. **RESULTS:** A total of 53 samples were obtained for histological examination or

molecular testing as a second biopsy was required in two patients in whom the pathological diagnosis was unclear following the first biopsy. The pathological diagnosis and lung cancer classification were confirmed in 48 patients. The epidermal growth factor receptor mutation status was determined in 23 biopsies, and the mutation rate was 30.4 % (7/23). The anaplastic lymphoma kinase mutation status was determined in 19 biopsies, and the mutation rate was 31.6 % (6/19). Two of the 51 biopsies were positive for non-Hodgkin's lymphoma and one was positive for metastatic renal cell carcinoma. The first-time diagnostic success rate of biopsy was 96.1 % (49/51) and the overall diagnostic success rate and sensitivity were 100 %. All 51 patients were eventually confirmed as having stage IV disease. No serious complications were encountered and the average biopsy time was 30 min. **CONCLUSION:** PET/CT-guided percutaneous biopsy of 18F-FDG-avid bone metastases is an effective and safe method that yields a high diagnostic success rate in the evaluation of hypermetabolic bone lesions in patients with suspected advanced lung cancer.

[**The five commandments of efficient and effective care in the initial evaluation of lung cancer.**](#) Chang CF1, Gould MK. Curr Opin Pulm Med. 2016 Jul;22(4):319-26. doi: 10.1097/MCP.0000000000000281. **PURPOSE OF REVIEW:** Multiple recent studies have found an astounding lack of concordance with national guidelines in the workup of lung cancer in both community and academic settings. The resultant increase in complications and delays may potentially contribute to the overall dismal outcomes, as well as cost. This article aims to increase awareness among clinicians about the scope of this problem, and provides a simplified primer on the core concepts of how to perform an efficient and effective workup that is in-line with national guidelines. **RECENT FINDINGS:** Although the basic principles underlying lung cancer evaluation have not changed in the last decade, there are new areas of debate which are outlined and discussed in this article. These include: the value of brain and bone imaging in asymptomatic patients, the best initial site to biopsy in the era of genomics, and the use of biomarkers with low-dose chest tomography screening. **SUMMARY:** Given the huge stakes in lung cancer, the current national quality gap in initial evaluation is unacceptable. However, physician re-education can change this. This article provides a quick review of how to properly evaluate a patient with potential lung cancer, as well as an update on new and continuing controversies in the field.

[**The impact on the prognosis of unsuspected N2 disease in non-small-cell lung cancer: indications for thorough mediastinal staging in the modern era.**](#) Tachi R1, Hattori A1, Matsunaga T1, Takamochi K1, Oh S1, Suzuki K2. Surg Today. 2016 Jul 21. [Epub ahead of print]
PURPOSE: Predicting the prognosis of advanced non-small-cell lung cancer (NSCLC) patients who present with clinically unsuspected N2 is very different due to the heterogeneity of this cohort. Thus, this study was undertaken to identify the clinicopathological features and survival of patients with clinical N0 or N1 and pathological N2, namely, unsuspected N2. **METHODS:** Among 239 patients with pathological N2 NSCLC, we reviewed the cases of 92 (38.5 %) patients who showed unsuspected N2. The prognosis was investigated using the Kaplan-Meier method and a Cox regression model. **RESULTS:** The 5-year overall survival (5yOS) of the patients with unsuspected N2 was 51.2 %. Based on a multivariate analysis, age and 18F-fluorodeoxyglucose (FDG) uptake in the lymph nodes were significant prognostic factors of unsuspected N2 (p = 0.0081, 0.0228, respectively). The 5yOS of PET-negative unsuspected N2 (n = 68) was 58.9 %, whereas that of PET-positive unsuspected N2 (n = 24) was 29.7 % (p = 0.0026). Furthermore, the 5yOS of PET-negative unsuspected N2 was significantly better than that of both clinical and pathological N2 s (i.e., suspected N2; n = 60; 5yOS, 42.1 %; p = 0.0051), while no significant difference was observed between PET-positive unsuspected N2 and suspected N2 (p = 0.6325). **CONCLUSIONS:** A preoperative evaluation of the lymph nodes by PET/CT has a potential benefit in predicting the prognosis. A thorough evaluation of the lymph nodes is, therefore, needed if the lymph nodes show an FDG uptake, even in cases that show a clinical N0 status on thin section CT scans.

Risk Factors for Predicting Occult Lymph Node Metastasis in Patients with Clinical Stage I Non-small Cell Lung Cancer Staged by Integrated Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography. Kaseda K1, Asakura K2, Kazama A3, Ozawa Y4. World J Surg. 2016 Jul 25. [Epub ahead of print]

BACKGROUND: Lymph nodes in patients with non-small cell lung cancer (NSCLC) are often staged using integrated 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT). However, this modality has limited ability to detect micrometastases. We aimed to define risk factors for occult lymph node metastasis in patients with clinical stage I NSCLC diagnosed by preoperative integrated FDG-PET/CT. **METHODS:** We retrospectively reviewed the records of 246 patients diagnosed with clinical stage I NSCLC based on integrated FDG-PET/CT between April 2007 and May 2015. All patients were treated by complete surgical resection. The prevalence of occult lymph node metastasis in patients with clinical stage I NSCLC was analysed according to clinicopathological factors. Risk factors for occult lymph node metastasis were defined using univariate and multivariate analyses. **RESULTS:** Occult lymph node metastasis was detected in 31 patients (12.6 %). Univariate analysis revealed CEA ($P = 0.04$), SUVmax of the primary tumour ($P = 0.031$), adenocarcinoma ($P = 0.023$), tumour size ($P = 0.002$) and pleural invasion ($P = 0.046$) as significant predictors of occult lymph node metastasis. Multivariate analysis selected SUVmax of the primary tumour ($P = 0.049$), adenocarcinoma ($P = 0.003$) and tumour size ($P = 0.019$) as independent predictors of occult lymph node metastasis. **CONCLUSIONS:** The SUVmax of the primary tumour, adenocarcinoma and tumour size were risk factors for occult lymph node metastasis in patients with NSCLC diagnosed as clinical stage I by preoperative integrated FDG-PET/CT. These findings would be helpful in selecting candidates for mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration.

Use of Positron Emission Tomography to Detect Recurrence and Associations With Survival in Patients With Lung and Esophageal Cancers. Healy MA1, Yin H2, Reddy RM2, Wong SL2. J Natl Cancer Inst. 2016 Feb 22;108(7). pii: djv429. doi: 10.1093/jnci/djv429. Print 2016 Jul.

BACKGROUND: Positron emission tomography (PET) scans are often used in cancer patients for staging, restaging, and monitoring for treatment response. These scans are also often used to detect recurrence in asymptomatic patients, despite a lack of evidence demonstrating improved survival. We sought to evaluate utilization of PET for this purpose and relationships with survival for patients with lung and esophageal cancers. **METHODS:** Using national Surveillance, Epidemiology, and End Results (SEER) and Medicare-linked data, we identified incident patient cases from 2005 to 2009, with follow-up through 2011. We identified cohorts with primary lung ($n = 97 152$) and esophageal ($n = 4446$) cancers. Patient and tumor characteristics were used to calculate risk-adjusted two-year overall survival. Using Medicare claims, we examined PET utilization in person-years (to account for variable time in cohorts), excluding scans for staging and for follow-up of CT findings. We then stratified hospitals by quintiles of PET utilization for adjusted two-year survival analysis. All statistical tests were two-sided. **RESULTS:** There was statistically significant variation in utilization of PET. Lowest vs highest utilizing hospitals performed .05 (SD = 0.04) vs 0.70 (SD = 0.44) scans per person-year for lung cancer and 0.12 (SD = 0.06) vs 0.97 (SD = 0.29) scans per person-year for esophageal cancer. Despite this, for those undergoing PET, lowest vs highest utilizing hospitals had an adjusted two-year survival of 29.0% (SD = 12.1%) vs 28.8% (SD = 7.2%) for lung cancer ($P = .66$) and 28.4% (SD = 7.2%) vs 30.3% (SD = 5.9%) for esophageal cancer ($P = .55$). **CONCLUSIONS:** Despite statistically significant variation in use of PET to detect tumor recurrence, there was no association with improved two-year survival. These findings suggest possible overuse of PET for recurrence detection, which current Medicare policy would not appear to substantially affect.

Clinical Utility of Liquid Diagnostic Platforms in Non-Small Cell Lung Cancer. Levy B1, Hu ZI2, Cordova KN3, Close S4, Lee K2, Becker D5. Oncologist. 2016 Jul 7. pii: theoncologist.2016-0082. [Epub ahead of print]

A firmer understanding of the genomic landscape of lung cancer has recently led to targeted, therapeutic advances in non-small cell lung cancer. Historically, the reference standard for the diagnosis and genetic interrogation for advanced-stage patients has been tissue acquisition via computed tomography-guided core or fine needle aspiration biopsy. However, this process can frequently put the patient at risk and remains complicated by sample availability and tumor heterogeneity. In addition, the time required to complete the diagnostic assays can negatively affect clinical care. Technological advances in recent years have led to the development of blood-based diagnostics or "liquid biopsies" with great potential to quickly diagnose and genotype lung cancer using a minimally invasive technique. Recent studies have suggested that molecular alterations identified in cell-free DNA (cfDNA) or circulating tumor DNA can serve as an accurate molecular proxy of tumor biology and reliably predict the response to tyrosine kinase therapy. In addition, several trials have demonstrated the high accuracy of microRNA (miRNA) platforms in discerning cancerous versus benign nodules in high-risk, screened patients. Despite the promise of these platforms, issues remain, including varying sensitivities and specificities between competing platforms and a lack of standardization of techniques and downstream processing. In the present report, the clinical applications of liquid biopsy technologies, including circulating tumor cells, proteomics, miRNA, and cfDNA for NSCLC, are reviewed and insight is provided into the diagnostic and therapeutic implications and challenges of these platforms. **IMPLICATIONS FOR PRACTICE:** Although tumor biopsies remain the reference standard for the diagnosis and genotyping of non-small cell lung cancer, they remain fraught with logistical complexities that can delay treatment decisions and affect clinical care. Liquid diagnostic platforms, including cell-free DNA, proteomic signatures, RNA (mRNA and microRNA) and circulating tumor cells have the potential to overcome many of these barriers, including rapid and accurate identification of de novo and resistant genetic alterations, real-time monitoring of treatment responses, prognosis of outcomes, and identification of minimal residual disease. The present report provides insights into new liquid diagnostic platforms in non-small cell lung cancer and discusses the promise and challenges of their current and future clinical use.

Readiness for Implementation of Lung Cancer Screening: A National Survey of VA Pulmonologists. Tukey MH1, Clark JA2,3, Bolton R4, et al. Ann Am Thorac Soc. 2016 Jul 13. [Epub ahead of print]

RATIONALE: To mitigate the potential harms of screening, professional societies recommend that lung cancer screening be conducted in multidisciplinary programs with the capacity to provide comprehensive care from screening through pulmonary nodule evaluation to treatment of screen-detected cancers. The degree to which this standard can be met at the national level is unknown. **OBJECTIVES:** To assess the readiness of clinical facilities in a national healthcare system for implementation of comprehensive lung cancer screening programs, as compared to the ideal described in policy recommendations. **METHODS:** Cross-sectional, self-administered survey of staff pulmonologists in pulmonary outpatient clinics in Veterans Health Administration (VA) facilities. **MEASUREMENTS AND MAIN RESULTS:** The facility-level response rate was 84.1% (106 of 126 facilities with pulmonary clinics). 88.7% of facilities showed favorable provider perceptions of the evidence for lung cancer screening and 73.6% of facilities had favorable provider-perceived local context for screening implementation. All elements of the policy-recommended infrastructure for comprehensive screening programs were present in 36 of 106 (34.0%) facilities; the most common deficiencies were on-site PET scanners or radiation oncology services. Overall, 26.5% of VA facilities were ideally prepared for lung cancer screening implementation (44.1% if the policy recommendations for on-site PET scanners and radiation oncology services were waived). **CONCLUSIONS:** Many facilities may be less than ideally positioned for implementation of comprehensive lung cancer screening programs. To ensure safe, effective screening, hospitals may need

to invest resources or coordinate care with facilities that can offer comprehensive care for screening through downstream evaluation and treatment of screen-detected cancers.

Endobronchial Ultrasound Guided Transbronchial Needle Aspiration for Mediastinal Staging in a Community Medical Center. Warren WA1, Hagaman JT2. Ann Am Thorac Soc. 2016 Jul 13. [Epub ahead of print]
RATIONALE: Endobronchial ultrasound guided transbronchial needle aspiration and positron emission tomography-computed tomography are valuable tools for lung cancer staging. Data from tertiary referral centers suggest these modalities are superior to mediastinoscopy in mediastinal staging. **OBJECTIVE:** Validate endobronchial ultrasound guided transbronchial needle aspiration for lung cancer staging in a community center with operators of varying experience. **METHODS:** At an 800-bed community hospital, we reviewed all cases where endobronchial ultrasound-guided transbronchial needle aspiration and positron emission tomography-computed tomography were performed for mediastinal staging by one of seven private practice pulmonologists. Cases were reviewed with lymph node dissection by mediastinoscopy following negative endobronchial ultrasound guided transbronchial needle aspiration. **MEASUREMENTS AND MAIN RESULTS:** Of the 333 cases that were reviewed, 44 underwent mediastinoscopy following negative endobronchial ultrasound-guided transbronchial needle aspiration. Four patients were positive for malignancy at station 4R and 7 lymph nodes. In none of these cases did endobronchial ultrasound-guided transbronchial needle aspiration reveal lymphoid tissue confirming the sample location. Positron emission tomography-computed tomography showed mediastinal lymph nodes with increased avidity in two of the false negative cases. Endobronchial ultrasound guided transbronchial needle aspiration plus positron emission tomography-computed tomography had a sensitivity, specificity and negative predictive value of 98.86%, 100% and 94.87% respectively compared to mediastinoscopy for detecting metastasis. **CONCLUSIONS:** Endobronchial ultrasound guided transbronchial needle aspiration is accurate in detecting mediastinal metastasis of lung cancer in the community setting. Positron emission tomography-computed tomography without uptake in lymph nodes reduces likelihood of malignancy but cannot rule out mediastinal involvement.

Predicting malignant nodules from screening CTs. Hawkins S1, Wang H2, Liu Y2, et al. J Thorac Oncol. 2016 Jul 12. pii: S1556-0864(16)30600-1. doi: 10.1016/j.jtho.2016.07.002. [Epub ahead of print]
PURPOSE: Determine if quantitative analyses ("radiomics") of low dose CT lung cancer screening images at baseline can predict subsequent emergence of cancer. **PATIENTS AND METHODS:** Public data from the National Lung Screening Trial (ACRIN 6684) were assembled into two cohorts of 104 and 92 patients with screen detected lung cancer (SDLC), then matched to cohorts of 208 and 196 screening subjects with benign pulmonary nodules (bPN). Image features were extracted from each nodule and used to predict the subsequent emergence of cancer. **RESULTS:** The best models used 23 stable features in a Random Forest classifier, and could predict nodules that will become cancerous 1 and 2 years hence with accuracies of 80% (AUC 0.83) and 79% (AUC 0.75), respectively. Radiomics outperformed Lung-RADS and volume. McWilliams' risk assessment model was commensurate. **CONCLUSION:** Radiomics of lung cancer screening CTs at baseline can be used to assess risk for development of cancer.

NSCLC - SURGERY

[Long term survival with stereotactic ablative radiotherapy (SABR) versus thoracoscopic sublobar lung resection in elderly people: national population based study with propensity matched comparative analysis.](#) Paul S1, Lee PC2, Mao J3, Isaacs AJ3, Sedrakyan A4. BMJ. 2016 Jul 8;354:i3570. doi: 10.1136/bmj.i3570.

OBJECTIVES: To compare cancer specific survival after thoracoscopic sublobar lung resection and stereotactic ablative radiotherapy (SABR) for tumors ≤2 cm in size and thoracoscopic resection (sublobar resection or lobectomy) and SABR for tumors ≤5 cm in size. **DESIGN:** National population based retrospective cohort study with propensity matched comparative analysis. **SETTING:** Surveillance, Epidemiology, and End Results (SEER) registry linked with Medicare database in the United States. **PARTICIPANTS:** Patients aged ≥66 with lung cancer undergoing SABR or thoracoscopic lobectomy or sublobar resection from 1 Oct 2007 to 31 June 2012 and followed up to 31 December 2013. **MAIN OUTCOME MEASURES:** Cancer specific survival after SABR or thoracoscopic surgery for lung cancer. **RESULTS:** 690 (275 (39.9%) SABR and 415 (60.1%) thoracoscopic sublobar lung resection) and 2967 (714 (24.1%) SABR and 2253 (75.9%) thoracoscopic resection) patients were included in primary and secondary analyses. The average age of the entire cohort was 76. Follow-up of the entire cohort ranged from 0 to 6.25 years, with an average of three years. In the primary analysis of patients with tumors sized ≤2 cm, 37 (13.5%) undergoing SABR and 44 (10.6%) undergoing thoracoscopic sublobar resection died from lung cancer, respectively. The cancer specific survival diverged after one year, but in the matched analysis (201 matched patients in each group) there was no significant difference between the groups (SABR v sublobar lung resection mortality: hazard ratio 1.32, 95% confidence interval 0.77 to 2.26; P=0.32). Estimated cancer specific survival at three years after SABR and thoracoscopic sublobar lung resection was 82.6% and 86.4%, respectively. The secondary analysis (643 matched patients in each group) showed that thoracoscopic resection was associated with improved cancer specific survival over SABR in patients with tumors sized ≤5 cm (SABR v resection mortality: hazard ratio 2.10, 1.52 to 2.89; P<0.001). Estimated cancer specific survival at three years was 80.0% and 90.3%, respectively. **CONCLUSIONS:** This propensity matched analysis suggests that patients undergoing thoracoscopic surgical resection, particularly for larger tumors, might have improved cancer specific survival compared with patients undergoing SABR. Despite strategies used in study design and propensity matching analysis, there are inherent limitations to this observational analysis related to confounding, similar to most studies in healthcare of non-surgical technologies compared with surgery. As the adoption of SABR for the treatment of early stage operable lung cancer would be a paradigm shift in lung cancer care, it warrants further thorough evaluation before widespread adoption in practice.

[Surgery for non-small cell lung cancer in patients with a history of cardiovascular surgery.](#) Maeda H1, Kanzaki M2, Sakamoto K1, Isaka T1, Yamazaki K3, Onuki T1. Surg Today. 2016 Jul 21. [Epub ahead of print]

PURPOSE: To clarify if previous cardiovascular surgery (CVS) affects the postoperative outcome of surgery for non-small cell lung cancer (NSCLC). **METHODS:** We reviewed, retrospectively, the medical records of 36 patients with a history of CVS, who underwent lung cancer surgery at a single institution (study group; SG) and compared their characteristics and postoperative outcomes with those of patients without a history of CVS history (control group; CG), and also with those of patients with coexisting cardiovascular diseases in the CG (specified control group; SCG). Finally, we used a thoracic revised cardiac risk index (ThRCRI) to evaluate the risk of perioperative cardiovascular events. **RESULTS:** There was a significant difference in the ThRCRI classifications between the SG and the SCG (p <

0.0001). There were no significant differences in the incidence of intraoperative and postoperative complications between the SG and CG, or between the SG and SCG. The 5-year survival rates of the SG, CG, and SCG were 69.3, 73.9, and 65.4 % in all stages, and 83.5, 82.2, and 70.4 % in stage I, respectively. **CONCLUSIONS:** Previous CVS did not increase the number of perioperative cardiovascular events in this study and had no significant influence on the prognosis of patients undergoing resection of NSCLC.

[Socioeconomic Factors Are Associated With Readmission After Lobectomy for Early Stage Lung Cancer.](#) Medbery RL1, Gillespie TW2, Liu Y3, Nickleach DC4, Lipscomb J5, Sancheti MS1, Pickens A1, Force SD1, Fernandez FG6. Ann Thorac Surg. 2016 Jul 28. pii: S0003-4975(16)30555-0. doi: 10.1016/j.athoracsur.2016.05.060. [Epub ahead of print]
BACKGROUND: Data regarding risk factors for readmissions after surgical resection for lung cancer are limited and largely focus on postoperative outcomes, including complications and hospital length of stay. The current study aims to identify preoperative risk factors for postoperative readmission in early stage lung cancer patients. **METHODS:** The National Cancer Data Base was queried for all early stage lung cancer patients with clinical stage T2N0M0 or less who underwent lobectomy in 2010 and 2011. Patients with unplanned readmission within 30 days of hospital discharge were identified. Univariate analysis was utilized to identify preoperative differences between readmitted and not readmitted cohorts; multivariable logistic regression was used to identify risk factors resulting in readmission. **RESULTS:** In all, 840 of 19,711 patients (4.3%) were readmitted postoperatively. Male patients were more likely to be readmitted than female patients (4.9% versus 3.8%, p < 0.001), as were patients who received surgery at a nonacademic rather than an academic facility (4.6% versus 3.6%; p = 0.001) and had underlying medical comorbidities (Charlson/Deyo score 1+ versus 0; 4.8% versus 3.7%; p < 0.001). Readmitted patients had a longer median hospital length of stay (6 days versus 5; p < 0.001) and were more likely to have undergone a minimally invasive approach (5.1% video-assisted thoracic surgery versus 3.9% open; p < 0.001). In addition to those variables, multivariable logistic regression analysis identified that median household income level, insurance status (government versus private), and geographic residence (metropolitan versus urban versus rural) had significant influence on readmission. **CONCLUSIONS:** The socioeconomic factors identified significantly influence hospital readmission and should be considered during preoperative and postoperative discharge planning for patients with early stage lung cancer.

NSCLC - CHEMOTHERAPY

[Predictive factors for a long-term response duration in non-squamous cell lung cancer patients treated with pemetrexed.](#) Park S1, Kim HJ2, Choi CM1,3, et al. BMC Cancer. 2016 Jul 7;16:417. doi: 10.1186/s12885-016-2457-0.
BACKGROUND: Pemetrexed is widely used for the treatment of advanced non-squamous non-small-cell lung cancer (NSCLC). However, factors that can predict the benefits of pemetrexed therapy have not yet been defined. **METHODS:** We compared the clinical and molecule pathological characteristics of good and poor responders among a cohort of 1,848 non-squamous NSCLC patients who had received at least two cycles of pemetrexed therapy between November 2006 and February 2015. Among these cases, 92 good responders who were the top 5 % in terms of progression-free survival (PFS) and 222 poor responders who had progressive disease after only 2 cycles of therapy were selected for the analysis. **RESULTS:** The median PFS of the good responders was 29.9 months (range; 20.9-90.0) and the median number of cycle was 37 (range; 18-129). Although 53.5 % of patients showed stable disease (SD), this response was sustained (median PFS in SD, 29.6 months). A never-smoking status was related to better survival outcome, whereas EGFR mutation, two or more metastatic sites, and intra-abdominal metastasis were each associated with a poor PFS. ALK translocation showed a tendency for a positive impact on

response to pemetrexed, whereas metastatic lesion to liver, adrenal gland or bone showed a tendency for a negative impact despite not reaching our threshold for statistical significance. **CONCLUSIONS:** Predictive factors, such as smoking status, the status of genetic alteration and tumor burden, should be considered when administering pemetrexed therapy for non-squamous NSCLC.

[Multicenter Phase II Study of Whole-Body and Intracranial Activity With Ceritinib in Patients With ALK-Rearranged Non-Small-Cell Lung Cancer Previously Treated With Chemotherapy and Crizotinib: Results From ASCEND-2.](#) Crinò L1, Ahn MJ2, De Marinis F2, et al. J Clin Oncol. 2016 Jul 18. pii: JCO655936. [Epub ahead of print]

PURPOSE: Phase I data (ASCEND-1) showed ceritinib efficacy in patients with ALK-rearranged non-small-cell lung cancer (NSCLC), regardless of brain metastases status and with or without prior therapy with an inhibitor of the ALK protein. Data are presented from a phase II trial (ASCEND-2) in which ceritinib efficacy and safety were evaluated in patients who had ALK-rearranged NSCLC previously treated with at least one platinum-based chemotherapy and who had experienced progression during crizotinib treatment as their last prior therapy. **PATIENTS AND METHODS:** Patients with advanced ALK-rearranged NSCLC, including those with asymptomatic or neurologically stable baseline brain metastases, received oral ceritinib 750 mg/d. Whole-body and intracranial responses were investigator assessed (according to RECIST version 1.1). Patient-reported outcomes were evaluated with the Lung Cancer Symptom Scale and European Organisation for Research and Treatment of Cancer surveys (the core-30 and the 13-item lung cancer-specific quality-of-life questionnaires). **RESULTS:** All 140 patients enrolled had received two or more previous treatment regimens, and all patients had received crizotinib. The median duration of exposure and the follow-up time with ceritinib were 8.8 months (range, 0.1 to 19.4 months) and 11.3 months (range, 0.1 to 18.9 months), respectively. Investigator-assessed overall response rate was 38.6% (95% CI, 30.5% to 47.2%). Secondary end points, all investigator assessed, included disease control rate (77.1%; 95% CI, 69.3% to 83.8%), time to response (median, 1.8 months; range, 1.6 to 5.6 months), duration of response (median, 9.7 months; 95% CI, 7.1 to 11.1 months), and progression-free survival (median, 5.7 months; 95% CI, 5.4 to 7.6 months). Of 100 patients with baseline brain metastases, 20 had active target lesions at baseline; investigator-assessed intracranial overall response rate was 45.0% (95% CI, 23.1% to 68.5%). The most common adverse events (majority, grade 1 or 2) for all treated patients were nausea (81.4%), diarrhea (80.0%), and vomiting (62.9%). Patient-reported outcomes showed a trend toward improved symptom burden. The global quality-of-life score was maintained during treatment. **CONCLUSION:** Consistent with its activity in ASCEND-1, ceritinib treatment provided clinically meaningful and durable responses with manageable tolerability in chemotherapy- and crizotinib-pretreated patients, including those with brain metastases.

[FDA Approval: Alectinib for the Treatment of Metastatic ALK-Positive Non-Small Cell Lung Cancer Following Crizotinib.](#) Larkins E1, Blumenthal GM2, Chen H3, et al. Clin Cancer Res. 2016 Jul 13. pii: clincanres.1293.2016. [Epub ahead of print]

On December 11, 2015, the FDA granted accelerated approval to alectinib (ALECENSA®; Genentech, Inc.) for the treatment of patients with anaplastic lymphoma receptor tyrosine kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This approval was based on two single-arm trials including 225 patients treated with alectinib 600 mg orally twice daily. The objective response rates (ORR) by independent review committee in these studies were 38% (95% CI, 36-52) and 44% (95% CI 36-53); the median durations of response (DOR) were 7.5 months and 11.2 months. In a pooled analysis of 51 patients with measurable disease in the central nervous system (CNS) at baseline, the CNS ORR was 61% (95% CI 46-74); the CNS DOR was 9.1 months. The primary safety analysis population included 253 patients. The most common adverse reactions were fatigue (41%), constipation (34%), edema (30%), and myalgia (29%). The most common

laboratory abnormalities were anemia (56%), increased aspartate aminotransferase (51%), increased alkaline phosphatase (47%), increased creatine phosphokinase (43%), hyperbilirubinemia (39%), hyperglycemia (36%), increased alanine aminotransferase (34%), and hypocalcemia (32%). Dose reductions due to adverse reactions occurred in 12% of patients, while 27% of patients had alectinib dosing interrupted for adverse reactions. Permanent discontinuation of alectinib due to adverse reactions occurred in only 6% of patients. With the clinically meaningful ORR and DOR and the safety profile observed in these trials, alectinib was determined to have a favorable benefit-risk profile for the treatment of the indicated population.

Brief Report: An Open-Label, Multicenter, Randomized, Phase II Study of Cisplatin and Pemetrexed With or Without Cixutumumab (IMC-A12) as a First-Line Therapy in Patients With Advanced Nonsquamous Non-Small Cell Lung Cancer. Novello S1, Scagliotti G2, de Castro G Jr3, et al. J Thorac Oncol. 2016 Jul 24. pii: S1556-0864(16)30631-1. doi: 10.1016/j.jtho.2016.07.013. [Epub ahead of print]

INTRODUCTION: Type 1 insulin-like growth factor receptor (IGF-IR) is deregulated in solid tumors. Cixutumumab, a monoclonal antibody that inhibits IGF-IR activity, was investigated in combination with pemetrexed/cisplatin in the front-line setting. **METHODS:** In this open-label, Phase II study, patients with Stage IV nonsquamous non-small cell lung cancer (NSq-NSCLC) and a performance status of 0-1 were randomized (1:1) to receive 20 mg/kg cixutumumab, 500 mg/m2 pemetrexed, and 75 mg/m2 cisplatin (cixutumumab; n = 87) or pemetrexed and cisplatin (control; n = 85). Eligible patients received pemetrexed-based maintenance therapy with (cixutumumab arm) or without (control arm) cixutumumab. The primary endpoint was progression-free survival (PFS). Secondary endpoints assessed overall survival (OS), objective response rate (ORR), and safety. Survival was analyzed by Kaplan-Meier method and Cox's proportional hazard model. Exploratory correlative analyses were also performed. **RESULTS:** The mean age of the intent-to-treat (ITT) population (n = 172) was 59 years (range, 32-83). Median PFS was 5.45 months with cixutumumab vs. 5.22 months with control (hazard ratio [HR] 1.15; 95% confidence interval [CI], 0.81-1.61; P = 0.44). Median OS was 11.33 months with cixutumumab vs. 10.38 months with control (HR 0.93, 95% CI, 0.64-1.36). ORR did not differ between treatments (P = 0.338). Grade 3/4 hyperglycemia occurred at a higher rate with cixutumumab than control (9.4% vs. 1.2%). One death possibly related to cixutumumab occurred. **CONCLUSIONS:** Efficacy was not improved in NSq-NSCLC patients when cixutumumab was added to pemetrexed/cisplatin. Combination therapy was well tolerated and no new safety concerns were reported.

Chemotherapy in elderly patients with nonsmall cell lung cancer. Veluswamy RR1, Levy B, Wisnivesky JP. Curr Opin Pulm Med. 2016 Jul;22(4):336-43. doi: 10.1097/MCP.0000000000000286.

PURPOSE OF REVIEW: Using chemotherapy in elderly nonsmall cell lung cancer (NSCLC) patients is often challenging given concerns of treatment-related toxicity. However, data have demonstrated that chemotherapy can lead to improved survival in this age group. In this review, we summarize existing data and discuss the role of chemotherapy in elderly patients with localized, locally advanced, and metastatic NSCLC. **RECENT FINDINGS:** Clear evidence-based guidelines for chemotherapy management in elderly patients is lacking given the limited prospective data available. However, there are more clinical trials investigating optimal chemotherapy agents and dosing schedules specific to the elderly. Comprehensive geriatric assessment-directed interventions are also being prospectively investigated to improve treatment selection for elderly patients. **SUMMARY:** Chronological age should not be a limiting factor for chemotherapy use in elderly NSCLC patients. Several studies have demonstrated similar survival benefits than in younger patients when chemotherapy is given as adjuvant treatment for localized disease; part of definitive treatment with radiation in locally advanced disease; and palliative treatment for advanced NSCLC, however, at the cost of greater toxicity. Tolerability of chemotherapy in this

heterogeneous group can be difficult to predict. Therefore, therapeutic decisions should be individualized based on performance status. Comprehensive geriatric assessment should be used to supplement performance status measures to minimize both under and overtreatment.

A multicenter phase II trial of S-1 combined with bevacizumab after platinum-based chemotherapy in patients with advanced non-squamous non-small cell lung cancer. Yamada K1, Ichiki M2, Takahashi K3, et al. Cancer Chemother Pharmacol. 2016 Jul 11. [Epub ahead of print]
OBJECTIVES: This phase II trial investigated the efficacy and safety of S-1 plus bevacizumab (SB) after failure of platinum-based chemotherapy in patients with non-squamous non-small cell lung cancer (non-sq NSCLC). **METHODS:** Patients with non-sq NSCLC who had undergone prior platinum-based chemotherapy, regardless of the use of bevacizumab, were eligible. S-1 (80 mg/m2) was administered orally twice daily for 14 days, and bevacizumab (15 mg/kg) on day 1 every 3 weeks until disease progression or unacceptable toxicity occurred. The primary endpoint was progression-free survival (PFS). **RESULTS:** Twenty-eight patients (14 males and 14 females; median age 62 years; performance status 0/1/2: 21/7/0) were accrued from 4 centers. Almost half (n = 15, 53.6 %) of these had received prior bevacizumab therapy. The median PFS and overall survival were 3.2 months [95 % confidence interval (CI) 2.2-4.0 months] and 11.4 months (95 % CI 8.9-13.9 months), respectively. Prior exposure to bevacizumab did not affect the PFS. An objective response was observed in 4 patients, the response rate and disease control rate being 14.3 and 85.7 %, respectively. The treatment was well tolerated, the most common treatment-related side effects being anorexia (75 %) and fatigue (68 %). **CONCLUSION:** Although SB was well tolerated, this combination did not provide any additional benefit in terms of PFS for patients with non-sq NSCLC after failure of platinum-based chemotherapy. It will be important to clarify the most suitable agent for use with bevacizumab, and the optimal timing of bevacizumab therapy for lung cancer.

NSCLC - RADIOTHERAPY

Regional Lung Function Profiles of Stage I and III Lung Cancer Patients: An Evaluation for Functional Avoidance Radiation Therapy. Vinogradskiy Y1, Schubert L2, Diot Q2, et al. Int J Radiat Oncol Biol Phys. 2016 Jul 15;95(4):1273-80. doi: 10.1016/j.ijrobp.2016.02.058.
PURPOSE: The development of clinical trials is underway to use 4-dimensional computed tomography (4DCT) ventilation imaging to preferentially spare functional lung in patients undergoing radiation therapy. The purpose of this work was to generate data to aide with clinical trial design by retrospectively characterizing dosimetric and functional profiles for patients with different stages of lung cancer.
METHODS AND MATERIALS: A total of 118 lung cancer patients (36% stage I and 64% stage III) rom 2 institutions were used for the study. A 4DCT-ventilation map was calculated using the patient's 4DCT imaging, deformable image registration, and a density-change-based algorithm. To assess each patient's spatial ventilation profile both quantitative and qualitative metrics were developed, including an observer-based defect observation and metrics based on the ventilation in each lung third. For each patient we used the clinical doses to calculate functionally weighted mean lung doses and metrics that assessed the interplay between the spatial location of the dose and high-functioning lung. **RESULTS:** Both qualitative and quantitative metrics revealed a significant difference in functional profiles between the 2 stage groups (P<.01). We determined that 65% of stage III and 28% of stage I patients had ventilation defects. Average functionally weighted mean lung dose was 19.6 Gy and 5.4 Gy for stage III and I patients, respectively, with both groups containing patients with large spatial overlap between dose and high-function regions. **CONCLUSION:** Our 118-patient retrospective study found that 65% of stage III patients have regionally variant ventilation profiles that are suitable for functional avoidance. Our results suggest that regardless of disease stage, it is possible to have unique spatial interplay between dose and

high-functional lung, highlighting the importance of evaluating the function of each patient and developing a personalized functional avoidance treatment approach.

Long-Term Survival after Radiofrequency Ablation of Lung Oligometastases from Five Types of Primary Lesions: A Retrospective Evaluation. Omae K1, Hiraki T2, Gobara H1, Iguchi T1, Fujiwara H1, Matsui Y1, Toyooka S3, Nagasaka T4, Kanazawa S1. J Vasc Interv Radiol. 2016 Jul 22. pii: S1051-0443(16)30168-3. doi: 10.1016/j.jvir.2016.05.017. [Epub ahead of print]

PURPOSE: To conduct a retrospective evaluation of long-term survival after radiofrequency (RF) ablation for lung oligometastases from 5 types of primary lesions. **MATERIALS AND METHODS:** The study population consisted of 123 patients with lung oligometastases from colorectal cancer (CRC), non-small-cell lung cancer, hepatocellular carcinoma, esophageal cancer, and renal-cell carcinoma treated with RF ablation. Lung oligometastases were defined as 1-5 metastases confined to the lung while the primary cancer and other metastases were eradicated. Overall survival (OS) and recurrence-free survival (RFS) were estimated for the overall study population and for patients with each type of primary lesion. The OS and RFS rates were compared with those of the patients with any of the other four primary lesion types. Finally, various variables were analyzed to determine what factors influenced OS and RFS. **RESULTS:** The median follow-up was 45.7 months, and the 5-year OS and RFS rates for all 123 patients were 62% and 25%, respectively. The OS time for patients with metastases from CRC was significantly longer (P = .042); it was significantly shorter (P = .022) in patients with metastases from esophageal cancer. Longer disease-free interval was significantly (P = .015) associated with better OS. There was no variable significantly associated with OS and RFS on multivariate analyses. **CONCLUSIONS:** Data from this single-center study appear promising in terms of long-term survival after RF ablation of lung oligometastases from 5 primary lesions.

Stereotactic Body Radiation Therapy for Stage I Non-Small Cell Lung Cancer: A Retrospective, Single-Center Study of 55 Patients. Bhandari RP1, Stanford JD, Packianathan S, et al. Oncology. 2016 Jul 19. [Epub ahead of print]

PURPOSE/OBJECTIVE(S): Stereotactic body radiation therapy (SBRT) is an effective treatment for patients with early-stage non-small cell lung cancer (NSCLC) who are not surgical candidates or who refuse surgical management. In this study, we report on our clinical outcomes and toxicity in the treatment of early-stage NSCLC with SBRT. **METHODS AND MATERIALS:** Fifty-five patients with 59 T1-2N0M0 NSCLC lesions were treated at our institution between December 2009 and August 2014. The majority of the patients [38 (69%)] were treated with 50 Gy in 5 fractions, 7 patients (13%) with 48 Gy in 4 fractions, 8 patients (14%) with 60 Gy in 3 fractions, 1 patient (2%) with 62.5 Gy in 10 fractions, and 1 patient (2%) with 54 Gy in 3 fractions. Tumor response was evaluated using RECIST 1.1, and toxicity was graded using the CTCAE (Common Terminology Criteria for Adverse Events) version 3.0. The primary endpoints of this retrospective review included rates of overall survival, disease-free and progression-free survival, local failure, regional failure, and distant failure. A secondary endpoint included radiation-related toxicities. **RESULTS:** The median follow-up was 23.8 months (range 1.1-57.6). The 3-year local control, progression-free survival, and overall survival rates were 91, 55, and 71%, respectively. The median age at diagnosis was 67.9 years (range 51.4-87.1). There were a total of 54 T1N0 tumors (92%) and 5 T2N0 lesions (8%). Adenocarcinoma was the most common pathology, comprising 54% of the lesions. A total of 16 of the patients (29%) failed. Among these, 5 local (9%), 14 regional (25%), and 4 distant failures (7%) were observed. On follow-up, one patient had grade 2 and another had grade 5 pneumonitis. Three patients experienced grade 2 chest wall tenderness. Two patients had grade 1 rib fractures, one of which could not be discerned from radiation-induced toxicity versus a traumatic fall. **CONCLUSION:** The University of Mississippi Medical Center SBRT experience has

shown that SBRT provides satisfactory local control and overall survival rates with minimal toxicity in early-stage NSCLC patients.

The effect of non-small cell lung cancer histology on survival as measured by the graded prognostic assessment in patients with brain metastases treated by hypofractionated stereotactic radiotherapy.
Ma LH1, Li G2, Zhang HW1, et al. Radiat Oncol. 2016 Jul 13;11(1):92. doi: 10.1186/s13014-016-0667-x.

BACKGROUND: The purpose of this study was to investigate the impact of histology on survival stratified by the Graded Prognostic Assessment (GPA) for non-small cell lung cancer (NSCLC) in a group of selected patients treated recently. **METHODS:** A total of 171 NSCLC patients with brain metastases treated by hypofractionated stereotactic radiotherapy with or without whole-brain radiotherapy between 2001 and 2011 were included. The GPA score was calculated for each patient. Tumor histologies were categorized into adenocarcinoma (ADCA) and non-ADCA. Median survival time (MST, in months) was calculated using the Kaplan-Meier method. The log-rank test was used to determine statistical differences. **RESULTS:** MSTs by histology were: ADCA 15 ($n = 92$) and non-ADCA 10 ($n = 79$) ($p < 0.001$). For all patients, the MSTs by GPA score were: GPA 3.5-4, 24; GPA 2.5-3, 15; GPA 1.5-2, 9 and GPA 0-1, 6 ($p < 0.001$). The histology of ADCA showed a statistically significant higher MST than non-ADCA for patients with GPA 2.5-4. For GPA 2.5-3, MSTs were: ADCA 18, non-ADCA 10 ($p = 0.007$); for GPA 3.5-4, MSTs were: ADCA 30, non-ADCA 17 ($p = 0.046$). For GPA 0-2, MSTs did not differ significantly by histology. For GPA 0-1, MSTs were: ADCA 8, non-ADCA 4 ($p = 0.146$); GPA 1.5-2, MSTs were: ADCA 10, non-ADCA 8 ($p = 0.291$). We further found that non-ADCA in upper GPA class (3.5-4) had similar survival with ADCA in lower GPA class (2.5-3) (MSTs were 17 and 18, respectively, $p = 0.775$). This phenomenon also happened between patients of non-ADCA in upper GPA class (2.5-3) and those of ADCA in lower GPA class (1.5-2) (MSTs were both 10, $p = 0.724$). **CONCLUSIONS:** We confirmed that the histology of NSCLC had effect on the GPA in these selected patients treated recently. ADCA showed a statistically significant higher MST than non-ADCA with GPA 2.5-4. The non-ADCA in upper GPA classes (3.5-4 and 2.5-3) had similar survival to ADCA in lower GPA classes (2.5-3 and 1.5-2, respectively). The histology as a new factor should be added to the original GPA for NSCLC.

SMALL CELL LUNG CANCER - SCLC

An orthotopic mouse model of small cell lung cancer reflects the clinical course in patients.
Taromi S1, Kayser G2, von Elverfeldt D3, et al. Clin Exp Metastasis. 2016 Jul 6. [Epub ahead of print]

Small cell lung cancer (SCLC) is a highly aggressive subtype of lung cancer with very poor prognosis due to early metastatic spread and development of chemoresistance. In the last 30 years the study of SCLC has been constrained by a lack of primary human tumor specimen thus highlighting the need of a suitable mouse model. In this article we present the establishment of an orthotopic xenograft mouse model which accurately reproduced the clinical course of SCLC. Orthotopic implantation enabled engraftment of primary lung tumors in all injected mice. Furthermore, immunodeficiency of mice allowed formation of spontaneous metastases in characteristic organs. Bioluminescence Imaging, Magnetic Resonance Imaging and Positron emission tomography were applied to monitor engraftment, metabolism and the exact growth of tumors over time. In order to mimic the extensive disease stage, mice were injected with aggressive human chemoresistant cells leading to development of chemoresistant tumors and early metastatic spread. As a proof of concept treatment of tumor-bearing mice with conventional chemotherapeutics reduced tumor volumes, but a complete regression of tumors was not achieved. By mimicking the extensive disease stage our mouse model can facilitate the study of mechanisms contributing to chemoresistance and metastasis formation, as well as drug screening and evaluation of new treatment strategies for SCLC patients.

WW domain binding protein 5 induces multidrug resistance of small cell lung cancer under the regulation of miR-335 through the Hippo pathway. Tang R1, Lei Y1,2, Hu B1, Yang J1, Fang S1, Wang Q1, Li M1, Guo L1. Br J Cancer. 2016 Jul 12;115(2):243-51. doi: 10.1038/bjc.2016.186. Epub 2016 Jun 23.

BACKGROUND: Our previous study indicated that WW domain binding protein 5 (WBP5) expression was elevated significantly in a drug-resistant cell compared with its parental cell. Nevertheless, its functional role and underlying mechanisms remain unknown. **METHODS:** In this study, WBP5 was examined in 62 small cell lung cancer (SCLC) patient samples by immunohistochemical technique. Stable WBP5-overexpressed and WBP5-underexpressed cells were further established to assess the role of WBP5 in drug resistance, apoptosis and tumour growth. We also conducted western blot to detect the expression of MST2 and YAP1 and their phosphorylated protein. **RESULTS:** The results revealed that WBP5 expression was significantly associated with the shorter survival time in SCLC patients. Upregulation of WBP5 induced multidrug resistance (MDR) and decreased apoptosis, whereas downregulation of WBP5 enhanced drug sensitivity and increased apoptosis. We also found that miR-335 negatively regulated the MDR of WBP5 by targeting its 3'UTR. Furthermore, WBP5 can lower YAP1 phosphorylation at Serine 127 and induce nuclear accumulation of YAP1. Inhibition of YAP1 by Verteporfin could blunt the MDR phenotype of WBP5. **CONCLUSIONS:** WW domain binding protein 5 can modulate MDR through the Hippo pathway under the regulation of miR-335. WW domain binding protein 5 may be a prognostic predictor and a potential target for interfering with MDR in SCLC.

PARP Inhibitor Activity Correlates with SLFN11 Expression and Demonstrates Synergy with Temozolomide in Small Cell Lung Cancer. Lok BH1, Gardner EE2, Schneeberger VE3, et al. Clin Cancer Res. 2016 Jul 20. pii: clincanres.1040.2016. [Epub ahead of print]

PURPOSE: PARP inhibitors (PARPi) are a novel class of small molecule therapeutics for small cell lung cancer (SCLC). Identification of predictors of response would advance our understanding, and guide clinical application, of this therapeutic strategy. **EXPERIMENTAL DESIGN:** Efficacy of PARP inhibitors olaparib, rucaparib, and veliparib, as well as etoposide and cisplatin in SCLC cell lines, and gene expression correlates, were analyzed using public datasets. HRD genomic scar scores were calculated from Affymetrix SNP 6.0 arrays. In vitro talazoparib efficacy was measured by cell viability assays. For functional studies, CRISPR-Cas9 and shRNA were used for genomic editing and transcript knockdown, respectively. Protein levels were assessed by immunoblotting and immunohistochemistry (IHC). Quantitative synergy of talazoparib and temozolomide were determined in vitro. In vivo efficacy of talazoparib, temozolomide, and the combination was assessed in patient-derived xenograft (PDX) models. **RESULTS:** We identified SLFN11, but not HRD genomic scars, as a consistent correlate of response to all three PARPi assessed, with loss of SLFN11 conferring resistance to PARPi. We confirmed these findings in vivo across multiple PDX and defined IHC staining for SLFN11 as a predictor of talazoparib response. As temozolomide has activity in SCLC, we investigated combination therapy with talazoparib and found marked synergy in vitro and efficacy in vivo, which did not solely depend on SLFN11 or MGMT status. **CONCLUSIONS:** SLFN11 is a relevant predictive biomarker of sensitivity to PARP inhibitor monotherapy in SCLC and we identify combinatorial therapy with TMZ as a particularly promising therapeutic strategy that warrants further clinical investigation.
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Prophylactic cranial irradiation in small cell lung cancer: A single institution experience. Nicholls L1, Keir GJ1, Murphy MA1, Mai T1, Lehman M1. Asia Pac J Clin Oncol. 2016 Jul 25. doi: 10.1111/ajco.12564. [Epub ahead of print]

AIM: To compare patient demographics, prophylactic cranial irradiation (PCI) utilization and overall survival (OS) of patients with small cell lung cancer (SCLC) referred to a large tertiary center with those reported in large clinical trials. **PATIENTS AND METHODS:** A retrospective review was conducted of consecutive patients with limited stage (LS) and extensive stage (ES) SCLC diagnosed at the Princess Alexandra Hospital between January 2008 and December 2013. **RESULTS:** Two hundred and three patients with a mean age of 65.4 (±10.7) years were followed for a median duration of 7.6 months (range 0.5-76.5). At diagnosis, 129 (64%) patients had ES-SCLC, including 39 (19.2%) with cerebral metastases. Median OS in LS-SCLC patients receiving PCI was 18.8 months (0.9-69.4), compared with 8.2 months (0.1-34.4) in patients who did not receive PCI (P < 0.001). Median OS in the ES-SCLC cohort receiving PCI was 13.6 months (5.2-37.5) compared to 5.6 months (0.1-73.6) in patients who did not receive the therapy (P < 0.001). There was a significant improvement in intracranial disease-free survival of 7.1 months in patients with ES-SCLC who received PCI. Forty-two LS-SCLC patients (57%) did not receive PCI due to patient suitability. **CONCLUSIONS:** In our SCLC cohort, median OS following PCI in LS-SCLC and ES-SCLC is comparable to published data. PCI use at our institution was lower than utilization rates in large meta-analyses, predominately due to poor chemotherapy tolerance and patient suitability. This may be more representative of patients treated in clinical practice rather than those recruited into large phase III trials.

[Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer.](#) Reck M1, Luft A2, Szczesna A2, et al. J Clin Oncol. 2016 Jul 25. pii: JCO676601. [Epub ahead of print]

PURPOSE: Patients with extensive-stage disease small-cell lung cancer (SCLC) have poor survival outcomes despite first-line chemotherapy with etoposide and platinum. This randomized, double-blind phase III study evaluated the efficacy and safety of ipilimumab or placebo plus etoposide and platinum in patients with newly diagnosed extensive-stage disease SCLC. **PATIENTS AND METHODS:** Patients were randomly assigned at a ratio of one to one to receive chemotherapy with etoposide and platinum (cisplatin or carboplatin) plus ipilimumab 10 mg/kg or placebo every 3 weeks for a total of four doses each in a phased induction schedule (chemotherapy in cycles one to four; ipilimumab or placebo beginning in cycle three up to cycle six), followed by ipilimumab or placebo maintenance every 12 weeks. Primary end point was overall survival (OS) among patients receiving at least one dose of blinded study therapy. **RESULTS:** Of 1,132 patients randomly assigned, 954 received at least one dose of study therapy (chemotherapy plus ipilimumab, n = 478; chemotherapy plus placebo, n = 476). Median OS was 11.0 months for chemotherapy plus ipilimumab versus 10.9 months for chemotherapy plus placebo (hazard ratio, 0.94; 95% CI, 0.81 to 1.09; P = .3775). Median progression-free survival was 4.6 months for chemotherapy plus ipilimumab versus 4.4 months for chemotherapy plus placebo (hazard ratio, 0.85; 95% CI, 0.75 to 0.97). Rates and severity of treatment-related adverse events were similar between arms, except for diarrhea, rash, and colitis, which were more frequent with chemotherapy plus ipilimumab. Rate of treatment-related discontinuation was higher with chemotherapy plus ipilimumab (18% v 2% with chemotherapy plus placebo). Five treatment-related deaths occurred with chemotherapy plus ipilimumab and two with chemotherapy plus placebo. **CONCLUSION:** Addition of ipilimumab to chemotherapy did not prolong OS versus chemotherapy alone in patients with newly diagnosed extensive-stage disease SCLC. No new or unexpected adverse events were observed with chemotherapy plus ipilimumab. Several ongoing studies are evaluating ipilimumab in combination with programmed death-1 inhibitors in SCLC.

Impact of thoracic radiotherapy timing in limited-stage small-cell lung cancer: usefulness of the individual patient data meta-analysis. De Ruysscher D1, Lueza B2, Le Péchoux C3, et al. Ann Oncol. 2016 Jul 19. pii: mdw263. [Epub ahead of print]

BACKGROUND: Chemotherapy combined with radiotherapy is the standard treatment of "limited-stage" small-cell lung cancer. However, controversy persists over the optimal timing of thoracic radiotherapy and chemotherapy. **MATERIAL AND METHODS:** We performed a meta-analysis of individual patient data in randomised trials comparing earlier versus later radiotherapy, or shorter vs. longer radiotherapy duration, as defined in each trial. We combined the results from trials using the stratified log-rank test to calculate pooled hazard ratios (HRs). The primary outcome was overall survival. **RESULTS:** Twelve trials with 2,668 patients were eligible. Data from nine trials comprising 2,305 patients were available for analysis. The median follow-up was 10 years. When all trials were analysed together, "earlier or shorter" vs. "later or longer" thoracic radiotherapy did not affect overall survival. However, the HR for overall survival was significantly in favour of "earlier or shorter" radiotherapy among trials with a similar proportion of patients who were compliant with chemotherapy (defined as having received 100% or more of the planned chemotherapy cycles) in both arms (HR 0.79, 95% CI 0.69-0.91) and in favour of "later or longer" radiotherapy among trials with different chemotherapy compliance (HR 1.19, 1.05-1.34, interaction test p<0.0001). The absolute gain between "earlier or shorter" vs. "later or longer" thoracic radiotherapy in 5-year overall survival for similar and for different chemotherapy compliance trials was 7.7% (95% CI 2.6-12.8 %) and -2.2% (-5.8-1.4 %), respectively. However, "earlier or shorter" thoracic radiotherapy was associated with a higher incidence of severe acute oesophagitis than "later or longer" radiotherapy. **CONCLUSION:** "Earlier or shorter" delivery of thoracic radiotherapy with planned chemotherapy significantly improves 5-year overall survival at the expense of more acute toxicity, especially oesophagitis.

Tumor infiltrating lymphocytes and PD-L1 expression in brain metastases of small cell lung cancer (SCLC). Berghoff AS1,2, Ricken G2,3, Wilhelm D4, Rajky O1,2, Widhalm 3,5, Dieckmann K2,6, Birner P2,7, Bartsch R1,2, Preusser M8,9. J Neurooncol. 2016 Jul 19. [Epub ahead of print]

Brain metastases (BM) are frequent in small cell lung cancer (SCLC). Novel insights into their pathobiology are needed for development of better therapies. We investigated tumor-infiltrating lymphocyte (TIL) subsets (CD3+, CD8+, CD45RO+, FOXP3+ and PD-1+) and expression of PD-L1 in a series of 32 SCLC BM specimens and four matched primary tumor specimens using immunohistochemistry. 30/32 (93.8 %) BM specimens showed TIL infiltration. CD3+ TILs were observed in 30/32 (93.8 %) BM specimens, CD8+ TILs in 25/32 (78.1 %), CD45RO+ TILs in 15/32 (46.9 %), FOXP3+ TILs in 15/32 (46.9 %) and PD-1+ TILs in 1/32 (3.1 %) BM specimens. Patients with infiltration of CD45RO+ TILS had a significantly longer median survival time (11 months; 95 % CI 0.000-26.148) as compared to patients without the presence of CD45RO+ TILs (5 months; 95 % CI 0.966-9.034; p = 0.007; log rank test). Membranous PD-L1 on tumor cells was observed in 24/32 (75.0 %) BM specimens, with 11/32 (34.4 %) cases showing PD-L1 expression in over 5 % of viable BM tumor cells. PD-L1 expression on TILs was seen in 8/32 (25.0 %) and on tumor infiltrating macrophages in 9/32 (28.1 %) cases. Patients with PD-L1 expression on TILs presented with improved survival prognosis (6 versus 29 months; p = 0.002; log rank test). Among matched primary tumors, all (4/4; 100 %) specimens showed TIL infiltration, while PD-L1 expression found in only 1/4 (25.0 %) specimen. TIL infiltration and PD-L1 expression are commonly found in SCLC BM and presence of CD45RO+ memory T-cells and PD-L1+ TILs in SCLC BM seem to associate with favorable survival times. Our data suggest an active immune microenvironment in SCLC BM that may be targetable by immune-modulating drugs.

PALLIATIVE AND SUPPORTIVE CARE

Palliative Care Specialist Consultation Is Associated with Supportive Care Quality in Advanced Cancer. Walling AM1, Tisnado D2, Ettner SL3, et al. J Pain Symptom Manage. 2016 Jul 8. pii: S0885-3924(16)30167-1. doi: 10.1016/j.jpainsymman.2016.04.005. [Epub ahead of print]
Although recent randomized controlled trials support early palliative care for patients with advanced cancer, the specific processes of care associated with these findings and whether these improvements can be replicated in the broader health care system is uncertain.
OBJECTIVES: Evaluate the occurrence of palliative care consultation and its association with specific processes of supportive care in a national cohort of Veterans using the Cancer Quality ASSIST (Assessing Symptoms Side Effects and Indicators of Supportive Treatment) measures. **METHODS:** We abstracted data from 719 patients' medical records diagnosed with advanced lung, colorectal, or pancreatic cancer in 2008 over a period of three years or until death who received care in the Veterans Affairs Health System (VA) to evaluate the association of palliative care specialty consultation with the quality of supportive care overall and by domain using a multivariate regression model. **RESULTS:** All but 54 of 719 patients died within three years and 293 received at least one palliative care consult. Patients evaluated by a palliative care specialist at diagnosis scored sevem percentage points higher overall (P< 0.001) and 11 percentage points higher (P<0.001) within the information and care planning domain compared to patients without a consult. **CONCLUSION:** Early palliative care specialist consultation is associated with better quality of supportive care in three advanced cancers, predominantly driven by improvements in information and care planning. This study supports the effectiveness of early palliative care consultation in three common advanced cancers within the VA and provides a greater understanding of what care processes palliative care teams influence.

The Association of Chemotherapy-Induced Peripheral Neuropathy Symptoms and the Risk of Falling. Kolb NA1, Smith AG1, Singleton JR1, Beck SL2, Stoddard GJ3, Brown S1, Mooney K2. JAMA Neurol. 2016 Jul 1;73(7):860-6. doi: 10.1001/jamaneurol.2016.0383.
IMPORTANCE: Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse effect of neurotoxic chemotherapy resulting in pain, sensory loss, and decreased quality of life. Few studies have prospectively examined the relationship between sensory neuropathy symptoms, falls, and fall-related injuries for patients receiving neurotoxic chemotherapy. **OBJECTIVE:** To determine the association between the symptoms of CIPN and the risk of falls for patients receiving neurotoxic chemotherapy. **DESIGN, SETTING, AND PARTICIPANTS:** In this secondary analysis of a prospective study, 116 patients with breast, ovarian, or lung cancer who were beginning neurotoxic chemotherapy with a taxane or platinum agent were recruited from oncology clinics. These patients would call a novel automated telephone system daily for 1 full course of chemotherapy. The telephone system (SymptomCare@Home) used a series of relevant CIPN questions to track symptoms on a 0 to 10 ordinal scale and contained a questionnaire about falls. Those reporting a numbness and tingling severity score of 3 or greater for at least 10 days were considered to have significant CIPN symptoms and were compared with those patients who did not. Data analysis was performed in November 2015. **EXPOSURE:** Chemotherapy with a neurotoxic taxane or platinum agent. **MAIN OUTCOMES AND MEASURES:** Patient-reported falls or near falls and fall-related injuries. The hypothesis was generated after data collection but prior to data analysis. **RESULTS:** Of the 116 patients who started neurotoxic chemotherapy (mean [SD] age was 55.5 [11.9] years, and 109 [94.0%] were female), 32 met the predetermined criteria for CIPN symptoms. The mean duration of follow-up was 62 days, with 51 telephone calls completed per participant. Seventy-four falls or near falls were reported. The participants with CIPN symptoms were nearly 3 times more likely to report a fall or near fall than the participants without CIPN symptoms (hazard ratio, 2.67 [95% CI, 1.62-

4.41]; P < .001). The participants with CIPN symptoms were more likely than the participants without CIPN symptoms to obtain medical care for falls (8 of 32 participants with CIPN symptoms [25.0%] vs 6 of 84 participants without CIPN symptoms [7.1%]; P = .01). **CONCLUSIONS AND RELEVANCE:** These findings suggest that the sensory symptoms of CIPN are an indicator of an increased risk of falling and an increased use of health care resources. This study demonstrates the utility of a novel telephone-based system to track neuropathy symptoms. Careful monitoring and coaching of patients receiving neurotoxic chemotherapy for new sensory symptoms may facilitate more effective fall prevention strategies.

POSITIVE study: physical exercise program in non-operable lung cancer patients undergoing palliative treatment. Wiskemann J1,2, Hummler S3,4,5, Diepold C6, et al. BMC Cancer. 2016 Jul 19;16(1):499. doi: 10.1186/s12885-016-2561-1.
BACKGROUND: Patients with advanced stage non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) often experience multidimensional impairments, affecting quality of life during their course of disease. In lung cancer patients with operable disease, several studies have shown that exercise has a positive impact on quality of life and physical functioning. There is limited evidence regarding efficacy for advanced lung cancer patients undergoing palliative treatment. Therefore, the POSITIVE study aims to evaluate the benefit of a 24-week exercise intervention during palliative treatment in a randomized controlled setting. **METHODS/DESIGN:** The POSITIVE study is a randomized, controlled trial investigating the effects of a 24-week exercise intervention during palliative treatment on quality of life, physical performance and immune function in advanced, non-operable lung cancer patients. 250 patients will be recruited in the Clinic for Thoracic Diseases in Heidelberg, enrolment begun in November 2013. Main inclusion criterion is histologically confirmed NSCLC (stage IIIa, IIIb, IV) or SCLC (Limited Disease-SCLC, Extensive Disease-SCLC) not amenable to surgery. Patients are randomized into two groups. Both groups receive weekly care management phone calls (CMPCs) with the goal to assess symptoms and side effects. Additionally, one group receives a combined resistance and endurance training (3x/week). Primary endpoints are quality of life assessed by the Functional Assessment of Cancer Therapy for patients with lung cancer (FACT-L, subcategory Physical Well-Being) and General Fatigue measured by the Multidimensional Fatigue Inventory (MFI-20). Secondary endpoints are physical performance (maximal voluntary isometric contraction, 6-min walk distance), psychosocial (depression and anxiety) and immunological parameters and overall survival. **DISCUSSION:** The aim of the POSITIVE trial is the evaluation of effects of a 24-week structured and guided exercise intervention during palliative treatment stages. Analysis of various outcomes (such as quality of life, physical performance, self-efficacy, psychosocial and immunological parameters) will contribute to a better understanding of the potential of exercise in advanced lung cancer patients. In contrast to other studies with advanced oncological patients the POSITIVE trial provides weekly phone calls to support patients both in the intervention and control group and to segregate the impact of physical activity on quality of life.

Characteristics of patients with advanced lung cancer referred to a rapid-access supportive care clinic. Yennurajalingam S1, Lu Z1, Williams JL1, Liu DD2, Arthur JA1, Bruera E1. Palliat Support Care. 2016 Jul 22:1-8. [Epub ahead of print]
OBJECTIVE: There is a limited number of pragmatic studies to evaluate the criteria for referral to outpatient palliative care. The aim of our study was to compare the characteristics, symptoms, and survival of patients with advanced non-small-cell lung cancer (NSCLC) referred (RF) versus not referred (NRF) to a novel embedded same-day rapid-access supportive care clinic (RASCC) and to compare the subgroups among referred patients. **METHOD:** We reviewed the medical records of all patients who received treatment at the thoracic oncology clinic for advanced non-small-cell lung cancer between

August 1, 2012, and June 30, 2013, who were referred to the RASCC and those who were not referred. An oncology-estimated prognosis of ≤6 months and/or severe symptom distress was employed as criteria for referral to the RASCC. **RESULTS:** Of 410 eligible patients, 155 (37.8%) were referred to the RASCC. RF patients had significantly higher patient-reported scores for pain, fatigue, lack of appetite, and symptom distress, as well as worse performance status and shorter survival than NRF patients. Among the RF patients, those who were referred early (≤3 months) had significantly worse symptom distress and shorter overall survival than patients who were referred later on. The patients treated by thoracic oncologists who referred a smaller proportion of their patients to the RASCC had significantly worse anxiety, well-being, spiritual pain, and symptom distress than patients treated by those who referred a larger proportion of their patients to the RASCC. **SIGNIFICANCE OF RESULTS:** We found that patients who were referred to the RASCC had higher reported symptom distress and worse survival ratings. Further studies are needed to evaluate the optimal criteria for timely integration of palliative care and oncology care.

[Analgesic effectiveness and tolerability of oral oxycodone/naloxone and pregabalin in patients with lung cancer and neuropathic pain: an observational analysis.](#) De Santis S1, Borghesi C1, Ricciardi S2, et al. Onco Targets Ther. 2016 Jul 4;9:4043-52. doi: 10.2147/OTT.S108144. eCollection 2016.
INTRODUCTION: Cancer-related pain has a severe negative impact on quality of life. Combination analgesic therapy with oxycodone and pregabalin is effective for treating neuropathic cancer pain. We investigated the efficacy and tolerability of a dose-escalation combination therapy with prolonged-release oxycodone/naloxone (OXN-PR) and pregabalin in patients with non-small-cell lung cancer and severe neuropathic pain. **METHODS:** This was a 4-week, open-label, observational study. Patients were treated with OXN-PR and pregabalin. Average pain intensity ([API] measured on a 0-10 numerical rating scale) and neuropathic pain (Douleur Neuropathique 4) were assessed at study entry and at follow-up visits. The primary endpoint was response to treatment, defined as a reduction of API at T28 ≥30% from baseline. Secondary endpoints included other efficacy measures, as well as patient satisfaction and quality of life (Brief Pain Inventory Short Form), Hospital Anxiety and Depression Scale, and Symptom Distress Scale; bowel function was also assessed. **RESULTS:** A total of 56 patients were enrolled. API at baseline was 8.0±0.9, and decreased after 4 weeks by 48% (4.2±1.9; P<0.0001 vs baseline); 46 (82.1%) patients responded to treatment. Significant improvements were also reported in number/severity of breakthrough cancer pain episodes (P=0.001), Brief Pain Inventory Short Form (P=0.0002), Symptom Distress Scale (P<0.0001), Hospital Anxiety and Depression Scale depression (P=0.0006) and anxiety (P<0.0001) subscales, and bowel function (P=0.0003). At study end, 37 (66.0%) patients were satisfied/very satisfied with the new analgesic treatment. Combination therapy had a good safety profile. **CONCLUSION:** OXN-PR and pregabalin were safe and highly effective in a real-world setting of severe neuropathic cancer pain, with a high rate of satisfaction, without interference on bowel function.

[Assessment of anxiety in advanced cancer patients: a mixed methods study.](#) Veldhuisen H1, Zweers D2, de Graaf E2, Teunissen S3. Int J Palliat Nurs. 2016 Jul 2;22(7):341-50. doi: 10.12968/ijpn.2016.22.7.341.
BACKGROUND: Anxiety is a risk for reduced quality of life in advanced cancer patients. However, it is an overlooked symptom without routine use of instruments to assess anxiety. **AIM:** To gain insight into the use of instruments by nurses to assess anxiety in advanced cancer patients and the rationale behind it. **METHODS:** Data with regard to nurses' use of instruments were collected from medical records of 154 patients in three settings. Additionally, 12 nurses were interviewed. **FINDINGS:** Four instruments were used to assess anxiety. The frequency of assessed anxiety differed among settings. The application of instruments guided patient care and improved communication. Lack of knowledge was the main reason not to use instruments. **CONCLUSIONS:** Application was influenced by patient and environmental

factors, knowledge, attitudes and beliefs of nurses. Multifaceted strategies, leadership and education of nurses in the assessment and analysis of anxiety are needed to improve symptom management in advanced cancer patients.

[Randomized Pilot Trial of a Telephone Symptom Management Intervention for Symptomatic Lung Cancer Patients and Their Family Caregivers.](#) Mosher CE1, Winger JG2, Hanna N3, et al. J Pain Symptom Manage. 2016 Jul 8. pii: S0885-3924(16)30173-7. doi: 10.1016/j.jpainsymman.2016.04.006. [Epub ahead of print]

Lung cancer is one of the most common cancers affecting both men and women and is associated with high symptom burden and psychological distress. Lung cancer patients' family caregivers also show high rates of distress. However, few interventions have been tested to alleviate significant problems of this population. **OBJECTIVES:** This study examined the preliminary efficacy of telephone-based symptom management (TSM) for symptomatic lung cancer patients and their family caregivers. **METHODS:** Symptomatic lung cancer patients and caregivers (N=106 dyads) were randomly assigned to 4 sessions of TSM consisting of cognitive-behavioral and emotion-focused therapy or an education/support condition. Patients completed measures of physical and psychological symptoms, self-efficacy for managing symptoms, and perceived social constraints from the caregiver; caregivers completed measures of psychological symptoms, self-efficacy for helping the patient manage symptoms and managing their own emotions, perceived social constraints from the patient, and caregiving burden. **RESULTS:** No significant group differences were found for all patient outcomes and caregiver self-efficacy for helping the patient manage symptoms and caregiving burden at 2 and 6-weeks post-intervention. Small effects in favor of TSM were found regarding caregiver self-efficacy for managing their own emotions and perceived social constraints from the patient. Study outcomes did not significantly change over time in either group. **CONCLUSION:** Findings suggest that our brief telephone-based psychosocial intervention is not efficacious for symptomatic lung cancer patients and their family caregivers. Next steps include examining specific intervention components in relation to study outcomes, mechanisms of change, and differing intervention doses and modalities.

[Toxicity-Related Factors Associated With Use of Services Among Community Oncology Patients.](#)
Harrison JM1, Stella PJ2, LaVasseur B2, Adams PT2, Swafford L2, Lewis J2, Mendelsohn-Victor K2, Friese CR2. J Oncol Pract. 2016 Jul 12. pii: JOPR010959. [Epub ahead of print]

PURPOSE: Community oncology practices frequently manage chemotherapy-associated toxicities, which may disrupt treatment, impair quality of life, and induce unplanned service use. We sought to understand the patterns and correlates of unplanned health care service use among patients receiving first-cycle chemotherapy at five community-based ambulatory oncology practices. **PATIENTS AND METHODS:** A survey study examined the dichotomous outcome of unplanned service use, defined as oncologist visits, emergency department visits, and hospitalizations, resulting from toxicity-related factors. Newly diagnosed patients with breast, lung, head and neck, or colorectal cancer or non-Hodgkin lymphoma were recruited during the first chemotherapy cycle. Before beginning the second cycle of chemotherapy, patients completed a questionnaire that measured unplanned service use and overall distress, plus severity of nausea, vomiting, diarrhea, constipation, mouth sores, intravenous catheter problems, pain, fever and chills, extremity edema, and dyspnea on a 5-point scale (1, did not experience; 5, disabling). Medical record reviews captured chemotherapy doses, comorbid conditions, and supportive care interventions. Mixed-effects logistic regression was used to identify factors associated with unplanned service use, with random effects specified for each clinic. **RESULTS:** Among 106 patients (white, 98%; female, 74.5%; mean age ± standard deviation, 60 ± 11 years), frequently reported toxicities were pain, nausea, diarrhea, and constipation. Thirty-six patients (34%) reported unplanned service use: 29% reported oncologist visits, 14% reported emergency department visits, and 8% reported

hospitalizations. Factors significantly associated with unplanned service use were high patient-reported distress and receipt of colony-stimulating factor. **CONCLUSION:** Service use resulting from toxicity-related factors occurs frequently in community oncology settings. Monitoring toxicity patterns and outcomes can inform proactive symptom management approaches to reduce toxicity burden between scheduled visits.

Espindolol for the treatment and prevention of cachexia in patients with stage III/IV non-small cell lung cancer or colorectal cancer: a randomized, double-blind, placebo-controlled, international multicentre phase II study (the ACT-ONE trial). Stewart Coats AJ1, Ho GF2, Prabhash K3, von Haehling S4, Tilson J5, Brown R5, Beadle J5, Anker SD4; for and on behalf of the ACT-ONE study group. J Cachexia Sarcopenia Muscle. 2016 Jun;7(3):355-65. doi: 10.1002/jcsm.12126. Epub 2016 Jul 1. **BACKGROUND:** Cancer cachexia is a major cause of morbidity and mortality with no widely approved treatment. **METHODS:** The ACT-ONE trial is a randomized, double-blind, parallel group, placebo-controlled, phase II multicentre trial in patients (25-80 years) with stages III or IV colorectal cancer or non-small cell lung cancer-related cachexia that tested two doses of espindolol (a novel non-selective β blocker with central 5-HT1a and partial β2 receptor agonist effects). The primary endpoint was the difference in the rate of weight change over 16 weeks (linear mixed-effect model for repeated measures) between high-dose espindolol and placebo. **RESULTS:** Eighty-seven patients were randomized centrally in blocks in a ratio 3:2:1 [42 high dose, 10 mg twice daily (bd):31 placebo:14 low dose, 2.5 mg bd]. High-dose espindolol produced a statistically and clinically significant weight gain (+0.54 kg/4 weeks, 95% CI 0.38-0.70) compared with a weight loss on placebo (-0.21 kg/4 weeks, 95% CI -0.37-0.05); P < 0.0001. High-dose espindolol produced a statistically significant increase in lean body mass, whilst changes in fat mass were neutral. Hand grip strength significantly (high dose -1.15 ± 0.7 kg, placebo -3.51 ± 0.8 kg change per 4 weeks; P = 0.0134), stair climbing power, and 6-min walk test non-significantly were all directionally in favour of high-dose espindolol. There were no clinically significant differences in safety signals or survival between treatment groups, although a numerical excess of dyspnoea was seen with high-dose espindolol (19.1%) compared with placebo (3.2%). **CONCLUSIONS:** This positive trial showed that espindolol 10 mg bd significantly reversed weight loss, improved fat free mass, and maintained fat mass in advanced colorectal cancer and non-small cell lung cancer-related cachexia. This was associated with a significant improvement in handgrip strength, supporting the further investigation of 10 mg bd espindolol for the treatment of cancer cachexia. Although not powered to look at dose response, most treatment effects for low dose lay between high dose and placebo, suggesting that there may be a dose response in the effects of espindolol.

COMPLEMENTARY & ALTERNATIVE THERAPY

Modified Panax ginseng Extract Inhibits uPAR-Mediated α[Formula: see text]β1-Integrin Signaling by Modulating Caveolin-1 to Induce Early Apoptosis in Lung Cancer Cells. Hwang IH1, Kwon YK2, Cho CK2, Lee YW2, Sung JS3, Joo JC4, Lee KB5, Yoo HS2, Jang IS5. Am J Chin Med. 2016;44(5):1081-97. doi: 10.1142/S0192415X16500609. Epub 2016 Jul 19.
Urokinase receptor (uPAR) is enhanced in many human cancer cells and is frequently an indicator of poor prognosis. Activation of [Formula: see text]1-integrin requires caveolin-1 and is regulated by uPAR. However, the underlying molecular mechanism responsible for the interaction between uPAR and [Formula: see text]1-integrin remains obscure. We found that modified regular Panax ginseng extract (MRGX) had a negative modulating effect on the uPAR/[Formula: see text]1-integrin interaction, disrupted the uPAR/integrin interaction by modulating caveoline-1, and caused early apoptosis in cancer cells. Additionally, we found that siRNA-mediated caveoline-1 downregulation inhibited uPAR-mediated [Formula: see text]1-integrin signaling, whereas caveoline-1 up-regulation stimulated the signaling, which

suppressed p53 expression, thereby indicating negative crosstalk exists between the integrin [Formula: see text]1 and the p53 pathways. Thus, these findings identify a novel mechanism whereby the inhibition of [Formula: see text]1 integrin and the activation of p53 modulate the expression of the anti-apoptotic proteins that are crucially involved in inducing apoptosis in A549 lung cancer cells. Furthermore, MRGX causes changes in the expressions of members of the Bcl-2 family (Bax and Bcl-2) in a pro-apoptotic manner. In addition, MGRX-mediated inhibition of [Formula: see text]1 integrin attenuates ERK phosphorylation (p-ERK), which up-regulates caspase-8 and Bax. Therefore, ERK may affect mitochondria through a negative regulation of caspase-8 and Bax. Taken together, these findings reveal that MRGX is involved in uPAR-[Formula: see text]1-integrin signaling by modulating caveolin-1 signaling to induce early apoptosis in A549 lung-cancer cells and strongly indicate that MRGX might be useful as a herbal medicine and may lead to the development of new herbal medicine that would suppress the growth of lung-cancer cells.

MISCELLANEOUS WORKS

Associations of Insulin and IGFBP-3 with Lung Cancer Susceptibility in Current Smokers.
Ho GY1, Zheng SL2, Cushman M2, et al. J Natl Cancer Inst. 2016 Apr 12;108(7). pii: djw012. doi: 10.1093/jnci/djw012. Print 2016 Jul.
BACKGROUND: The epidermal growth factor receptor (EGFR) signaling network is involved in lung carcinogenesis. This study examined whether ligands that activate or suppress the EGFR signaling network were associated with lung cancer risk in ever smokers. **METHODS:** A nested case-control study within the Women's Health Initiative assessed baseline plasma levels of insulin, insulin-like growth factor (IGF)-1, insulin-like growth factor binding protein (IGFBP)-3, interleukin (IL)-6, hepatocyte growth factor (HGF), and nerve growth factor (NGF) in 1143 ever-smoking lung cancer cases and 1143 controls. Leptin was measured as an adiposity biomarker. Conditional logistic regression was used in data analyses. **RESULTS:** Leptin was inversely associated with lung cancer risk (odds ratio [ORcontinuous] per Ln [pg/mL] = 0.85, 95% confidence interval [CI] = 0.74 to 0.98). After adjusting for adiposity and other risk factors, null associations were found for IL-6, HGF, and NGF. In current smokers, but not former smokers, high insulin levels were associated with increased lung cancer risk (OR for 4th quartile vs others [ORq4] = 2.06, 95% CI = 1.30 to 3.26) whereas IGFBP-3 had a linear inverse association (ORcontinuous per μg/mL = 0.64, 95% CI = 0.41 to 0.98). The insulin association was consistent across subgroups defined by body mass index and histological type, but the IGFBP-3 association was specific to small cell lung cancer. There was a modest positive association between IGF-1 and lung cancer risk in current smokers (ORq4 = 1.44, 95% CI = 0.90 to 2.29). **CONCLUSIONS:** Independent of obesity, high insulin levels but reduced levels of IGFBP-3 were associated with increased lung cancer risk in current smokers.

Radon, Secondhand Smoke, and Children in the Home: Creating a Teachable Moment for Lung Cancer Prevention.
Huntington-Moskos L1, Rayens MK2, Wiggins A2, Hahn EJ2. Public Health Nurs. 2016 Jul 22. doi: 10.1111/phn.12283. [Epub ahead of print]
OBJECTIVE: This study determined whether having minor children in the home was associated with the teachable moment (TM) constructs of lung cancer worry, perceived risk, health-related self-concept, and the novel construct of synergistic risk. **DESIGN AND SAMPLE:** Secondary data analysis of baseline data from a randomized controlled trial of an intervention to reduce home exposure to radon and secondhand smoke (SHS). Quota sample of adults recruited at a Central Kentucky academic medical center (N = 556). **MEASURES:** Survey items assessed lung cancer worry, perceived risk, synergistic risk perception, and health-related self-concept. **RESULTS:** The presence of children in the home was not a significant predictor of any construct needed to create a TM for lung cancer prevention. Individuals with children living in the home were more likely to be younger, a racial/ethnic minority, a current smoker, and

live with a smoker compared to those without children in the home. **CONCLUSIONS:** There is a critical need to raise parental awareness on child health inequities related to the home exposure to radon and SHS. Public health nurses can create TMs for lung cancer prevention through greater awareness of the risks posed by radon and SHS along with promoting home testing and low-cost resources to reduce risk.

[Five-Year Survival Among Stage IIIA Lung Cancer Patients Receiving Two Different Treatment Modalities.](#) Bilfinger T1, Keresztes R2, Albano D1, Nemesure B3. Med Sci Monit. 2016 Jul 21;22:2589-94.
BACKGROUND: Five-year survival rates among stage IIIA lung cancer patients range between 2% and 15%, and there is currently no consensus regarding optimal treatment approaches for these patients. The current investigation evaluated survival outcomes among stage IIIA lung cancer patients receiving 2 different treatment modalities, neoadjuvant chemotherapy followed by resection versus chemoradiation alone. **MATERIAL AND METHODS:** This retrospective study is based on 127 patients attending the Lung Cancer Evaluation Center at Stony Brook Cancer Center between 2002 and 2014. Patients were treated either with neoadjuvant chemotherapy followed by resection or a regimen of chemoradiation alone. Kaplan-Meier curves were used to compare survival outcomes between groups and Cox proportional hazard models were used to evaluate treatment effects on survival, while adjusting for possible confounders. **RESULTS:** Approximately one-fourth (n=33) of patients received neoadjuvant chemotherapy followed by surgery, whereas 94 patients received definitive chemoradiation. Patients in the surgical group were found to be significantly younger than those receiving chemoradiation alone (60.1 vs. 67.9 years, respectively; p=0.001). Five-year survival among patients receiving preoperative chemotherapy followed by resection was significantly higher than that among patients receiving chemoradiation alone (63% vs. 19%, respectively; p<0.001), whereas the hazard ratio (HR) was 3-4 times greater in the latter group (HR=3.77, 95% confidence interval=1.87, 7.61). **CONCLUSIONS:** Findings from this study indicate that preoperative chemotherapy followed by resection can improve survival outcomes for stage IIIA lung cancer patients compared with chemoradiation alone. The results reflect a select surgical group of patients; thus, the data highlight the need to develop new therapies that may result in more patients being viable surgical candidates.

[Physical activity and sedentary behavior in relation to lung cancer incidence and mortality in older women: The Women's Health Initiative.](#) Wang A1, Qin F2, Hedlin H2, et al. Int J Cancer. 2016 Jul 20. doi: 10.1002/ijc.30281. [Epub ahead of print]
Physical activity has been associated with lower lung cancer incidence and mortality in several populations. We investigated these relationships in the Women's Health Initiative Observational Study (WHI-OS) and Clinical Trial (WHI-CT) prospective cohort of postmenopausal women. The WHI study enrolled 161,808 women aged 50-79 years between 1993-1998 at 40 U.S. clinical centers; 129,401 were eligible for these analyses. Cox proportional hazards models were used to assess the association of baseline physical activity levels [metabolic equivalent (MET)-minutes/week: none <100 (reference), low 100-<500, medium 500-<1200, high 1200+] and sedentary behavior with total lung cancer incidence and mortality. Over 11.8 mean follow-up years, 2,148 incident lung cancer cases and 1,365 lung cancer deaths were identified. Compared to no activity, higher physical activity levels at study entry were associated with lower lung cancer incidence [p=0.009; hazard ratios (95% confidence intervals) for each physical activity category: low, HR: 0.86 (0.76-0.96); medium, HR: 0.82 (0.73-0.93); and high, HR: 0.90 (0.79-1.03)], and mortality [p<0.0001; low, HR: 0.80 (0.69-0.92); medium, HR: 0.68 (0.59-0.80); and high, HR: 0.78 (0.66-0.93)]. Body mass index (BMI) modified the association with lung cancer incidence (p=0.01), with a stronger association in women with BMI<30 kg/m2 . Significant associations with sedentary behavior were not observed. In analyses by lung cancer subtype, higher total physical activity levels were associated with lower lung cancer mortality for both overall NSCLC and adenocarcinoma. In conclusion,

physical activity may be protective for lung cancer incidence and mortality in postmenopausal women, particularly in non-obese women.