Caring Ambassadors Lung Cancer Program
Literature Review - May 2017

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Serological proteome analysis approach-based identification of ENO1 as a tumor-associated antigen and its autoantibody could enhance the sensitivity of CEA and CYFRA 21-1 in the detection of non-small cell lung cancer. Dai L1,2,3, Qu Y3,4, Li J2, Wang X1, Wang K3,5, Wang P3,5, Jiang BH6, Zhang J1,2,3. Oncotarget. 2017 Apr 12. doi: 10.18632/oncotarget.17067. [Epub ahead of print]
PURPOSE: Lung cancer (LC) is the leading cause of cancer-related deaths for both male and female worldwide. Early detection of LC could improve five-year survival rate up to 48.8% compared to 3.3% of late/distant stage. Autoantibodies to tumor-associated antigens (TAAs) have been described as being present before clinical symptoms in lung and other cancers. We aimed to identify more TAAs to improve the performance for discovering non-small cell lung cancer (NSCLC) patients from healthy individuals. **METHODS:** Two independent sets were included in this study. Serological proteome analysis (SERPA) was used to identify TAAs from NSCLC cell line H1299 in a discovery set. In validation study, anti-ENO1 autoantibody was examined by immunoassay in sera from 242 patients with NSCLC and 270 normal individuals. **RESULTS:** A 47 KDa protein was identified to be alpha-enolase (ENO1) by using SERPA. Analysis of sera from 512 participants by ELISA showed significantly higher frequency of anti-ENO1 autoantibodies in NSCLC sera compared with the sera from normal individuals, with AUC (95%CI) of 0.589 (0.539-0.638, P=0.001). There was no significant difference in frequency of anti-ENO1 in different stages, histological or metastasis status of NSCLC. When anti-ENO1 detection was combined with other two tumor protein biomarkers (CEA and CYFRA 21-1), the sensitivity of NSCLC increased to 84%. **CONCLUSIONS:** ENO1 can elicit humoral immune response in NSCLC and its autoantibody has association with the tumorigenesis of NSCLC. Furthermore, these intriguing results suggest the possibility of autoantibody against ENO1 serving as a potential diagnostic biomarker in NSCLC and have implications for defining novel histological determinants of NSCLC.

Microparticles containing erlotinib-loaded solid lipid nanoparticles for treatment of non-small cell lung cancer. Bakhtiary Z1, Barar J2,3, Aghanejad A2, Saei AA4, Nemati E2, Ezzati Nazhad Dolatabadi J2, Omidi Y2,3. Drug Dev Ind Pharm. 2017 Apr 10:1-10. doi: 10.1080/03639045.2017.1310223. [Epub ahead of print]

Non-small cell lung cancer (NSCLC) patients with sensitizing mutations in the exons 18-21 of the epithelial growth factor receptor (EGFR) gene show increased kinase activity of EGFR. Hence, tyrosine kinase inhibitors (TKIs) such as erlotinib (ETB) have commonly been used as the second line therapeutic option for the treatment of metastatic NSCLC. While the ETB is available as an oral dosage form, the local delivery of this TKI to the diseased cells of the lung may ameliorate its therapeutic impacts. In the current study, we report on the development of ETB-loaded solid lipid nanoparticle (SLN) based formulation of dry powder inhaler (ETB-SLN DPI). ETB-SLNs were formulated using designated amount of compritol/poloxamer 407. The engineered ETB-SLNs showed sub-100 nm spherical shape with an encapsulation efficiency of 78.21%. MTT assay and DAPI staining revealed that the ETB-SLNs enhanced the cytotoxicity of cargo drug molecules in the human alveolar adenocarcinoma epithelial A549 cells as a model for NSCLC. To attain the ETB-SLN DPI, the ETB-SLNs were efficiently spray dried into microparticles (1-5 μm) along with mannitol. The ETB-SLN DPI powder displayed suitable flowability and aerodynamic traits. The Carr's Index, Hausner ratio and Next Generation Impactor (NGI) analyses confirmed deep inhalation pattern of the formulation. Based on these findings, we propose the ETB-SLN DPI as a promising treatment modality for the NSCLC patients.

Proliferation of PD-1+ CD8 T cells in peripheral blood after PD-1-targeted therapy in lung cancer patients. Kamphorst AO1, Pillai RN2, Yang S1, et al. Proc Natl Acad Sci U S A. 2017 Apr 26. pii: 201705327. doi: 10.1073/pnas.1705327114. [Epub ahead of print]
Exhausted T cells in chronic infections and cancer have sustained expression of the inhibitory receptor programmed cell death 1 (PD-1). Therapies that block the PD-1 pathway have shown promising clinical results in a significant number of advanced-stage cancer patients. Nonetheless, a better understanding of the immunological responses induced by PD-1 blockade in cancer patients is lacking. Identification of predictive biomarkers is a priority in the field, but whether peripheral blood analysis can provide biomarkers to monitor or predict patients' responses to treatment remains to be resolved. In this study, we analyzed longitudinal blood samples from advanced stage non-small cell lung cancer (NSCLC) patients (n = 29) receiving PD-1-targeted therapies. We detected an increase in Ki-67+ PD-1+ CD8 T cells following therapy in ∼70% of patients, and most responses were induced after the first or second treatment cycle. This T-cell activation was not indiscriminate because we observed only minimal effects on EBV-specific CD8 T cells, suggesting that responding cells may be tumor specific. These proliferating CD8 T cells had an effector-like phenotype (HLA-DR+, CD38+, Bcl-2lo), expressed costimulatory molecules (CD28, CD27, ICOS), and had high levels of PD-1 and coexpression of CTLA-4. We found that 70% of patients with disease progression had either a delayed or absent PD-1+ CD8 T-cell response, whereas 80% of patients with clinical benefit exhibited PD-1+ CD8 T-cell responses within 4 wk of treatment initiation. Our results suggest that peripheral blood analysis may provide valuable insights into NSCLC patients' responses to PD-1-targeted therapies.

Nrf2 promotes progression of non-small cell lung cancer through activating autophagy. Wang J1, Liu Z1,2, Hu T3, et al. Cell Cycle. 2017 Apr 12:0. doi: 10.1080/15384101.2017.1312224. [Epub ahead of print]
The transcription factor, NFE2-related factor 2 (Nrf2) and autophagy have been implicated in the oxidative-stress response during tumor evolution. However, few studies focus on crosstalk between Nrf2 and autophagy in cancer progression of non-small cell lung cancer (NSCLC). Herein, we evaluated the effect of Nrf2 on autophagy in NSCLC and their role in development of NSCLC. Effect of Nrf2 on overal survival (OS) of NSCLC patients were evaluated. Cell biological behaviors in response to Nrf2 were evaluated by MTT, colony formation assay and flow cytometry. Effect of 3-MA (a classical inhibitor of autophagy) on 95D-Nrf2 cells was also analyzed using flow cytometry. After up/down-regulating Nrf2 in NSCLC cell lines, expression of autophagy-related proteins were evaluated with western blot analysis.

The results revealed that Nrf2 was an independent prognositc factor negtively associated with OS of NSCLC patients. Elevated Nrf2 expression promotes NSCLC progression, enhancing the escape of tumor cells from apoptosis in vivo and in vitro. Double staining with Annexin V-APC and 7-AAD showed that the proportions of apoptotic cells in 95D-Nrf2 cells were gradually increased after the addition of 3-MA. Importently, Nrf2 induced autophagosome formation and enhanced autophagic activity, which subsequently inhibits NSCLC cell apoptosis. In conclusion, our present study demonstrates that Nrf2 promotes progression of non-small cell lung cancer through activating autophagy. It provides novel insights into Nrf2-mediated of cell proliferation in NSCLC and may facilitate therapeutic development against NSCLC.

ImmunoPET Imaging of CTLA-4 Expression in Mouse Models of Non-small Cell Lung Cancer.
Ehlerding EB1, England CG1, Majewski RL2, et al. Mol Pharm. 2017 Apr 12. doi: 10.1021/acs.molpharmaceut.7b00056. [Epub ahead of print]
Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is expressed on the surface of activated T cells and some tumor cells, and is the target of the clinically approved monoclonal antibody ipilimumab. In this study, we investigate specific binding of radiolabeled ipilimumab to CTLA-4 expressed by human non-small cell lung cancer cells in vivo using positron emission tomography (PET). Ipilimumab was radiolabeled with 64Cu (t1/2 = 12.7 h) through the use of the chelator 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) to formulate 64Cu-DOTA-ipilimumab. CTLA-4 expression in three non-small cell lung cancer (NSCLC) cell lines (A549, H460, and H358) was verified and quantified by Western blot and enzyme-linked immunosorbent assays (ELISA). A receptor binding assay was utilized to monitor the binding and internalization of 64Cu-DOTA-ipilimumab in the NSCLC cell lines. Next, the biodistribution of 64Cu-DOTA-ipilimumab was mapped by longitudinal PET imaging up to 48 h after injection. Ex vivo biodistribution and histological studies were employed to verify PET results. By in vitro analysis, CTLA-4 was found to be expressed on all three NSCLC cell lines with A549 and H358 showing the highest and lowest level of expression, respectively. PET imaging and quantification verified these findings as the tracer accumulated highest in the A549 tumor model (9.80 ± 0.22%ID/g at 48 h after injection; n = 4), followed by H460 and H358 tumors with uptakes of 9.37 ± 0.26%ID/g and 7.43 ± 0.05%ID/g, respectively (n = 4). The specificity of the tracer was verified by injecting excess ipilimumab in A549 tumor-bearing mice, which decreased tracer uptake to 6.90 ± 0.51%ID/g at 48 after injection (n = 4). Ex vivo analysis following the last imaging session also corroborated these findings. 64Cu-DOTA-ipilimumab showed enhanced and persistent accumulation in CTLA-4-expressing tissues, which will enable researchers further insight into CTLA-4 targeted therapies in the future.

miR-19 targeting of GSK3β mediates sulforaphane suppression of lung cancer stem cells. Zhu J1, Wang S1, Chen Y1, et al. J Nutr Biochem. 2017 Apr 5;44:80-91. doi: 10.1016/j.jnutbio.2017.02.020. [Epub ahead of print]
Cancer stem cells (CSCs) play a central role in the development of cancer. The canonical Wnt/β-catenin pathway is critical for maintaining stemness of CSCs. Phytochemicals from dietary compounds possess anti-CSCs properties and have been characterized as promising therapeutic agents for the prevention and treatment of many cancers. To date, the involvement and function of miR-19, a key oncogenic miRNA, in regulating Wnt/β-catenin pathway and lung CSCs has not been defined. Meanwhile, the effect of sulforaphane (SFN) on lung CSCs also remains to be elucidated. Here, we reported that lung CSCs up-regulated miR-19a and miR-19b expression. Overexpression of miR-19a/19b enhanced the ability of tumorsphere formation, up-regulated the expression of lung CSCs markers, increased Wnt/β-catenin pathway activation and β-catenin/TCF transcriptional activity in lung CSCs. In contrary, down-regulation of miR-19 suppressed lung CSCs activity and Wnt/β-catenin activation. We further revealed that miR-19 activated Wnt/β-catenin pathway by directly targeting GSK3β, the key negative modulator of this

pathway. Moreover, we showed that SFN exhibited inhibitory effect on lung CSCs through suppressing miR-19 and Wnt/β-catenin pathway. Taken together, these data illustrate the role of miR-19 in regulating lung CSCs traits and miR-19/GSK3β/β-catenin axis in SFN intervention of lung CSCs. Findings from this study could provide important new insights into the molecular mechanisms of lung CSCs regulation as well as its target intervention.

SCREENING, DIAGNOSIS AND STAGING

Evaluation of Appropriate Mediastinal Staging among EBUS Bronchoscopists. Miller RJ1, Mudambi L2, Vial MR3, Hernandez M4, Eapen GA5. Ann Am Thorac Soc. 2017 Apr 11. doi: 10.1513/AnnalsATS.201606-487OC. [Epub ahead of print]
RATIONALE: Endobronchial ultrasound (EBUS) has transformed mediastinal staging in lung cancer. A systematic approach, beginning with lymph nodes contralateral to the primary tumor (N3), is considered superior to selective sampling of radiographically abnormal nodes. However, the extent to which this recommendation is followed in practice remains unknown. **OBJECTIVES:** To assess the frequency in which pulmonologists, pulmonary fellows, and interventional pulmonologists endoscopically stage lung cancer appropriately. **METHODS:** Bronchoscopists currently performing EBUS were surveyed about their practice patterns, procedural volume, and self-confidence in EBUS skills and then performed a proctored simulated staging EBUS. The primary outcome was the proportion of participants who appropriately initiated ultrasonographic evaluation with the N3 nodal stations in a simulated patient undergoing EBUS for mediastinal staging. **RESULTS:** Sixty physicians (22 interventional pulmonologists, 18 general pulmonologists, and 20 pulmonary fellows) participated in the study. The rates of appropriate staging by study group were 95.5% (21/22) for interventional pulmonologists, 44.4% (8/18) for general pulmonologists, and 30.0% (6/20) for pulmonary fellows ($p < 0.001$). Increased procedural volume correlated with appropriate staging practices ($p<0.001$). Within each group, we assessed the concordance between self-confidence in EBUS and simulation performance. Among interventional pulmonologists, the concordance was 95.4%, followed by 61.1% for general pulmonologists and 40.0% for pulmonary fellows. **CONCLUSIONS:** General pulmonologists and pulmonary fellows were less likely than interventional pulmonologists to perform appropriate EBUS staging. In addition, the lack of concordance between self-confidence and appropriate staging performance among non-interventionists signals a need for improved dissemination of guidelines for EBUS-guided mediastinal staging.

The Diagnostic Value of Carcinoembryonic Antigen and Squamous Cell Carcinoma Antigen in Lung Adenosquamous Carcinoma. Jin X, Xu X, Xu H, Lv L, Lu H. Clin Lab. 2017 Apr 1;63(4):801-808. doi: 10.7754/Clin.Lab.2016.160921.
BACKGROUND: Lung adenosquamous carcinoma (ASC) is a rare malignant tumor with an adenocarcinoma and a squamous cell carcinoma component and associated with a lower 5-year survival rate than lung squamous cell carcinoma and lung adenocarcinoma. Surgical specimen histology revealed the inadequacy of conventional transbronchial needle aspiration samples in the diagnosis of lung ASC. Most lung ASC patients are not suitable to receive surgery, and it is difficult to diagnose ASC. This study is to explore the possibility of using serum carcinoembryonic antigen (CEA) and squamous cell carcinoma antigen (SCC) as a supplementary diagnostic test for ASC. **METHODS:** We retrospectively analyzed the preoperative serum CEA and SCC levels in 34 patients with lung ASC, 35 cases of lung adenocarcinoma patients, 35 cases of lung squamous cell carcinoma patients. 36 cases of lung benign disease patients and 35 cases of healthy people as a control group were also retrospectively collected and analyzed from January 2012 to December 2014 at the Zhejiang Cancer Hospital, China. The differences of CEA and SCC among the groups were evaluated, and the area under the curve (AUC), sensitivity, and

specificity were calculated. **RESULTS:** The levels of SCC and CEA in the lung ASC group were significantly higher than those in the healthy control group and benign disease group ($p < 0.05$). The SCC level in lung ASC group was significantly higher than that in lung adenocarcinoma group ($p < 0.05$). CEA and SCC had good diagnostic sensitivity and specificity compared with the healthy control group, and the difference was statistically significant ($p < 0.05$). **CONCLUSIONS:** Our retrospective study suggested a role for serum CEA and SCC levels as reference markers in the diagnosis of lung ASC. Patients with elevated CEA and SCC levels and diagnosed as lung adenocarcinoma by limited biopsy materials should be offered further work-up to reach an accurate diagnosis and treatment.

Relationship between endobronchial ultrasound-guided (EBUS)-transbronchial needle aspiration utility and computed tomography staging, node size at EBUS, and positron emission tomography scan node standard uptake values: A retrospective analysis. Marchand C1, Medford ARL1. Thorac Cancer. 2017 Apr 24. doi: 10.1111/1759-7714.12438. [Epub ahead of print]
BACKGROUND: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) diagnoses and stages mediastinal lymph node pathology. This retrospective study determined the relationship between EBUS-TBNA utility and non-small cell lung cancer (NSCLC) stage, lymph node size, and positron emission tomography (PET) standard uptake values (SUV), and the utility of neck ultrasound in bulky mediastinal disease. **METHODS:** Data of 284 consecutive patients who had undergone EBUS-TBNA was collected. Two hundred patients had suspected NSCLC, with 148 confirmed NSCLC cases. The diagnostic utility of EBUS-TBNA was determined according to NSCLC stage, EBUS lymph node size, PET SUV, use in distal metastases, and mutation testing. The utility of neck ultrasound for N3 disease was calculated in patients with bulky mediastinal disease. **RESULTS:** EBUS-TBNA was well tolerated with 97% sensitivity in distant metastatic disease, avoiding the need for distal metastases biopsy in 81% of cases. It had equivalent diagnostic accuracy in all NSCLC stages and in lymph nodes <10 mm, <20 mm or >20 mm (sensitivity >92% in all cases), with no mutation testing failures. EBUS-TBNA had 33% sensitivity in PET indolent (SUV < 4) nodes and 79% sensitivity in PET active nodes (SUV > 4). EBUS-TBNA diagnosed 12 cases of lymphoma without flow cytometry. **CONCLUSIONS:** The use of EBUS-TBNA meant that distant metastatic biopsy was avoided in 81% of cases, performing well irrespective of cancer stage, node size, and facilitating mutation testing. Neck ultrasound failed to detect N3 disease in patients with bulky mediastinal disease. EBUS-TBNA had a sensitivity of 33% for metastases in PET negative nodes, highlighting PET limitations.

Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. Paci E1, Puliti D1, Lopes Pegna A2, et al. Thorax. 2017 Apr 4. pii: thoraxjnl-2016-209825. doi: 10.1136/thoraxjnl-2016-209825. [Epub ahead of print]
BACKGROUND: ITALUNG is contributing to the European evaluation of low-dose CT (LDCT) screening for lung cancer (LC). **METHODS:** Eligible subjects aged 55-69 years, smokers or ex-smokers (at least 20 pack-years in the last 10 years), were randomised to receive an annual invitation for LDCT screening for 4 years (active group) or to usual care (control group). All participants were followed up for vital status and cause of death (at the end of 2014) and LC incidence (at the end of 2013). Pathological and clinical information was collected from the Tuscan Cancer Registry data. **RESULTS:** 1613 subjects were randomly assigned to the active group and 1593 to the control group. At the end of the follow-up period 67 LC cases were diagnosed in the active group and 71 in the control group (rate ratio (RR)=0.93; 95% CI 0.67 to 1.30). A greater proportion of stage I LC was observed in the active group (36% vs 11%, p<0.001). Non-significant reductions of 17% (RR=0.83; 95% CI 0.67 to 1.03) for overall mortality and 30% (RR=0.70; 95% CI 0.47 to 1.03) for LC-specific mortality were estimated. **CONCLUSIONS:** Despite the lack of statistical significance, the ITALUNG trial outcomes suggest that LDCT screening could reduce LC and overall mortality. Moreover, the comparison of the number of LC cases diagnosed in

the two groups does not show overdiagnosis after an adequate follow-up period. A pooled analysis of all European screening trials is advocated to assess the benefit-to-harm ratio of LDCT screening and its implementation in public health settings.

Electromagnetic navigation bronchoscopy to access lung lesions in 1,000 subjects: first results of the prospective, multicenter NAVIGATE study. Khandhar SJ1, Bowling MR2, Flandes J3, Gildea TR4, Hood KL5, Krimsky WS6, Minnich DJ7,8, Murgu SD9, Pritchett M10, Toloza EM11,12, Wahidi MM13, Wolvers JJ5, Folch EE14; NAVIGATE Study Investigators. BMC Pulm Med. 2017 Apr 11;17(1):59. doi: 10.1186/s12890-017-0403-9.

BACKGROUND: Electromagnetic navigation bronchoscopy (ENB) is an image-guided, minimally invasive approach that uses a flexible catheter to access pulmonary lesions. **METHODS:** NAVIGATE is a prospective, multicenter study of the superDimension™ navigation system. A prespecified 1-month interim analysis of the first 1,000 primary cohort subjects enrolled at 29 sites in the United States and Europe is described. Enrollment and 24-month follow-up are ongoing. **RESULTS:** ENB index procedures were conducted for lung lesion biopsy (n = 964), fiducial marker placement (n = 210), pleural dye marking (n = 17), and/or lymph node biopsy (n = 334; primarily endobronchial ultrasound-guided). Lesions were in the peripheral/middle lung thirds in 92.7%, 49.7% were <20 mm, and 48.4% had a bronchus sign. Radial EBUS was used in 54.3% (543/1,000 subjects) and general anesthesia in 79.7% (797/1,000). Among the 964 subjects (1,129 lesions) undergoing lung lesion biopsy, navigation was completed and tissue was obtained in 94.4% (910/964). Based on final pathology results, ENB-aided samples were read as malignant in 417/910 (45.8%) subjects and non-malignant in 372/910 (40.9%) subjects. An additional 121/910 (13.3%) were read as inconclusive. One-month follow-up in this interim analysis is not sufficient to calculate the true negative rate or diagnostic yield. Tissue adequacy for genetic testing was 80.0% (56 of 70 lesions sent for testing). The ENB-related pneumothorax rate was 4.9% (49/1,000) overall and 3.2% (32/1,000) CTCAE Grade ≥2 (primary endpoint). The ENB-related Grade ≥2 bronchopulmonary hemorrhage and Grade ≥4 respiratory failure rates were 1.0 and 0.6%, respectively. **CONCLUSIONS:** One-month results of the first 1,000 subjects enrolled demonstrate low adverse event rates in a generalizable population across diverse practice settings. Continued enrollment and follow-up are required to calculate the true negative rate and delineate the patient, lesion, and procedural factors contributing to diagnostic yield.

The Frequency of Incidental Findings and Subsequent Evaluation in Low-Dose CT Scans for Lung Cancer Screening. Morgan L1, Choi H2, Reid M3, Khawaja A4, Mazzone PJ5. Ann Am Thorac Soc. 2017 Apr 19. doi: 10.1513/AnnalsATS.201612-1023OC. [Epub ahead of print]

RATIONALE: The USPSTF recommends lung cancer screening with low-dose chest CT scans (LDCT) for a well-defined high-risk population. Data on the frequency and impact of incidental findings on LDCT scans performed within a centralized lung cancer screening program has not been reported. **OBJECTIVES:** Previous studies have reported IFs in the setting of clinical trials. We present our findings in a real clinical setting where the decision to manage these findings may depend on factors that are not captured in a research trial such as disclosing IFs, patient preferences, severity of comorbidities, and physician expertise. **METHODS:** We conducted a retrospective chart review of participants in the Cleveland Clinic Lung Cancer Screening Program from April 1, 2015 to February 17th, 2016. LungRads categories and all reported findings were extracted from the structured radiology report. Downstream investigations that occurred as a result of the imaging findings were recorded. Medicare reimbursement rates were documented for all screen related testing and treatment. **RESULTS:** 320 LDCT screened patients' records were reviewed. The most commonly reported incidental findings were pulmonary (69.6%), cardiovascular (67.5%) and gastrointestinal (25.9%). Fifteen percent of the scans had an incidental finding that resulted in further evaluation. The majority of patients who underwent further

testing had cardiovascular findings (10.3%), less frequently thyroid or adrenal nodules (2.1%), hepatic lesions (0.9%), renal mass (0.6%), or pulmonary disease (0.6%). The most frequently ordered investigations were echocardiography (n=9), cardiac stress test (n=9) and CT angiography (n=6). Reimbursement for the screening process, evaluation and treatment of screen detected findings, averaged $817 per screened patient. **CONCLUSIONS:** Clinically significant incidental findings on LDCT scans for lung cancer screening are common and their potential impact should be included in the shared decision making process. Screening programs should develop a standard approach for the evaluation of these findings, and consider the financial impact when seeking infrastructure support for screening program implementation.

Evaluation of Appropriate Mediastinal Staging among EBUS Bronchoscopists. Miller RJ1, Mudambi L2, Vial MR3, Hernandez M4, Eapen GA5. Ann Am Thorac Soc. 2017 Apr 11. doi: 10.1513/AnnalsATS.201606-487OC. [Epub ahead of print]
RATIONALE: Endobronchial ultrasound (EBUS) has transformed mediastinal staging in lung cancer. A systematic approach, beginning with lymph nodes contralateral to the primary tumor (N3), is considered superior to selective sampling of radiographically abnormal nodes. However, the extent to which this recommendation is followed in practice remains unknown. **OBJECTIVES:** To assess the frequency in which pulmonologists, pulmonary fellows, and interventional pulmonologists endoscopically stage lung cancer appropriately. **METHODS:** Bronchoscopists currently performing EBUS were surveyed about their practice patterns, procedural volume, and self-confidence in EBUS skills and then performed a proctored simulated staging EBUS. The primary outcome was the proportion of participants who appropriately initiated ultrasonographic evaluation with the N3 nodal stations in a simulated patient undergoing EBUS for mediastinal staging. **RESULTS:** Sixty physicians (22 interventional pulmonologists, 18 general pulmonologists, and 20 pulmonary fellows) participated in the study. The rates of appropriate staging by study group were 95.5% (21/22) for interventional pulmonologists, 44.4% (8/18) for general pulmonologists, and 30.0% (6/20) for pulmonary fellows ($p < 0.001$). Increased procedural volume correlated with appropriate staging practices ($p<0.001$). Within each group, we assessed the concordance between self-confidence in EBUS and simulation performance. Among interventional pulmonologists, the concordance was 95.4%, followed by 61.1% for general pulmonologists and 40.0% for pulmonary fellows. **CONCLUSIONS:** General pulmonologists and pulmonary fellows were less likely than interventional pulmonologists to perform appropriate EBUS staging. In addition, the lack of concordance between self-confidence and appropriate staging performance among non-interventionists signals a need for improved dissemination of guidelines for EBUS-guided mediastinal staging.

Effect of an Automated Tracking Registry on the Rate of Tracking Failure in Incidental Pulmonary Nodules. Shelver J1, Wendt CH2, McClure M1, Bell B3, Fabbrini AE3, Rector T3, Rice K3. J Am Coll Radiol. 2017 Apr 20. pii: S1546-1440(17)30176-X. doi: 10.1016/j.jacr.2017.02.001. [Epub ahead of print]
OBJECTIVE: Following incidental lung nodules with interval CT scanning is an accepted method to detect early lung cancer, but delayed tracking or failure to track is reported in up to 40% of patients. **METHODS:** Our institution developed and implemented an automated lung nodule registry tracking system. This system uses a code at the time that a suspicious nodule is discovered to populate the registry. Suspicious nodules were defined as any nodule, solid or ground glass, <3 cm that the radiologist recorded as a potential malignancy or recommended for follow-up imaging. We exported the system to eight other Veterans Administration Medical Centers (VAMCs) with over 10,000 patients enrolled. We retrospectively reviewed 200 sequential CT scan reports containing incidental nodule(s) from two tertiary care university-affiliated VAMCs, both before and after the implementation of the registry tracking

system. The primary outcome was the rate of tracking failure, defined as suspicious nodules that had no follow-up imaging or whose follow-up was delayed when compared with published guidelines. Secondary outcomes were predictors of tracking failure and reasons for tracking failure. **RESULTS:** After implementation of the registry tracking system in the two VAMCs, we found a significant decrease in tracking failure, from a preimplementation rate of 74% to a postimplementation rate of 10% ($P < .001$). We found that age, nodule size, number, and nodule characteristics were significant predictors. **CONCLUSIONS:** The automated lung nodule registry tracking system can be exported to other health care facilities and significantly reduces the rate of tracking failure.

Lymph node volume predicts survival but not nodal clearance in Stage IIIA-IIIB NSCLC. Agrawal V1,2, Coroller TP1,2, Hou Y1, et al. PLoS One. 2017 Apr 20;12(4):e0174268. doi: 10.1371/journal.pone.0174268. eCollection 2017.
BACKGROUND: Locally advanced non-small cell lung cancer (LA-NSCLC) patients have poorer survival and local control with mediastinal node (N2) tumor involvement at resection. Earlier assessment of nodal burden could inform clinical decision-making prior to surgery. This study evaluated the association between clinical outcomes and lymph node volume before and after neoadjuvant therapy. **MATERIALS AND METHODS:** CT imaging of patients with operable LA-NSCLC treated with chemoradiation and surgical resection was assessed. Clinically involved lymph node stations were identified by FDG-PET or mediastinoscopy. Locoregional recurrence (LRR), distant metastasis (DM), progression free survival (PFS) and overall survival (OS) were analyzed by the Kaplan Meier method, concordance index and Cox regression. **RESULTS:** 73 patients with Stage IIIA-IIIB NSCLC treated with neoadjuvant chemoradiation and surgical resection were identified. The median RT dose was 54 Gy and all patients received concurrent chemotherapy. Involved lymph node volume was significantly associated with LRR and OS but not DM on univariate analysis. Additionally, lymph node volume greater than 10.6 cm3 after the completion of preoperative chemoradiation was associated with increased LRR ($p<0.001$) and decreased OS ($p = 0.04$). There was no association between nodal volumes and nodal clearance. **CONCLUSION:** For patients with LA-NSCLC, large volume nodal disease post-chemoradiation is associated with increased risk of locoregional recurrence and decreased survival. Nodal volume can thus be used to further stratify patients within the heterogeneous Stage IIIA-IIIB population and potentially guide clinical decision-making.

Changing the Therapeutic Landscape in Non-small Cell Lung Cancers: the Evolution of Comprehensive Molecular Profiling Improves Access to Therapy. Sabari JK1, Santini F1, Bergagnini I1, Lai WV1, Arbour KC1, Drilon A2. Curr Oncol Rep. 2017 Apr;19(4):24. doi: 10.1007/s11912-017-0587-4.
Targeting genomic alterations has led to a paradigm shift in the treatment of patients with lung cancer. In an effort to better identify potentially actionable alterations that may predict response to FDA-approved and or investigational therapies, many centers have migrated towards performing targeted exome sequencing in patients with stage IV disease. The implementation of next-generation sequencing (NGS) in the evaluation of tumor tissue from patients with NSCLC has led to the discovery of targetable alterations in tumors that previously had no known actionable targets by less comprehensive profiling. An improved understanding of the molecular pathways that drive oncogenesis in NSCLC and a revolution in the technological advances in NGS have led to the development of new therapies through biomarker-driven clinical trials. This review will focus on the advances in molecular profiling that continue to fuel the revolution of precision medicine, identifying targets such as MET exon 14 skipping alterations and select recurrent gene alterations with increasing frequency.

Diagnostic performance of different imaging modalities in the assessment of distant metastasis and local recurrence of tumor in patients with non-small cell lung cancer. Ohno Y1,2, Yoshikawa T1,2, Kishida Y3, Seki S3, Koyama H3, Yui M4, Kassai Y4, Aoyagi K4, Kaminaga S4, Sugimura K3. J Magn Reson Imaging. 2017 Apr 17. doi: 10.1002/jmri.25726. [Epub ahead of print]
PURPOSE: To compare the diagnostic performance of positron emission tomography with [18F] fluoro-2-deoxy-glucose (FDG-PET) coregistered with magnetic resonance imaging (FDG-PET/MRI), MRI with and without diffusion-weighted imaging (DWI), FDG-PET fused with computed tomography (FDG-PET/CT) with brain contrast-enhanced (CE-) MRI, and routine radiological examination for assessment of postoperative recurrence in nonsmall-cell lung cancer (NSCLC) patients. **MATERIALS AND METHODS:** 96 consecutive postoperative NSCLC patients (52 men, 44 women; mean age 72 years) prospectively underwent whole-body 3T MRI with and without DWI; PET/CTs and routine radiological examinations consisted of CE-brain MRI, whole-body CE-CT, and bone scintigraphy. The patients were divided into a recurrence (n = 17) and a nonrecurrence (n = 79) group based on pathological and follow-up examinations. All coregistered PET/MRIs were generated by proprietary software. The probability of recurrence was visually assessed on a per-patient basis. Receiver operating characteristic analyses were used to compare the diagnostic performance of all methods. Finally, diagnostic capabilities were compared by means of McNemar's test. **RESULTS:** Areas under the curves (Azs) were significantly larger for PET/MRI and whole-body MRI with DWI (Az = 0.99) than for PET/CT (Az = 0.92, $P < 0.05$) and conventional radiological examination (Az = 0.91, $P < 0.05$). Specificity and accuracy of PET/MRI and MRI with and without DWI were significantly higher than those of PET/CT ($P < 0.05$) and routine radiological examination ($P < 0.05$). **CONCLUSION:** Whole-body FDG-PET/MRI and MRI with DWI were found to be more specific and accurate than FDG-PET/CT and routine radiological examinations for assessment of recurrence in NSCLC patients, although MRI with and without DWI demonstrated slightly lower sensitivity than PET/CT. **LEVEL OF EVIDENCE:** 2 J. Magn. Reson. Imaging 2017.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

The Feasibility of Thoracoscopic Resection in Bronchiectasis. Baysungur V1, Dogruyol T, Ocakcioglu I, Misirlioglu A, Evman S, Kanbur S, Alpay L, Tezel C. Surg Laparosc Endosc Percutan Tech. 2017 Apr 14. doi: 10.1097/SLE.0000000000000408. [Epub ahead of print]
INTRODUCTION: Minimally invasive surgery is the treatment of choice in early-stage lung cancer. However, experience in infectious lung disease, primarily bronchiectasis, is limited probably because of the presence of dense pleural adhesions, multiple lymph nodes, and spiral bronchial arteries. The present study shows our experience of video-assisted thoracoscopic surgery (VATS) lobectomy and segmentectomy in the treatment of bronchiectasis. **MATERIALS AND METHODS:** Patients who underwent VATS lobectomy or segmentectomy in our clinic between April 2008 and 2015 were retrospectively evaluated. Surgery was indicated in patients with radiologic localized bronchiectasis who also had a history of recurrent lower respiratory tract infection or expectorating mucopurulent secretion. The patients were analyzed in terms of age, sex, thoracotomy conversion rate, postoperative drainage amount, chest tube removal time, length of hospital stay, morbidity, and mortality. **RESULTS:** A total of 44 patients initially underwent VATS pulmonary anatomic resection and 41 procedures were completed on 40 patients. One patient had bilateral resection. Fifteen patients were male individuals and 26 were female individuals. The average age was 31.4 (15 to 57) years. Forty lobectomies and 1 segmentectomy were performed. The conversion rate was 6.8%. VATS was performed on 28 patients by 3 ports, 8 patients by 2 ports, and 5 patients by a single port. In terms of anatomic resections, 18 patients underwent

left lower lobectomy, 8 right lower lobectomy, 8 middle lobectomy, 6 right upper lobectomy, and 1 patient underwent lingular segmentectomy. No major postoperative complication or mortality was observed. Prolonged air leak was observed in 2 patients and subcutaneous emphysema occurred in 2 patients. The average postoperative drainage amount, chest tube removal time, and length of hospital stay were 320 mL, 3.1 (1 to 11) days, and 4.6 (2 to 11) days, respectively. **CONCLUSIONS:** VATS pulmonary resection is a safe, feasible, and effective treatment in the surgery of bronchiectasis with low morbidity and mortality rates. Moreover, because of cosmetic results, patients with benign diseases such as bronchiectasis could be initiated by minimally invasive surgery options just like patients with malignancies.

Temporal trends in centralization and racial disparities in utilization of high-volume hospitals for lung cancer surgery. Lieberman-Cribbin W1, Liu B, Leoncini E, Flores R, Taioli E. Medicine (Baltimore). 2017 Apr;96(16):e6573. doi: 10.1097/MD.0000000000006573.
Racial disparities have been suggested in hospital utilization and outcome for lung cancer surgery, but the effect of hospital centralization on closing this gap is unknown. We hypothesized that centralization has increased the utilization of high- or very-high-volume (HV/VHV) hospitals, a proxy for access to high-quality care, over the study period independently from race.Inpatient records were extracted from the New York Statewide Planning and Research Cooperative System database (1995-2012) according to Clinical Modification of the International Classification of Diseases, 9th Revision diagnosis codes 162.* and 165.* and surgical procedure codes 32.2-32.6 (n=31,931). Patients treated exclusively with surgery of black or white race with a valid zip code were included. Logistic models were performed to determine factors associated with utilization of HV/VHV or low- or very-low-volume (LV/VLV) hospitals; these models were subsequently stratified by race.The percentage of both black and white patients utilizing HV/VHV hospitals increased over the study period (+22.7% and 13.9%, respectively). The distance to the nearest HV/VHV hospital and patient-hospital distance were significantly lower in black compared to white patients, however, blacks were consistently less likely to use HV/VHV than whites (odds ratioadj: 0.26; 95% confidence interval: 0.23-0.29), and were significantly more likely to utilize urban, teaching, and lower volume hospitals than whites. Likelihood of HV/VHV utilization decreased with an increasing distance from a HV/VHV hospital, overall and separately for black and white patients.Although centralization has increased the utilization of HV/VHV for both black and white patients, racial differences in access and utilization of HV hospitals persisted.

The Influence of Physician and Patient Gender on Risk Assessment for Lung Cancer Resection. Ferguson MK1, Huisingh-Scheetz M2, Thompson K2, Wroblewski K3, Farnan J2, Acevedo J4. Ann Thorac Surg. 2017 Apr 12. pii: S0003-4975(17)30176-5. doi: 10.1016/j.athoracsur.2017.01.066. [Epub ahead of print]
BACKGROUND: Women do not receive appropriate surgical therapy for lung cancer as often as men. Patient gender may influence treatment recommendations; less is known about the effect of physician gender on recommendations. **METHODS:** Gender-neutral vignettes representing low-risk, average-risk, and high-risk candidates for lung resection were paired with concordant videos of standardized patients (SPs). Cardiothoracic trainees and practicing thoracic surgeons read a vignette, provided an initial estimate of the percentage risk of major adverse events after lung resection, viewed a video (randomized to male or female SP), provided a final estimate of risk, and ranked the importance of the video in the final risk estimate. **RESULTS:** Overall, 107 surgeons participated, of whom 90 were men. Initial estimated risks mirrored actual vignette risks: 10.4% ± 9.9 for low risk, 17.6% ± 13.2 for average risk, and 21.0% ± 14.7 for high risk ($p < 0.001$). After SP videos were viewed and final risk estimates were rendered, there was a significant difference between male and female physicians in the absolute change in estimated risk ($p = 0.002$), with male physicians having larger changes than female physicians. There was

also an effect of SP gender that varied by vignette type ($p < 0.001$). Increasing video importance scores were directly associated with increasing change in risk scores for average-risk and high-risk vignette/video combinations ($p < 0.001$ for each). **CONCLUSIONS:** Differences in estimating complication risk for lung resection candidates are related to physician and patient gender. This may influence recommendations for surgical treatment. Understanding such differences may help reduce inequities in treatment recommendations.

Surgical resection for clinical-Stage I radiological pure-solid lung cancer that met the current high risk criteria. Hattori A1, Matsunaga T1, Takamochi K1, Oh S1, Suzuki K1. Jpn J Clin Oncol. 2017 Apr 13:1-9. doi: 10.1093/jjco/hyx054. [Epub ahead of print]
OBJECTIVE: We assessed whether surgical resection is acceptable for radiological invasive non-small cell lung cancer (NSCLC) that met the current high-risk criteria. **METHODS:** We reviewed 500 clinical-Stage I NSCLCs with a radiological pure-solid appearance. High-risk criterion was defined as follows: (1) preoperative FEV1% ≤ 50% or DLco% ≤ 50%, (2) age > 75y with 50% < FEV1% < 60% or 50% < DLco% < 60%, and (3) three or more severe general comorbidities. **RESULTS:** The high-risk group comprised 184 (37%) patients. The percentages for elderly, male, smoker, non-adenocarcinoma histology were significantly higher than those of the normal-risk group ($P < 0.001$). Lobectomy was performed in 148 (80%) patients. Overall survival (OS) was significantly worse in the high-risk group (59.4% vs 73.1%, $P = 0.004$), however, a multivariate analysis revealed that high-risk was not associated with poor survival ($P = 0.519$). Furthermore, there were no significant differences between the high-risk and normal-risk groups regarding cancer-specific survival (74.5% vs 79.2%, $P = 0.569$). Postoperative morbidity rates were significantly different between the two study arms (45% vs 25%, $P < 0.001$), however, the 30-day and 90-day mortality rates for the high-risk group were 1.6% and 3.8%, respectively. In the high-risk patients, the difference in survival between lobectomy and sublobar resection was not significant (69.4% vs 78.6%, $P = 0.716$), and was also proven in the propensity-score matched patients (82.1% vs 76.0%, $P = 0.623$). **CONCLUSIONS:** Conventional high-risk criteria are not always appropriate prognostic variables, and lung cancer specific survival or short-term mortalities for high-risk patients were fully acceptable. Surgical therapy including lobectomy should not be readily excluded from radical local management even when a patient meets the high-risk criteria.

Advances in the use of surgery and multimodality treatment for N2 non-small cell lung cancer. Van Schil PE1, Yogeswaran K1, Hendriks JM1, Lauwers P1, Faivre-Finn C2. Expert Rev Anticancer Ther. 2017 Apr 21:1-7. doi: 10.1080/14737140.2017.1319766. [Epub ahead of print]
INTRODUCTION: Stage IIIA-N2 non-small cell lung cancer (NSCLC) represents a heterogeneous group of bronchogenic carcinomas with locoregional involvement. Different categories of N2 disease exist, ranging from unexpectedly encountered N2 involvement after detailed preoperative staging or 'surprise' N2, to potentially resectable disease treated within a combined modality setting, and finally, bulky N2 involvement treated by chemoradiation. Areas covered: Large randomised controlled trials and meta-analyses on stage IIIA-N2 NSCLC have been published but their implications for treatment remain a matter of debate. No definite recommendations can be provided as diagnostic and therapeutic algorithms vary according to local, national or international guidelines. Expert commentary: From the literature, it is clear that patients with stage IIIA-N2 NSCLC should be treated by combined modality therapy including chemotherapy, radiotherapy and surgery. The relative contribution of each modality has not been firmly established. For patients undergoing induction therapy, adequate restaging is important as only down-staged patients will clearly benefit from surgical resection. Each patient should be discussed within a multidisciplinary team to determine the best diagnostic and therapeutic approach according to the specific local expertise. In the near future, it might be expected that targeted therapies and immunotherapy will be incorporated as possible therapeutic options.

Induction chemotherapy for T3N0M0 non-small-cell lung cancer increases the rate of complete resection but does not confer improved survival. Anderson KL Jr1, Mulvihill MS2, Yerokun BA2, Speicher PJ2, D'Amico TA3, Tong BC3, Berry MF4, Hartwig MG3. Eur J Cardiothorac Surg. 2017 Apr 11. doi: 10.1093/ejcts/ezx091. [Epub ahead of print]
OBJECTIVES: The objective of this study was to evaluate outcomes of induction therapy prior to an operation in patients with cT3 non-small-cell lung cancer (NSCLC). **METHODS:** Patients diagnosed with cT3N0M0 NSCLC from 2006 to 2011 in the National Cancer Database who were treated with lobectomy or pneumonectomy were stratified by treatment strategy: an operation first versus induction chemotherapy. Propensity scores were developed and matched cohorts were generated. Short-term outcomes included margin status, 30- and 90-day mortality rates, readmission and length of stay. Survival analyses using Kaplan-Meier methods were performed on both the unadjusted and propensity matched cohorts. **RESULTS:** A total of 3791 cT3N0M0 patients were identified for inclusion, of which 580 (15%) were treated with induction chemotherapy. Prior to adjustment, patients treated with induction chemotherapy were younger, had a higher comorbidity burden and were more likely to have private insurance (all $P < 0.001$). Following matching, patients receiving induction chemotherapy were more likely to subsequently undergo an open procedure (87.3 vs 77.8%, $P = 0.005$). These patients were more likely to obtain R0 resection (93.1% vs 90.0%, $P = 0.04$) and were thereby less likely to have positive margins at the time of resection (6.9% vs 10.0%, $P = 0.03$). Patients who received induction therapy had higher rates of 90-day mortality (6.6% vs 3.4%) but there was no difference in long-term survival between the groups. **CONCLUSIONS:** Despite yielding increased rates of R0 resection, induction chemotherapy for cT3N0M0 NSCLC is not associated with improved survival and should not be considered routinely. Further studies are warranted to elucidate cohorts that may benefit from induction therapy.

Surgery Versus Optimal Medical Management for N1 Small Cell Lung Cancer. Yang CJ1, Chan DY2, Speicher PJ2, et al. Ann Thorac Surg. 2017 Apr 3. pii: S0003-4975(17)30090-5. doi: 10.1016/j.athoracsur.2017.01.043. [Epub ahead of print]
Gulack BC2, Tong BC2, Hartwig MG2, Kelsey CR2, D'Amico TA2, Berry MF3, Harpole DH2.
BACKGROUND: Adjuvant chemotherapy has been demonstrated to improve the outcomes of patients with N1 non-small cell lung cancer. It is unknown whether patients previously thought to have unresectable small cell lung cancer (SCLC) may have tumors amenable to surgery if adjuvant therapies can be given. This study was undertaken to evaluate whether surgery, in the setting of modern adjuvant therapies, can be beneficial for patients with N1-positive SCLC. **METHODS:** Patients with clinical T1-3 N1 M0 SCLC who underwent concurrent chemoradiation versus surgery and adjuvant therapy in the National Cancer Data Base from 2003 to 2011 were examined. Overall survival was assessed using Kaplan-Meier and Cox proportional hazards analysis and propensity score-matched analysis.
RESULTS: Of 1,041 patients with cT1-3 N1 M0 SCLC who met inclusion criteria, 96 patients (9%) underwent surgery and adjuvant chemotherapy with or without radiation and 945 (91%) underwent concurrent chemoradiation alone. Multivariable Cox modeling demonstrated that surgery with adjuvant chemotherapy with or without radiation (hazard ratio 0.74, 95% confidence interval: 0.56 to 0.97) was associated with improved survival compared with concurrent chemoradiation. After propensity matching, surgery with adjuvant chemotherapy with or without radiation was associated with improved 5-year survival compared with concurrent chemoradiation (31.4% versus 26.3%). **CONCLUSIONS:** In an analysis of a national population-based cancer database, surgery followed by adjuvant chemotherapy with or without radiation for cT1-3 N1 SCLC had improved outcomes compared with concurrent chemoradiation. These results support the re-evaluation of the role of surgery in multimodality therapy for N1 SCLC in a clinical trial setting.

Sublobar resection for stage IA non-small cell lung cancer. Berfield KS1, Wood DE1. J Thorac Dis. 2017 Apr;9(Suppl 3):S208-S210. doi: 10.21037/jtd.2017.03.135.
Advancements in the diagnosis, staging and management of lung cancer have all led to improvements in outcomes associated with sublobar resection. Lobectomy, for early stage lung cancers has been the treatment of choice for many years. However, there is mounting evidence that sublobar resection when applied to the appropriate patient population can provide not only excellent oncologic results but also equivalent survival to lobectomy. Therefore, it is time that we reevaluate the management of peripheral stage IA lung cancers.

Incidence of occult pN2 disease following resection and mediastinal lymph node dissection in clinical stage I lung cancer patients. Bille A1, Woo KM2, Ahmad U1, Rizk NP1, Jones DR1. Eur J Cardiothorac Surg. 2017 Apr 1;51(4):674-679. doi: 10.1093/ejcts/ezw400.
OBJECTIVES: Early clinical stage (T1 and T2) non-small cell lung cancer (NSCLC) is commonly treated with anatomic lung resection and lymph node sampling or dissection. The aims of this study were to evaluate the incidence and the distribution of occult N2 disease according to tumour location and the short- and long-term outcomes. **METHODS:** We performed a retrospective review of patients with clinical stage I NSCLC who underwent anatomic lung resection and lymphadenectomy. Mediastinal lymphadenectomy (ML) was defined as resection of at least 2 mediastinal stations, always including station 7 lymph nodes. Patients who had a lobe-specific lymphadenectomy were excluded. **RESULTS:** One thousand six hundred and sixty-seven consecutive patients met inclusion criteria and were included. Overall, 9% (146/1667) of the patients had occult pN2 disease. At multivariable analysis, adenocarcinoma histology and vascular invasion were independently associated with greater risk of occult pN2 disease. In left and right upper lobe tumours, station 7 nodes were involved in 5 and 13% of pN2 positive cases, respectively. Station 5 and station 2/4 nodes were involved in 29 and 18% of left and right lower lobe pN2 tumours, respectively. There was no postoperative mortality, and postoperative morbidity was 28%. The median overall survival was 77.4 months. N0 patients had a median overall survival of 83.7 months vs 48.0 months and 37.9 months in N1 and N2 populations, respectively ($P < 0.001$). **CONCLUSIONS:** Sixteen percent of pN2 patients had mediastinal lymph node metastasis beyond the lobe-specific lymphatic drainage. We recommend a complete lymphadenectomy be performed, even in clinical stage I NSCLC.

NSCLC – Systemic Therapies (Chemotherapy, Targeted Therapy, and Immunotherapy)

Update on Programmed Death-1 and Programmed Death-Ligand 1 Inhibition in the Treatment of Advanced or Metastatic Non-Small Cell Lung Cancer. Iafolla MAJ1, Juergens RA1. Front Oncol. 2017 Apr 6;7:67. doi: 10.3389/fonc.2017.00067. eCollection 2017.
PURPOSE: Non-small-cell lung cancer (NSCLC) has a large worldwide prevalence with a high mortality rate. Chemotherapy has offered modest improvements in survival over the past two decades. Immune checkpoint modulation with programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibition has shown the promise of changing the future landscape of cancer therapy. This update reviews recent advances in the treatment of NSCLC with immune checkpoint modulation. **METHODS:** Publications and proceedings were identified from searching PubMed and proceedings from the annual meetings of the American Society of Clinical Oncology, European Society for Medical Oncology, and European Lung Cancer Conference. **RESULTS:** Atezolizumab, nivolumab, and pembrolizumab increase overall survival in second-line treatment of Stage III/IV squamous and non-squamous NSCLC when compared to docetaxel. Pembrolizumab increases progression-free survival in the first-line treatment of Stage IV NSCLC with 50% PD-L1 expression when compared to platinum-based chemotherapy. Combination therapy with chemotherapy and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)

inhibitors has shown promise in early trials. **CONCLUSION:** Immune checkpoint modulation produces durable responses and overall survival benefits with less toxicity compared to conventional chemotherapy. Future investigations are combining PD-1/L1 inhibition with chemotherapy, targeted therapy, or other immuno-oncology agents in an effort to further improve efficacy.

Post-Progression Survival Associated with Overall Survival in Patients with Advanced Non-Small-Cell Lung Cancer Receiving Docetaxel Monotherapy as Second-Line Chemotherapy. Kotake M1, Miura Y, Imai H, Mori K, Sakurai R, Kaira K, Tomizawa Y, Minato K, Saito R, Hisada T. Chemotherapy. 2017 Apr 6;62(4):205-213. doi: 10.1159/000456534. [Epub ahead of print]
BACKGROUND: In patients with non-small-cell lung cancer (NSCLC), the effects of second-line chemotherapy on overall survival (OS) might be confounded by subsequent therapies. Therefore, using individual-level data, we aimed to determine the relationships between progression-free survival (PFS) and post-progression survival (PPS) with OS in patients with advanced NSCLC treated with docetaxel monotherapy as second-line chemotherapy. **METHODS:** Between April 2002 and December 2014, data from 86 patients with advanced NSCLC who underwent second-line docetaxel monotherapy following first-line treatment with platinum combination chemotherapy were analyzed. The relationships of PFS and PPS with OS were analyzed at the individual level. **RESULTS:** Spearman rank correlation and linear regression analyses showed that PPS was strongly associated with OS ($r = 0.86$, $p < 0.05$, $R2 = 0.93$), whereas PFS was moderately correlated with OS ($r = 0.50$, $p < 0.05$, $R2 = 0.21$). Performance status at the end of second-line treatment and the number of regimens after progression beyond second-line chemotherapy were significantly associated with PPS ($p < 0.05$). **CONCLUSIONS:** In patients with advanced NSCLC with unknown oncogenic driver mutations undergoing docetaxel monotherapy as second-line chemotherapy, when compared with PFS, PPS had a stronger association with OS. This finding suggests that subsequent treatment after disease progression following second-line docetaxel monotherapy has a significant influence on OS.

A Diagnostic Microdosing Approach to Investigate Platinum Sensitivity in Non-Small Cell Lung Cancer. Wang SS1, Zimmermann M1,2, Zhang H1, et al. Int J Cancer. 2017 Apr 24. doi: 10.1002/ijc.30747. [Epub ahead of print]
The platinum-based drugs cisplatin, carboplatin and oxaliplatin are often used for chemotherapy, but drug resistance is common. The prediction of resistance to these drugs via genomics is a challenging problem since hundreds of genes are involved. A possible alternative is to use mass spectrometry to determine the propensity for cells to form drug-DNA adducts-the pharmacodynamic drug-target complex for this class of drugs. The feasibility of predictive diagnostic microdosing was assessed in non-small cell lung cancer (NSCLC) cell culture and a pilot clinical trial. Accelerator mass spectrometry (AMS) was used to quantify [14 C]carboplatin-DNA monoadduct levels in the cell lines induced by microdoses and therapeutic doses of carboplatin, followed by correlation with carboplatin IC50 values for each cell line. The adduct levels in cell culture experiments were linearly proportional to dose ($R2 = 0.95$, $p<0.0001$) and correlated with IC50 across all cell lines for microdose and therapeutically relevant carboplatin concentrations ($p=0.02$ and $p=0.01$, respectively). A pilot microdosing clinical trial was conducted to define protocols and gather preliminary data. Plasma pharmacokinetics (PK), and [14 C]carboplatin-DNA adducts in white blood cells and tumor tissues from six NSCLC patients were quantified via AMS. The blood plasma half-life of [14 C]carboplatin administered as a microdose was consistent with the known PK of therapeutic dosing. The optimal [14 C]carboplatin formulation for the microdose was 107 dpm/kg of body weight and 1% of the therapeutic dose for the total mass of carboplatin. No microdose-associated toxicity was observed in the patients. Additional accruals are required to significantly correlate adduct levels with response. This article is protected by copyright. All rights reserved.

Response to the treatment immediately before nivolumab monotherapy may predict clinical response to nivolumab in patients with non-small cell lung cancer. Kobayashi H1, Omori S2, Nakashima K2, et al. Int J Clin Oncol. 2017 Apr 5. doi: 10.1007/s10147-017-1118-x. [Epub ahead of print]

BACKGROUND: Currently, no markers predictive of response to nivolumab monotherapy in patients with advanced non-small cell lung cancer (NSCLC) are currently recognized in Japan. The present study was undertaken to identify such markers. **MATERIALS AND METHODS:** Medical records of 50 patients with advanced NSCLC and treated with nivolumab monotherapy at Shizuoka Cancer Center between December 2015 and April 2016 were retrospectively reviewed. The parameters studied were age, sex, Eastern Cooperative Oncology Group performance status, smoking history, histological diagnosis, epidermal growth factor receptor or anaplastic lymphoma kinase status, therapeutic line of nivolumab, efficacy of treatment immediately before nivolumab monotherapy, and time since previous therapy. **RESULTS:** The objective response rate to nivolumab monotherapy was 18% [95% confidence interval (CI) 10-31]. Multivariate logistic regression identified "squamous histology" [odds ratio (OR) 0.00054; 95% CI 0-0.27] and "response to the treatment immediately before nivolumab monotherapy" (OR 0.0011; 95% CI 0-0.092) as independently associated with response to nivolumab monotherapy. **CONCLUSION:** "Response to the treatment immediately before nivolumab monotherapy" might be a predictive marker of response to nivolumab in patients with advanced NSCLC.

Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA Completely Resected Non-Small-Cell Lung Cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update. Kris MG1, Gaspar LE1, Chaft JE1, et al. J Clin Oncol. 2017 Apr 24:JCO2017724401. doi: 10.1200/JCO.2017.72.4401. [Epub ahead of print]

PURPOSE: The panel updated the American Society of Clinical Oncology (ASCO) adjuvant therapy guideline for resected non-small-cell lung cancers. **METHODS:** ASCO convened an update panel and conducted a systematic review of the literature, investigating adjuvant therapy in resected non-small-cell lung cancers. **RESULTS:** The updated evidence base covered questions related to adjuvant systemic therapy and included a systematic review conducted by Cancer Care Ontario current to January 2016. A recent American Society for Radiation Oncology guideline and systematic review, previously endorsed by ASCO, was used as the basis for recommendations for adjuvant radiation therapy. An update of these systematic reviews and a search for studies related to radiation therapy found no additional randomized controlled trials. **RECOMMENDATIONS:** Adjuvant cisplatin-based chemotherapy is recommended for routine use in patients with stage IIA, IIB, or IIIA disease who have undergone complete surgical resections. For individuals with stage IB, adjuvant cisplatin-based chemotherapy is not recommended for routine use. However, a postoperative multimodality evaluation, including a consultation with a medical oncologist, is recommended to assess benefits and risks of adjuvant chemotherapy for each patient. The guideline provides information on factors other than stage to consider when making a recommendation for adjuvant chemotherapy, including tumor size, histopathologic features, and genetic alterations. Adjuvant chemotherapy is not recommended for patients with stage IA disease. Adjuvant radiation therapy is not recommended for patients with resected stage I or II disease. In patients with stage IIIA N2 disease, adjuvant radiation therapy is not recommended for routine use. However, a postoperative multimodality evaluation, including a consultation with a radiation oncologist, is recommended to assess benefits and risks of adjuvant radiation therapy for each patient with N2 disease. Additional information is available at www.asco.org/lung-cancer-guidelines and www.asco.org/guidelineswiki .

Tumor Immune Microenvironment and Nivolumab Efficacy in EGFR Mutation-Positive Non-Small Cell Lung Cancer Based on T790M Status after Disease Progression During EGFR-TKI Treatment. Haratani K1, Hayashi H1, Tanaka T2, et al. Ann Oncol. 2017 Apr 12. doi: 10.1093/annonc/mdx183. [Epub ahead of print]

BACKGROUND: The efficacy of programmed death-1 (PD-1) blockade in epidermal growth factor receptor gene (EGFR) mutation-positive non-small cell lung cancer (NSCLC) patients with different mechanisms of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) is unknown. We retrospectively evaluated nivolumab efficacy and immune-related factors in such patients according to their status for the T790M resistance mutation of EGFR. **PATIENTS AND METHODS:** We identified 25 patients with EGFR mutation-positive NSCLC who were treated with nivolumab after disease progression during EGFR-TKI treatment (cohort A). Programmed death-ligand 1 (PD-L1) expression and tumor-infiltrating lymphocyte (TIL) density in tumor specimens obtained after acquisition of EGFR-TKI resistance were determined by immunohistochemistry. Whole-exome sequencing of tumor DNA was performed to identify gene alterations. The relation of T790M status to PD-L1 expression or TIL density was also examined in an independent cohort of 60 patients (cohort B). **RESULTS:** In cohort A, median progression-free survival (PFS) was 2.1 and 1.3 months for T790M-negative and T790M-positive patients, respectively (P = 0.099; hazard ratio [HR] of 0.48 with a 95% confidence interval [CI] of 0.20-1.24). Median PFS was 2.1 and 1.3 months for patients with a PD-L1 expression level of ≥ 1% or < 1%, respectively (P = 0.084; HR of 0.37, 95% CI of 0.10-1.21). PFS tended to increase as the PD-L1 expression level increased with cutoff values of ≥ 10% and ≥50%. The proportion of tumors with a PD-L1 level of ≥ 10% or ≥ 50% was higher among T790M-negative patients than among T790M-positive patients of both cohorts A and B. Nivolumab responders had a significantly higher CD8 + TIL density and nonsynonymous mutation burden. **CONCLUSION:** T790M-negative patients with EGFR mutation-positive NSCLC are more likely to benefit from nivolumab after EGFR-TKI treatment, possibly as a result of a higher PD-L1 expression level, than are T790M-positive patients.

The Emerging Role of Targeted Therapy and Immunotherapy in the Management of Brain Metastases in Non-Small Cell Lung Cancer. Wong A1,2. Front Oncol. 2017 Apr 5;7:33. doi: 10.3389/fonc.2017.00033. eCollection 2017.

Lung cancer is the worldwide leading cause of cancer-related mortality in men and second leading in women. Brain metastases (BM) account for 10% of non-small cell lung cancer (NSCLC) patients at initial presentation, with another 25-40% developing BM during the course of their disease. In the last decade, the field of precision oncology has led to the discovery of a multitude of heterogenous molecular abnormalities within NSCLC as well as the development of tyrosine kinase inhibitors that target them. In this review, the focus will be on targeted therapy and immunotherapy that show efficacy in BM rather than conventional treatment for multiple BM (such as surgical resection, WBRT, or stereotactic radiosurgery).

Pembrolizumab for the treatment of non-small cell lung cancer. Muller M1, Schouten RD1, De Gooijer CJ1, Baas P1. Expert Rev Anticancer Ther. 2017 May;17(5):399-409. doi: 10.1080/14737140.2017.1311791. Epub 2017 Apr 3.

INTRODUCTION: In the last years, a spectacular development of immunotherapeutic agents aimed at the PD-1/PD-L1 axis has taken place. This development of these checkpoint inhibitors has greatly influenced our approach to the treatment of lung cancer in first and second line. The limited toxicity profile and the ability to treat for prolonged periods, even in smokers, is a welcome expansion of the therapeutic arsenal of the oncologist. Areas covered: This review highlights the results of recent clinical trials on pembrolizumab for the treatment of non-small cell lung cancer. The authors discuss both first and second line treatment with pembrolizumab as monotherapy and in combination therapies. Additionally,

implications of the PD-L1 immunohistochemistry assay with the 22C3 antibody and its use in clinical practice and trials is discussed. Expert commentary: A higher overall response, overall survival and a moderate toxicity profile is observed with the use of pembrolizumab, compared to chemotherapy, in both first and second line. These promising results have already translated into the registration of pembrolizumab in first and second line in patients with a high expression of PD-L1. However, as PD-L1 staining does not sufficiently discriminate responders from non-responders for all checkpoint inhibitors, there still is a need for a better predictive biomarker.

Immunotherapy revolutionises non-small-cell lung cancer therapy: Results, perspectives and new challenges. Giroux Leprieur E1, Dumenil C2, Julie C3, Giraud V2, Dumoulin J2, Labrune S2, Chinet T4. Eur J Cancer. 2017 Apr 10;78:16-23. doi: 10.1016/j.ejca.2016.12.041. [Epub ahead of print]
Immune checkpoint inhibitors (ICIs) are antibodies that target key signalling pathways such as programmed death 1 (PD1)/programmed death-ligands 1 and 2 (PDL1 and PDL2) to improve anti-tumour immune responses. Until recently, nivolumab was the only ICI validated for advanced non-small-cell lung cancer (NSCLC) in a second-line treatment setting. Results from recent phase II and phase III randomised trials testing other ICIs have been presented. In Keynote-024, pembrolizumab, an anti-PD1 antibody, was reported to have great efficacy in the first-line treatment of PDL1 ≥ 50% tumours (30% of screened tumours), with a progression-free survival (PFS, median) of 10.4 months versus 6.0 months with chemotherapy (CT; hazard ratio [HR] = 0.50; 95% confidence interval [95% CI] 0.37-0.68, P < 0.001), overall response rate (ORR) of 45% versus 28% with CT (P = 0.0011), and a 1-year overall survival (OS) of around 70%. In contrast, Checkmate-026 reported that nivolumab failed to show any benefit compared with standard platinum-based CT, with a PFS (median) in the PDL1 ≥ 5% NSCLC group of 4.2 months (nivolumab) versus 5.9 months (CT; HR = 1.15: 95% CI 0.91-1.45, P = 0.25). No benefit was observed in the PDL1 ≥ 50% subgroup. An encouraging report of the efficacy of pembrolizumab in addition to CT in first-line treatment in unselected NSCLC was also presented (Keynote-021) with an ORR of 55% versus 29% with CT alone (P = 0.0016). Atezolizumab, an anti-PDL1 antibody, showed efficacy for second-line treatment compared with docetaxel (OAK phase III study) with an OS (median) of 13.8 months versus 9.6 months with docetaxel. These results suggest a new paradigm for the treatment of advanced NSCLC using pembrolizumab for the first-line treatment of PDL1 ≥ 50% tumours.

Pembrolizumab as first-line therapy for patients with PD-L1-positive advanced non-small cell lung cancer: a phase 1 trial. Hui R1, Garon EB2, Goldman JW2, et al. Ann Oncol. 2017 Apr 1;28(4):874-881. doi: 10.1093/annonc/mdx008.
BACKGROUND: Pembrolizumab improved survival as first- and second-line therapy compared with chemotherapy in patients with highly programmed death ligand 1 (PD-L1) expressing advanced non-small cell lung cancer (NSCLC). We report the long-term safety and clinical activity of pembrolizumab as first-line therapy for patients with advanced NSCLC and the correlation between PD-L1 expression and efficacy. **PATIENTS AND METHODS:** In the open-label phase 1b KEYNOTE-001 trial, treatment-naive patients with advanced NSCLC whose tumors expressed PD-L1 (≥1% staining, assessed using a prototype assay) were randomly assigned to intravenous pembrolizumab 2 or 10 mg/kg every 3 (Q3W) or 2 (Q2W) weeks. Response was assessed per central RECIST v1.1 every 9 weeks in all patients who received ≥1 pembrolizumab dose. Using pre-treatment tumor tissue, a clinical assay quantified the percentage of tumor cells expressing PD-L1 as tumor proportion score (TPS). **RESULTS:** Between 1 March 2013 and 18 September 2015, 101 patients received pembrolizumab 2 mg/kg Q3W (n = 6), 10 mg/kg Q3W (n = 49), or 10 mg/kg Q2W (n = 46). Of these, 27 (26.7%) had TPS ≥50%, 52 (51.5%) had TPS 1%-49%, and 12 (11.9%) had TPS <1%. The objective response rate (ORR) was 27% (27/101, 95% CI 18-37) and median overall survival was 22.1 months (95% CI 17.1-27.2). In patients with PD-L1 TPS ≥50%, ORR, 12-month PFS, and 12-month OS were higher [14/27 (51.9%; 95% CI 32%-71%), 54%,

and 85%, respectively] than the overall population [27/101 (26.7%; 95% CI 18.4%-36.5%), 35%, 71%]. Pembrolizumab was well tolerated, with only 12 (11.9%) patients experiencing grade 3/4 treatment-related adverse events and no treatment-related deaths. **CONCLUSIONS:** Pembrolizumab provides promising long-term OS benefit with a manageable safety profile for PD-L1-expressing treatment-naive advanced NSCLC, with greatest efficacy observed in patients with TPS ≥50%.

Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial.
Liang J1, Bi N1, Wu S2, et al.
BACKGROUND: The optimal chemotherapy regimen administered currently with radiation in patients with stage III non-small cell lung cancer (NSCLC) remains unclear. A multicenter phase III trial was conducted to compare the efficacy of concurrent thoracic radiation therapy with either etoposide/cisplatin (EP) or carboplatin/paclitaxel (PC) in patients with stage III NSCLC. **PATIENTS AND METHODS:** Patients were randomly received 60-66 Gy of thoracic radiation therapy concurrent with either etoposide 50 mg/m2 on days 1-5 and cisplatin 50 mg/m2 on days 1 and 8 every 4 weeks for two cycles (EP arm), or paclitaxel 45 mg/m2 and carboplatin (AUC 2) on day 1 weekly (PC arm). The primary end point was overall survival (OS). The study was designed with 80% power to detect a 17% superiority in 3-year OS with a type I error rate of 0.05. **RESULTS:** A total of 200 patients were randomized and 191 patients were treated (95 in the EP arm and 96 in the PC arm). With a median follow-up time of 73 months, the 3-year OS was significantly higher in the EP arm than that of the PC arm. The estimated difference was 15.0% (95% CI 2.0%-28.0%) and P value of 0.024. Median survival times were 23.3 months in the EP arm and 20.7 months in the PC arm (log-rank test P = 0.095, HR 0.76, 95%CI 0.55-1.05). The incidence of Grade ≥2 radiation pneumonitis was higher in the PC arm (33.3% versus 18.9%, P = 0.036), while the incidence of Grade ≥3 esophagitis was higher in the EP arm (20.0% versus 6.3%, P = 0.009). **CONCLUSION:** EP might be superior to weekly PC in terms of OS in the setting of concurrent chemoradiation for unresectable stage III NSCLC.

Prolactin as a Potential Early Predictive Factor in Metastatic Non-Small Cell Lung Cancer Patients Treated with Nivolumab. Caponnetto S1, Iannantuono GM, Barchiesi G, Magri V, Gelibter A, Cortesi E. Oncology. 2017 Apr 14. doi: 10.1159/000464328. [Epub ahead of print]
BACKGROUND/AIMS: Prolactin (PRL) is a peptide hormone and several studies have demonstrated its role as a cytokine in human T cell-mediated immunity. We are unaware if PRL is a positive or negative immunomodulator, but its effects on the regulation of T cells could inhibit the antitumor activity elicited by nivolumab (NIVO). We aimed to assess whether the occurrence of hyperprolactinemia in metastatic non-small cell lung cancer (mNSCLC) patients treated with NIVO is associated with poor clinical outcomes. **METHODS:** We evaluated 26 mNSCLC patients treated with NIVO. Blood samples were collected in every patient to evaluate PRL basal levels before starting the therapy with NIVO and before each following administration of NIVO. All patients underwent a conventional CT to investigate the effect of therapy according to Immune-related Response Evaluation Criteria in Solid Tumors (IrRECIST). **RESULTS:** Twenty patients (77%) developed hyperprolactinemia during the treatment, whereas 6 patients (23%) had stable levels of PRL during the therapy (p = 0.001). A total of 95% of the 20 patients with hyperprolactinemia had progressive disease (PD), according to CT results, whereas only 2 patients (33%) out of 6 with stable PRL levels had PD (p = 0.004). **CONCLUSIONS:** Hyperprolactinemia in mNSCLC patients treated with NIVO could potentially represent a negative early predictive factor for poor clinical outcomes, thus anticipating PD shown by CT scan.

Treatment Patterns and Early Outcomes of ALK-Positive Non-Small Cell Lung Cancer Patients Receiving Ceritinib: A Chart Review Study. Bendaly E1, Dalal AA2, Culver K2, et al. Adv Ther. 2017 Apr 12. doi: 10.1007/s12325-017-0527-6. [Epub ahead of print]
INTRODUCTION: This study aimed to provide the first real-world description of the characteristics, treatments, dosing patterns, and early outcomes of patients with ALK-positive non-small cell lung cancer (NSCLC) who received ceritinib in US clinical practice. **METHODS:** US oncologists provided data from medical charts of adult patients diagnosed with locally advanced or metastatic ALK-positive NSCLC who received ceritinib following crizotinib. Patient characteristics, treatment patterns, ceritinib dosing, early outcomes, and occurrence of gastrointestinal adverse events (AEs) by dose and instructions on food intake were assessed, and Kaplan-Meier analysis was used to describe clinician-defined progression-free survival (PFS) on ceritinib. **RESULTS:** Medical charts of 58 ALK-positive NSCLC patients treated with ceritinib were reviewed (median age 63 years; 41% male; 21% with prior chemotherapy experience). At ceritinib initiation, 44 patients had multiple distant metastases, most commonly in the liver (60%), bone (53%), and brain (38%). Initial ceritinib dose varied: 71% received 750 mg, 19% 600 mg, and 10% 450 mg. Although median follow-up after ceritinib initiation was short (3.8 months), most patients achieved either a complete or partial response (69%) on ceritinib, regardless of metastatic sites present at initiation or initial dose. Median PFS on ceritinib was 12.9 months. 17% of patients had a gastrointestinal AE reported during follow-up. The majority of events occurred in patients instructed to fast; no patients instructed to take a lower dose of ceritinib with food reported gastrointestinal AEs. **CONCLUSION:** These early findings of ceritinib use in clinical practice suggest that ceritinib is effective at treating crizotinib-experienced ALK-positive NSCLC patients, regardless of metastatic sites or initial dose, and dosing ceritinib with food may lead to fewer gastrointestinal AEs. Future studies with larger sample size and longer follow-up are warranted, including an ongoing randomized trial to assess the gastrointestinal tolerability of ceritinib 450 and 600 mg with low-fat meals. **FUNDING:** Novartis Pharmaceutical Corporation.

Adjuvant Chemotherapy Is Associated With Improved Survival in Locally Invasive Node Negative Non-Small Cell Lung Cancer. Ahmad U1, Crabtree TD2, Patel AP2, et al. Ann Thorac Surg. 2017 Apr 19. pii: S0003-4975(17)30179-0. doi: 10.1016/j.athoracsur.2017.01.069. [Epub ahead of print]
BACKGROUND: The objectives of this study are to explore factors that are associated with use of adjuvant chemotherapy and to evaluate its impact on overall survival in node-negative patients who undergo lung and chest wall resection for non-small cell lung cancer (NSCLC). **METHODS:** Patients who underwent concomitant lung and chest wall resection for NSCLC were abstracted from the National Cancer Database. Clinical, pathologic, treatment, and follow-up data were obtained. Patients with pathologic nodal metastases or patients who received any radiation treatment were excluded, and the cohort was dichotomized based on administration of adjuvant postoperative chemotherapy.
RESULTS: Between 1998 and 2010, 824 patients met the inclusion criteria. This cohort exclusively consisted of pT3 N0 patients who did not receive any induction treatment or adjuvant radiation treatment. Adjuvant chemotherapy was administered to 255 patients (31%). Patients in the chemotherapy group were younger and had shorter inpatient length of stay. Both groups had similar comorbidities, tumor size, unplanned readmission rate, and incomplete resection rate. In multivariable analysis, younger age and shorter length of stay were associated with a greater likelihood of receiving adjuvant chemotherapy. Adjuvant chemotherapy was associated with improved survival (hazard ratio 0.74, 95% CI: 0.6 to 0.9), whereas increasing age, Caucasian race, length of inpatient stay, tumor size, and residual tumor were independently associated with greater risk of death. **CONCLUSIONS:** Patients who undergo lobectomy with chest wall resection for locally advanced NSCLC should be strongly considered for postoperative adjuvant chemotherapy even in the absence of nodal disease. Actual selection of patients for adjuvant chemotherapy is affected by perioperative factors.

Clinical Significance of Prognostic Nutritional Index After Surgical Treatment in Lung Cancer. Okada S1, Shimada J1, Kato D1, Tsunezuka H1, Teramukai S2, Inoue M3. Ann Thorac Surg. 2017 Apr 19. pii: S0003-4975(17)30199-6. doi: 10.1016/j.athoracsur.2017.01.085. [Epub ahead of print]
BACKGROUND: The prognostic nutritional index (PNI), calculated as 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (cells/mm3), can reportedly predict postoperative complications and prognosis for various types of malignancy. However, the clinical significance and prognostic value of the PNI for both short- and long-term outcomes remains uncertain in patients with lung cancer. **METHODS:** We retrospectively reviewed 248 patients with completely resected non-small cell lung cancer (NSCLC). Clinicopathologic characteristics were evaluated according to the PNI, and the prognostic significance for postoperative outcomes was assessed using Cox proportional regression analysis. The survival rate was calculated using the Kaplan-Meier method. **RESULTS:** An optimal cutoff of 48 for recurrence-free survival (RFS) was determined using the minimum p value approach. Old age, low body mass index, large tumor size, and elevated C-reactive protein levels correlated significantly with low PNI. Logistic regression analysis demonstrated that low PNI status was statistically related to postoperative complications (Clavien-Dindo grade ≥II) and pulmonary air leakage. Five-year overall survival (OR) rates in the high- and low-PNI groups were 80.6% and 58.5%, respectively ($p = 0.002$). Five-year RFS rates were 73.6% and 48.6%, respectively ($p < 0.001$). Furthermore, PNI was identified as an independent prognostic factor for OS (hazard ratio [HR], 2.18; 95% confidence interval [CI], 1.08-4.21) and RFS (HR, 2.57; 95% CI, 1.46-4.38) by multivariate analysis. **CONCLUSIONS:** The PNI could represent a useful biomarker to predict postoperative complications and survival in patients with completely resected NSCLC.

Assessment of drug-drug interaction potential between ceritinib and proton pump inhibitors in healthy subjects and in patients with ALK-positive non-small cell lung cancer. Lau YY1, Gu W2, Lin T2, Viraswami-Appanna K2, Cai C2, Scott JW2, Shi M2. Cancer Chemother Pharmacol. 2017 Apr 19. doi: 10.1007/s00280-017-3308-7. [Epub ahead of print]
PURPOSE: The impact of proton pump inhibitors (PPIs) on the pharmacokinetics (PK) and efficacy of ceritinib was evaluated. **METHODS:** A healthy subject drug-drug interaction (DDI) study was conducted to assess the effect of esomeprazole on the PK of a single 750 mg dose of ceritinib. To further investigate the impact of PPIs on the PK and efficacy of ceritinib in ALK-positive cancer patients, two subgroup analyses were performed. Analysis 1 evaluated ceritinib steady-state trough concentration (Ctrough,ss) and overall response rate (ORR) by concomitant use of PPIs in patients from the ASCEND-1, -2, and -3 studies; analysis 2 evaluated ceritinib single-dose and steady-state AUC0-24h and C max by concomitant PPI use in patients from ASCEND-1 using a definition of PPI usage similar to that used in the healthy subject study. **RESULTS:** In the healthy subject study, co-administration of a single 750 mg dose of ceritinib with esomeprazole 40 mg for 6 days decreased ceritinib AUC0-∞ by 76% and C max by 79%. However, based on subgroup analysis 1, patients had similar C trough,ss and ORR regardless of concomitant PPI usage. Based on analysis 2, co-administration of a single 750 mg ceritinib dose with PPIs for 6 days in patients suggested less effect on ceritinib exposure than that observed in healthy subjects as AUC0-24h decreased by 30% and C max decreased by 25%. No clinically meaningful effect on steady-state exposure was observed after daily dosing. **CONCLUSIONS:** Long-term administration of ceritinib with PPIs does not adversely affect the PK and efficacy of ceritinib in ALK-positive cancer patients.

Triplet therapy with afatinib, cetuximab and bevacizumab induces deep remission in lung cancer cells harboring EGFR T790M in vivo. Kudo K1, Ohashi K2, Makimoto G1, et al. Mol Oncol. 2017 Apr 7. doi: 10.1002/1878-0261.12063. [Epub ahead of print]
Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have changed the treatment strategy for EGFR-mutant lung cancers; however, resistance usually occurs due to a secondary mutation, T790M, in EGFR. Combination therapy using afatinib and cetuximab has had good results in lung tumors harboring EGFRT790M mutations in clinical trials. The effect of bevacizumab, an anti-vascular endothelial growth factor (VEGF) antibody, combined with EGFR-TKIs has also been investigated. We hypothesized that the dosage of afatinib and cetuximab could be reduced by combination with bevacizumab, and that the triplet therapy may result in better tumor inhibition with tolerable toxicity. Using a xenograft mouse model with H1975-harboring EGFRL858R+T790M and RPC-9-harboring EGFR19DEL+T790M , we tested the efficacy of the triplet therapy with a modified dosage of afatinib, cetuximab, and bevacizumab, and compared this therapy to single and double therapies. Triplet therapy with afatinib, cetuximab, and bevacizumab induced pathological complete remission in xenograft tumors with H1975 and RPC-9 cells versus tumors treated with single- or double-therapies. We saw no body weight loss in the mice. The triple therapy induced a significant reduction in CD31-positive vascular endothelial cells and increased cleaved caspase-3-positive cells in the tumors. This suggests that one mechanism underlying the deep remission could be suppression of neovascularization and induction of apoptosis by intensive inhibition of driver oncoproteins and VEGF. These results highlight the potential of afatinib, cetuximab, and bevacizumab to induce deep remission in tumors harboring EGFRT790M mutations. Therefore, clinical trials of this combination therapy are warranted.

NSCLC - RADIOTHERAPY

Variations of target volume definition and daily target volume localization in stereotactic body radiotherapy for early-stage non-small cell lung cancer patients under abdominal compression. Han C1, Sampath S2, Schultheisss TE2, Wong JYC2. Med Dosim. 2017 Apr 19. pii: S0958-3947(17)30018-3. doi: 10.1016/j.meddos.2017.01.008. [Epub ahead of print]
We aimed to compare gross tumor volumes (GTV) in 3-dimensional computed tomography (3DCT) simulation and daily cone beam CT (CBCT) with the internal target volume (ITV) in 4-dimensional CT (4DCT) simulation in stereotactic body radiotherapy (SBRT) treatment of patients with early-stage non-small cell lung cancer (NSCLC) under abdominal compression. We retrospectively selected 10 patients with NSCLC who received image-guided SBRT treatments under abdominal compression with daily CBCT imaging. GTVs were contoured as visible gross tumor on the planning 3DCT and daily CBCT, and ITVs were contoured using maximum intensity projection (MIP) images of the planning 4DCT. Daily CBCTs were registered with 3DCT and MIP images by matching of bony landmarks in the thoracic region to evaluate interfractional GTV position variations. Relative to MIP-based ITVs, the average 3DCT-based GTV volume was 66.3 ± 17.1% (range: 37.5% to 92.0%) ($p < 0.01$ in paired t-test), and the average CBCT-based GTV volume was 90.0 ± 6.7% (daily range: 75.7% to 107.1%) ($p = 0.02$). Based on bony anatomy matching, the center-of-mass coordinates for CBCT-based GTVs had maximum absolute shift of 2.4 mm (left-right), 7.0 mm (anterior-posterior [AP]), and 5.2 mm (superior-inferior [SI]) relative to the MIP-based ITV. CBCT-based GTVs had average overlapping ratio of 81.3 ± 11.2% (range: 45.1% to 98.9%) with the MIP-based ITV, and 57.7 ± 13.7% (range: 35.1% to 83.2%) with the 3DCT-based GTV. Even with abdominal compression, both 3DCT simulations and daily CBCT scans significantly underestimated the full range of tumor motion. In daily image-guided patient setup corrections, automatic bony anatomy-based image registration could lead to target misalignment. Soft tissue-based image registration should be performed for accurate treatment delivery.

A phase I/II study on stereotactic body radiotherapy with real-time tumor tracking using CyberKnife based on the Monte Carlo algorithm for lung tumors. Iwata H1,2, Ishikura S3, Murai T3, et al. Int J Clin Oncol. 2017 Apr 20. doi: 10.1007/s10147-017-1123-0. [Epub ahead of print]
BACKGROUND: In this phase I/II study, we assessed the safety and initial efficacy of stereotactic body radiotherapy (SBRT) for lung tumors with real-time tumor tracking using CyberKnife based on the Monte Carlo algorithm. **METHODS:** Study subjects had histologically confirmed primary non-small-cell lung cancer staged as T1a-T2aN0M0 and pulmonary oligometastasis. The primary endpoint was the incidence of Grade ≥3 radiation pneumonitis (RP) within 180 days of the start of SBRT. The secondary endpoint was local control and overall survival rates. Five patients were initially enrolled at level 1 [50 Gy/4 fractions (Fr)]; during the observation period, level 0 (45 Gy/4 Fr) was opened. The dose was escalated to the next level when grade ≥3 RP was observed in 0 out of 5 or 1 out of 10 patients. Virtual quality assurance planning was performed for 60 Gy/4 Fr; however, dose constraints for the organs at risk did not appear to be within acceptable ranges. Therefore, level 2 (55 Gy/4 Fr) was regarded as the upper limit. After the recommended dose (RD) was established, 15 additional patients were enrolled at the RD. The prescribed dose was normalized at the 95% volume border of the planning target volume based on the Monte Carlo algorithm. **RESULTS:** Between September 2011 and September 2015, 40 patients (primary 30; metastasis 10) were enrolled. Five patients were enrolled at level 0, 15 at level 1, and 20 at level 2. Only one grade 3 RP was observed at level 1. Two-year local control and overall survival rates were 98 and 81%, respectively. **CONCLUSION:** The RD was 55 Gy/4 Fr. SBRT with real-time tumor tracking using CyberKnife based on the Monte Carlo algorithm was tolerated well and appeared to be effective for solitary lung tumors.

Changes in systemic immune response after stereotactic ablative radiotherapy. Preliminary results of a prospective study in patients with early lung cancer. Rutkowski J, Ślebioda T, Kmieć Z, Zaucha R. Pol Arch Intern Med. 2017 Apr 28;127(4):245-253. doi: 10.20452/pamw.3997. Epub 2017 Apr 18.
INTRODUCTION: Non small cell lung cancer (NSCLC) is the most common lung tumor. Conventional conservative treatment in medically inoperable patients with early stage NSCLC has poor outcome. To improve treatment efficacy, stereotactic ablative radiotherapy (SABR) has been developed, which enables the delivery of high dose radiation to the tumor. OBJECTIVES This prospective study was conducted to confirm the hypothesis that a sudden death of cancer cells after SABR may lead to changes in systemic immune response. **PATIENTS AND METHODS**: We enrolled 89 treatment naive patients with stage T1/2aN0 NSCLC. All patients received SABR, in accordance with treatment standards at our department. Blood samples were collected 3 times: before treatment (n = 89), and then at 2 (n = 86) and 12 weeks (n = 75) after treatment completion to assess the proportion of CD4(+) and CD8(+) T cells, and the expression of T lymphocyte transcription factors: T bet, GATA 3, ROR γt, and FoxP3. Serum C reactive protein (CRP) levels, absolute neutrophil count (ANC), absolute lymphocyte count, and white blood cell (WBC) count were measured to exclude the impact of nonspecific inflammatory reaction. The expression levels of lymphocyte antigens were measured by flow cytometry. **RESULTS:** Serum CRP levels, ANC, and WBC count remained stable during the study. We observed slight lymphopenia correlating with irradiated lung volume. After SABR, the proportion of CD8(+), CD4(+), as well as the proportion of CD4(+) T cells expressing GATA 3(+), T bet(+), or ROR γt(+) increased, while the number of CD4(+)FoxP3(+) cells (specific for regulatory T cells) decreased. **CONCLUSIONS:** Our findings may suggest that SABR enhances the systemic immune response by increasing the proportion of proinflammatory T cell subpopulations.

Does the addition of postoperative radiotherapy to adjuvant chemotherapy offer any benefit in patients with non-small cell lung cancer and mediastinal lymphadenopathy? Koulaxouzidis G1, Toufektzian L2, Ashrafian L2, Veres L2. Interact Cardiovasc Thorac Surg. 2017 Apr 1;24(4):625-630. doi: 10.1093/icvts/ivw380.
A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was whether the addition of postoperative radiotherapy (PORT) to adjuvant chemotherapy offers any benefit in patients undergoing curative resection for non-small cell lung cancer found to harbour mediastinal lymphadenopathy. A total of 77 papers were identified using the reported search, of which 11 represented the best evidence to answer the clinical question. Only studies reporting on survival data of patients receiving adjuvant chemotherapy with and without PORT were included in this analysis. The authors, date, journal, country, study type, population, outcomes and key results are tabulated. Six studies reported a statistically significant positive impact of PORT on long-term or disease-free survival (DFS) (P = 0.048-0.0001). Five more studies found no difference in terms of survival between patients receiving and not receiving PORT. Among the 11 studies, only two were randomized controlled, with one of them reporting improved disease-free (P = 0.041) but not overall survival (P = 0.073), while the other finding no difference in survival. Furthermore, three more studies reported on DFS and/or locoregional recurrence of the disease. One of these studies reported a significantly improved DFS among patients receiving PORT (P = 0.003), while two of them reported a reduced rate of locoregional recurrence in this group (P = 0.032-0.009). Many studies report a positive effect of PORT when combined in parallel or sequentially with adjuvant chemotherapy in terms of long-term, disease free survival or locoregional control of the disease in patients who have undergone surgical resection of NSCLC and are found to harbour N2 disease. However, these reports are counterbalanced by an almost equal number of studies which show no difference between PORT and no PORT. Only one study reported significantly increased radiation related adverse effects in patients undergoing chemotherapy and PORT.

SMALL CELL LUNG CANCER - SCLC

Surgery for limited-stage small-cell lung cancer. Barnes H1, See K2, Barnett S3, Manser R4. Cochrane Database Syst Rev. 2017 Apr 21;4:CD011917. doi: 10.1002/14651858.CD011917.pub2. [Epub ahead of print]
BACKGROUND: Current treatment guidelines for limited-stage small-cell lung cancer (SCLC) recommend concomitant platinum-based chemo-radiotherapy plus prophylactic cranial irradiation, based on the premise that SCLC disseminates early, and is chemosensitive. However, although there is usually a favourable initial response, relapse is common and the cure rate for limited-stage SCLC remains relatively poor. Some recent clinical practice guidelines have recommended surgery for stage 1 (limited) SCLC followed by adjuvant chemotherapy, but this recommendation is largely based on the findings of observational studies. **OBJECTIVES:** To determine whether, in patients with limited-stage SCLC, surgical resection of cancer improves overall survival and treatment-related deaths compared with radiotherapy or chemotherapy, or a combination of radiotherapy and chemotherapy, or best supportive care. **SEARCH METHODS:** We performed searches on CENTRAL, MEDLINE, Embase, CINAHL, and Web of Science up to 11 January 2017. We handsearched review articles, clinical trial registries, and reference lists of retrieved articles. **SELECTION CRITERIA:** We included randomised controlled trials (RCTs) with adults diagnosed with limited-stage SCLC, confirmed by cytology or histology, and radiological assessment, considered medically suitable for resection and radical radiotherapy, which randomised participants to surgery versus any other intervention. **DATA COLLECTION AND ANALYSIS:** We imported studies identified by the search into a reference manager database. We retrieved the full-text version of relevant studies, and two review authors independently extracted data. The primary outcome measures were overall survival and treatment-related deaths; and secondary

outcome measures included loco-regional progression, quality of life, and adverse events. **MAIN RESULTS:** We included three trials with 330 participants. We judged the quality of the evidence as very low for all the outcomes. The quality of the data was limited by the lack of complete outcome reporting, unclear risk of bias in the methods in which the studies were conducted, and the age of the studies (> 20 years). The methods of cancer staging and types of surgical procedures, which do not reflect current practice, reduced our confidence in the estimation of the effect.Two studies compared surgery to radiation therapy, and in one study chemotherapy was administered to both arms. One study administered initial chemotherapy, then responders were randomised to surgery versus control; following, both groups underwent chest and whole brain irradiation.Due to the clinical heterogeneity of the trials, we were unable to pool results for meta-analysis.All three studies reported overall survival. One study reported a mean overall survival of 199 days in the surgical arm, compared to 300 days in the radiotherapy arm (P = 0.04). One study reported overall survival as 4% in the surgical arm, compared to 10% in the radiotherapy arm at two years. Conversely, one study reported overall survival at two years as 52% in the surgical arm, compared to 18% in the radiotherapy arm. However this difference was not statistically significant (P = 0.12).One study reported early postoperative mortality as 7% for the surgical arm, compared to 0% mortality in the radiotherapy arm. One study reported the difference in mean degree of dyspnoea as -1.2 comparing surgical intervention to radiotherapy, indicating that participants undergoing radiotherapy are likely to experience more dyspnoea. This was measured using a non-validated scale. **AUTHORS' CONCLUSIONS:** Evidence from currently available RCTs does not support a role for surgical resection in the management of limited-stage small-cell lung cancer; however our conclusions are limited by the quality of the available evidence and the lack of contemporary data. The results of the trials included in this review may not be generalisable to patients with clinical stage 1 small-cell lung cancer carefully staged using contemporary staging methods. Although some guidelines currently recommend surgical resection in clinical stage 1 small-cell lung cancer, prospective randomised controlled trials are needed to determine if there is any benefit in terms of short- and long-term mortality and quality of life compared with chemo-radiotherapy alone.

The role of postoperative radiotherapy (PORT) in combined small cell lung cancer (C-SCLC).
Men Y1, Luo Y2, Zhai Y1, Liang J1, Feng Q1, Chen D1, Xiao Z1, Zhou Z1, Hui Z3, Wang L1. Oncotarget. 2017 Apr 6. doi: 10.18632/oncotarget.16885. [Epub ahead of print]
PURPOSE: To explore the value of radiotherapy in C-SCLC patients, especially in those receiving a radical resection. **RESULTS:** The differences of survivals between the postoperative radiotherapy (PORT) and non-PORT groups were not statistically significant. But analyzing the benefits in subgroups, PORT significantly improved OS (p = 0.015), DFS (p = 0.026), LRFS (p = 0.008) and DMFS (p = 0.030) in stage III patients. For the patients with N2 stage, all survivals of the PORT group were also statistically significantly higher than non-PORT group (p = 0.018, 0.032, 0.008, 0.042). Patients with more than 10% of metastatic lymph nodes could get a significant benefit survivals by receiving PORT (p = 0.033, 0.030, 0.025, 0.031). Having a systematic dissection of more than 17 lymph nodes was a subset which could get better OS and LRFS by receiving PORT (p = 0.045, 0.048). **METHODS:** Between Jan. 2004 to Dec. 2012, fifty-five patients diagnosed as C-SCLC after complete surgical resection in our center were retrospectively analyzed. The overall survival (OS), disease free survival (DFS), loco-regional recurrence free survival (LRFS), and distant metastasis free survival (DMFS) were calculated by Kaplan-Meier method. **CONCLUSIONS:** PORT can significantly improve the survival of C-SCLC patients with resected pathological pN2 stage. For the patients with a large percent of metastatic lymph nodes, PORT can also improve survivals.

Prognostic significance of cachexia score assessed by CT in male patients with small cell lung cancer. Kim EY1, Lee HY1, Kim YS2, et al. Eur J Cancer Care (Engl). 2017 Apr 20. doi: 10.1111/ecc.12695. [Epub ahead of print]
To determine the prognostic significance of CT-determined cachexia scores (CSs) in 127 consecutive male small cell lung cancer (SCLC) patients, cross-sectional areas of muscle and fat tissues at the third lumbar vertebra (L3) were retrospectively measured on baseline CT images. CSs were determined based on the presence of sarcopenia and/or adipopenia. According to the presence of sarcopenia (L3 muscle index <55 cm2 /m2 , 86.8%) and adipopenia (L3 fat index <22 cm2 /m2 , 11.8%), CSs were defined as follows: CS2 (sarcopenia and adipopenia, 11.8%), CS1 (sarcopenia only, 74.8%) and CS0 (13.4%). CS2 was significantly related to lower body mass index ($p < .001$) and poor performance status ($p = .002$), and patients with CS2 had shorter OS than patients with CS1 or CS0 (median OS, 5.0 months vs. 8.9 months vs. 18.3 months; $p = .007$). Multivariable analysis revealed that CS was an independent prognostic factor of poor survival (HR, 1.99 for CS1 and 2.59 for CS2, $p = .036$ and .023, CS0 as a reference), along with extensive stage ($p < .001$), supportive care only ($p < .001$) and an elevated lactate dehydrogenase ($p = .005$). CT-determined CSs, based on the presence of sarcopenia and/or adipopenia, could be used to predict prognosis in male SCLC.

Progress and challenges in the treatment of small cell lung cancer. Tartarone A1, Giordano P2, Lerose R3, Rodriquenz MG2, Conca R2, Aieta M2. Med Oncol. 2017 Jun;34(6):110. doi: 10.1007/s12032-017-0966-6. Epub 2017 Apr 29.
Small cell lung cancer (SCLC) is a very aggressive malignancy characterized by high cellular proliferation and early metastatic spread. In fact, although SCLC is a chemosensitive and radiosensitive disease, the initial responsiveness to chemotherapy is usually followed by development of resistance and the prognosis remains poor with a median survival of less than 12 months in patients with extensive disease (ED-SCLC). Furthermore, no significant progress has been made over the last years, with no newly approved drug. For all these reasons, SCLC represents for the oncologists a major challenge and an exciting field of clinical research. In this review, we analyze the most promising advances in development for SCLC with a special focus on antiangiogenic treatments, immunotherapy, novel chemotherapeutic and targeted agents.

Evaluation of short-term and long-term efficacy of surgical and non-surgical treatment in patients with early-stage small cell lung cancer: A comparative study. Hou SZ, Cheng ZM, Wu YB, Sun Y, Liu B, Yuan MX, Wang XD. Cancer Biomark. 2017 Apr 21. doi: 10.3233/CBM-160332. [Epub ahead of print]
OBJECTIVE: The aim of this study is to compare surgery with adjuvant chemoradiotherapy versus non-surgical treatments for patients with early-stage small cell lung cancer (SCLC) based on the short-term and long-term efficacy. **METHODS:** SCLC patients who underwent a pulmonary lobectomy with post-surgical radiotherapy or chemotherapy were assigned to the surgical group. SCLC patients who received radiotherapy or chemotherapy alone were classified into the non-surgical group. The clinical efficacy was evaluated as complete remission (CR), partial remission (PR), stable disease (SD), or progressive disease (PD). The total effectiveness rate was calculated as CR + PR. The 1-, 3-, and 5-year survival rates of the two groups were compared. **RESULTS:** Compared with the non-surgical group, the CR rate and the total effectiveness rate were higher in the surgical group, and the total effectiveness rate for male patients and patients without a smoking history were also higher in the surgical group. Distant metastasis and local recurrence concurrent with distant metastasis in the surgical group were both lower in the surgical group than in the non-surgical group. Compared with the non-surgical group, the local recurrence in male patients was lower in the surgical group, and patients in the surgical group had lower distant metastasis at TNM stage IIb. The 1-, 3-, and 5-year survival rates were higher in the surgical group than in the non-

surgical group. **CONCLUSION:** These findings indicate that for patients with early-stage SCLC, better scores in effectiveness rate, disease progression, and 1-, 3-, and 5-year survival rates were observed in patients who underwent surgery followed by adjuvant chemoradiotherapy when compared with patients without surgical treatment.

Changing epidemiology of elderly small cell lung cancer patients over the last 40 years; a SEER database analysis. Abdel-Rahman O1. Clin Respir J. 2017 Apr 1. doi: 10.1111/crj.12632. [Epub ahead of print]
BACKGROUND: Small cell lung cancer (SCLC) is a distinct clinical and pathological entity within the spectrum of lung cancer. It was observed that the relative age distribution of the disease changed over years. **METHODS:** Surveillance, epidemiology, and end results (SEER) database (1973-2013) was utilized to determine the incidence, presentation and treatment outcomes of elderly patients (>70 years) with SCLC. Join point regression analysis was then conducted to analyze age-adjusted trends in incidence for the elderly as well as the whole SCLC population. Survival analysis was conducted through Kaplan-Meier analysis. Clinicopathological characteristics and survival outcomes were compared between patients diagnosed at 70-79 years old and those older than 80 years old (octogenarian group). **RESULTS:** The proportion of elderly patients among all cases of SCLC increased from 23% in 1975 to 44% in 2010. Moreover, the proportion of elderly female patients among all cases of elderly SCLC increased from 25% in 1975 to 49% in 2010. When categorizing patients into four subgroups "70-74," "75-79," "80-84," and "85+", there was a trend toward a lower cancer-specific survival with increasing age ($P < .0001$). A limited improvement in 5-year survival was observed during the study period and it is less apparent as the age increases. **CONCLUSION:** The proportion of elderly patients among all cases of SCLC has increased over the past 40 years. Further studies are needed to better select appropriate treatments for this subset of patients.

Correlation between histone acetylation and expression of Notch1 in human lung carcinoma and its possible role in combined small-cell lung carcinoma. Hassan WA1,2, Takebayashi SI3, Abdalla MOA4,5, et al. Lab Invest. 2017 Apr 17. doi: 10.1038/labinvest.2017.36. [Epub ahead of print]
Combined small-cell lung carcinoma (cSCLC) is composed of small-cell lung carcinoma (SCLC) admixed with non-small-cell lung carcinoma (NSCLC). Evaluating the molecular differences between SCLC and NSCLC could lead to a better understanding of the pathogenesis of such neoplasms. Therefore, in this study, we investigated the correlation between histone acetylation and Notch1 expression in lung carcinoma. Using chromatin immunoprecipitation (ChIP) assay, we measured the level of acetylated histone H3 around the promoter region of Notch1 in SCLC and NSCLC cells. We then treated SCLC cells with trichostatin A (TSA) and characterized the level of histone H3 acetylation at Notch1. In addition, TSA-treated cells were injected into immune-compromised mice, for analysis of the ex vivo tumor xenograft phenotype. The level of acetylated histone H3 surrounding the Notch1 promoter was lower in lung cancer cells not expressing Notch1. Tumors originated from TSA-treated SCLC cells occasionally formed an epithelial-like glandular arrangement of cells; with Notch1 expression and decreased expression of neuroendocrine (NE) markers. Histone deacetylation around the promoter region of Notch1 inhibits Notch1 protein expression in SCLC and the restoration of Notch1 expression in SCLC leads to the concurrent appearance of epithelial-like areas within the SCLC, which could provide a possible mechanism for histogenesis of cSCLC.Laboratory Investigation advance online publication, 17 April 2017; doi:10.1038/labinvest.2017.36.

The role of postoperative radiotherapy (PORT) in combined small cell lung cancer (C-SCLC).
Men Y1, Luo Y2, Zhai Y1, Liang J1, Feng Q1, Chen D1, Xiao Z1, Zhou Z1, Hui Z3, Wang L1.
Department of Radiation Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China. Oncotarget. 2017 Apr 6. doi: 10.18632/oncotarget.16885. [Epub ahead of print]
PURPOSE: To explore the value of radiotherapy in C-SCLC patients, especially in those receiving a radical resection. **RESULTS:** The differences of survivals between the postoperative radiotherapy (PORT) and non-PORT groups were not statistically significant. But analyzing the benefits in subgroups, PORT significantly improved OS (p = 0.015), DFS (p = 0.026), LRFS (p = 0.008) and DMFS (p = 0.030) in stage III patients. For the patients with N2 stage, all survivals of the PORT group were also statistically significantly higher than non-PORT group (p = 0.018, 0.032, 0.008, 0.042). Patients with more than 10% of metastatic lymph nodes could get a significant benefit survivals by receiving PORT (p = 0.033, 0.030, 0.025, 0.031). Having a systematic dissection of more than 17 lymph nodes was a subset which could get better OS and LRFS by receiving PORT (p = 0.045, 0.048). **METHODS:** Between Jan. 2004 to Dec. 2012, fifty-five patients diagnosed as C-SCLC after complete surgical resection in our center were retrospectively analyzed. The overall survival (OS), disease free survival (DFS), loco-regional recurrence free survival (LRFS), and distant metastasis free survival (DMFS) were calculated by Kaplan-Meier method. **CONCLUSIONS:** PORT can significantly improve the survival of C-SCLC patients with resected pathological pN2 stage. For the patients with a large percent of metastatic lymph nodes, PORT can also improve survivals.

PALLIATIVE AND SUPPORTIVE CARE

Association between aggressive care and bereaved families' evaluation of end-of-life care for veterans with non-small cell lung cancer who died in Veterans Affairs facilities.
Ersek M1,2, Miller SC3, Wagner TH4,5, et al. Cancer. 2017 Apr 17. doi: 10.1002/cncr.30700. [Epub ahead of print]
BACKGROUND: To the authors' knowledge, little is known regarding the relationship between patients' and families' satisfaction with aggressive end-of-life care. Herein, the authors examined the associations between episodes of aggressive care (ie, chemotherapy, mechanical ventilation, acute hospitalizations, and intensive care unit admissions) within the last 30 days of life and families' evaluations of end-of-life care among patients with non-small cell lung cancer (NSCLC). **METHODS:** A total of 847 patients with NSCLC (34% of whom were aged <65 years) who died in a nursing home or intensive care, acute care, or hospice/palliative care (HPC) unit at 1 of 128 Veterans Affairs Medical Centers between 2010 and 2012 were examined. Data sources included Veterans Affairs administrative and clinical data, Medicare claims, and the Bereaved Family Survey. The response rate for the Bereaved Family Survey was 62%.
RESULTS: Greater than 72% of veterans with advanced lung cancer who died in an inpatient setting had at least 1 episode of aggressive care and 31% received chemotherapy within the last 30 days of life. For all units except for HPC, when patients experienced at least 1 episode of aggressive care, bereaved families rated care lower compared with when patients did not receive any aggressive care. For patients dying in an HPC unit, the associations between overall ratings of care and ≥2 inpatient admissions or any episode of aggressive care were not found to be statistically significant. Rates of aggressive care were not associated with age, and family ratings of care were similar for younger and older patients.
CONCLUSIONS: Aggressive care within the last month of life is common among patients with NSCLC and is associated with lower family evaluations of end-of-life care. Specialized care provided within an HPC unit may mitigate the negative effects of aggressive care on these outcomes. Cancer 2017. © 2017 American Cancer Society.

Interrelationships Between Health Behaviors and Coping Strategies Among Informal Caregivers of Cancer Survivors. Litzelman K1,2, Kent EE3, Rowland JH3. Health Educ Behav. 2017 Apr 1:1090198117705164. doi: 10.1177/1090198117705164. [Epub ahead of print]
BACKGROUND: Recent research among cancer survivors suggests that health behaviors and coping are intertwined, with important implications for positive behavior change and health. Informal caregivers may have poor health behaviors, and caregivers' health behaviors have been linked to those of survivors. **AIMS:** This hypothesis generating study assessed the correlations among health behaviors and coping strategies in a population of lung and colorectal cancer caregivers. **METHOD:** This cross-sectional study used data from the Cancer Care Outcomes Research & Surveillance Consortium. Caregivers (n = 1,482) reported their health behaviors, coping, and sociodemographic and caregiving characteristics. Descriptive statistics assessed the distribution of caregivers' health and coping behaviors, and multivariable linear regressions assessed the associations between health behaviors and coping styles. **RESULTS:** Many informal caregivers reported regular exercise (47%) and adequate sleep (37%); few reported smoking (19%) or binge drinking (7%). Problem-focused coping was associated with greater physical activity and less adequate sleep (effect sizes [ESs] up to 0.21, $p < .05$). Those with some physical activity scored higher on emotion-focused coping, while binge drinkers scored lower (ES = 0.16 and 0.27, $p < .05$). Caregivers who reported moderate daily activity, current smoking, binge drinking, and feeling less well rested scored higher on dysfunctional coping (ES up to 0.49, $p < .05$). **DISCUSSION:** Health behaviors and coping strategies were interrelated among informal cancer caregivers. The relationships suggest avenues for future research, including whether targeting both factors concurrently may be particularly efficacious at improving informal caregiver self-care. **CONCLUSION:** Understanding the link between health behaviors and coping strategies may inform health behavior research and practice.

The influence of different muscle mass measurements on the diagnosis of cancer cachexia. Blauwhoff-Buskermolen S1,2, Langius JAE1,3, Becker A4, Verheul HMW2, de van der Schueren MAE1,5. J Cachexia Sarcopenia Muscle. 2017 Apr 26. doi: 10.1002/jcsm.12200. [Epub ahead of print]
BACKGROUND: Progressive loss of muscle mass is a major characteristic of cancer cachexia. Consensus definitions for cachexia provide different options to measure muscle mass. This study describes the effect of different methods to determine muscle mass on the diagnosis of cancer cachexia. In addition, the association of cachexia with other features of cachexia, quality of life, and survival was explored. **METHODS:** Prior to chemotherapy, cachexia was assessed by weight loss, body mass index, and muscle mass measurements, the latter by mid-upper arm muscle area (MUAMA), computed tomography (CT) scans, and bio-electrical impedance analysis (BIA). In addition, appetite, inflammation, muscle strength, fatigue, quality of life, and survival were measured, and associations with cachexia were explored. **RESULTS:** Included were 241 patients with advanced cancer of the lung (36%), colon/rectum (31%), prostate (18%), or breast (15%). Mean age was 64 ± 10 years; 54% was male. Prevalence of low muscle mass was as follows: 13% with MUAMA, 59% with CT, and 93% with BIA. In turn, the prevalence of cachexia was 37, 43, and 48%, whereby weight loss >5% was the most prominent component of being defined cachectic. Irrespective of type of muscle measurement, patients with cachexia presented more often with anorexia, inflammation, low muscle strength, and fatigue and had lower quality of life. Patients with cachexia had worse overall survival compared with patients without cachexia: HRs 2.00 (1.42-2.83) with MUAMA, 1.64 (1.15-2.34) with CT, and 1.50 (1.05-2.14) with BIA. **CONCLUSIONS:** Although the prevalence of low muscle mass in patients with cancer depended largely on the type of muscle measurement, this had little influence on the diagnosis of cancer cachexia (as the majority of patients was already defined cachectic based on weight loss). New studies are warranted to further elucidate the additional role of muscle measurements in the diagnosis of cachexia and the association with clinical outcomes.

Playing the odds: lung cancer surveillance after curative surgery. Chang CF1, Gould M. Curr Opin Pulm Med. 2017 Apr 11. doi: 10.1097/MCP.0000000000000381. [Epub ahead of print]
PURPOSE OF REVIEW: After so-called 'curative' resection, many patients are still at risk for further lung cancer, either as a recurrence or a new metachronous primary. In theory, close follow-up should improve survival by catching relapse early - but in reality, many experts feel that surveillance for recurrence is a waste of time and money. In this article, we explore the reasons behind the controversy, what the current guidelines recommend, and what future solutions are in development that may ultimately resolve this debate. **RECENT FINDINGS:** Although postoperative surveillance for a new lung cancer has been demonstrated to impart a survival advantage, this benefit does not appear to extend to the setting of recurrence. Nevertheless, close radiographic follow-up after curative resection is still recommended by most professional societies, with more frequent scanning in the first 2 years, and then annual screening thereafter. Given the radiation risk, however, low-dose and minimal-dose computed tomography options are under investigation, as well as timing scans around expected peaks of recurrence rather than a set schedule. **SUMMARY:** Applying the same surveillance algorithm to all lung cancer patients after curative resection may not be cost-effective or reasonable, especially if there is no demonstrable mortality benefit. Therefore, future research should focus on finding safer nonradiographic screening options, such as blood or breath biomarkers, or developing nonograms for predicting which patients will relapse and require closer follow-up. Ultimately, however, better tools for surveillance may be moot until we develop better treatment options for lung cancer recurrence.

Malnutrition and Quality of Life in Patients with Non-Small-Cell Lung Cancer. Polański J1, Jankowska-Polańska B2, Uchmanowicz I2, Chabowski M3,4, Janczak D5, Mazur G6, Rosińczuk J7. Adv Exp Med Biol. 2017 Apr 6. doi: 10.1007/5584_2017_23. [Epub ahead of print]
Progressive weight loss, common reduces performance and quality of life in patients with advanced lung cancer. However, there is a paucity of studies that focus on nutritional status and quality of life of non-small cell lung cancer (NSCLC) patients. The present study seeks to determine the nutritional status, and its relation to quality of life, of NSCLC patients. One hundred and eighty NSCLC patients (mean age 62.8 ± 9.6 years) were evaluated during therapy at the Lower Silesian Center of Lung Diseases in Wroclaw, Poland. Nutritional status was evaluated by means of the Mini-Nutritional Assessment (MNA) and quality of life by means of two instruments developed by the European Organization for the Research and Treatment of Cancer (EORTC): QLQ-C30 and QLQ-LC13 questionnaires. The MNA revealed that up to 51.1% of patients were undernourished, 23.9% were at risk of malnutrition, and only 25.0% showed a normal nutrition. The well-nourished respondents evaluated their quality of life better in all functional scales (33.3 vs. 41.7 vs. 66.7, respectively) and presented less intensive symptoms in general QLQ-C30 and specific LC13 questionnaires. In univariate analysis, malnutrition significantly correlated with decreased quality of life and the intensity of symptoms in both questionnaires. In multivariate analysis, malnutrition was an independent determinant of decreased quality of life in physical functioning domain ($\beta = -0.015$; $p < 0.001$). We conclude that malnutrition has an impact on quality of life and on the presentation of symptoms in NSCLC patients. Therefore, nutritional care should be integrated into the global oncology as an adjunct to symptomatic treatment.

Feasibility and Acceptability of "Healthy Directions" a Lifestyle Intervention for Adults with Lung Cancer. Blok AC1, Blonquist TM2, Nayak MM2, et al. Psychooncology. 2017 Apr 20. doi: 10.1002/pon.4443. [Epub ahead of print]
OBJECTIVE: The aims of this feasibility study of an adapted lifestyle intervention for adults with lung cancer were to: 1) determine rates of enrollment, attrition and completion of five nurse-patient contacts, 2) examine demographic characteristics of those more likely to enroll into the program, 3) determine acceptability of the intervention, and 4) identify patient preferences for the format of supplemental

educational intervention materials. **METHODS:** This study used a single arm, pre-and post-test design. Feasibility was defined as > 20% enrollment and a completion rate of 70% for five nurse-patient contact sessions. Acceptability was defined as 80% of patients recommending the program to others. Data was collected through electronic data-bases and phone interviews. Descriptive statistics, Fisher's exact test and Wilcoxon rank sum test were used for analyses. **RESULTS:** Of 147 eligible patients, 42 (28.6%) enrolled and of these, 32 (76.2%) started the intervention and 27 (N = 27/32; 84.4%; 95% CI: 67.2-94.7%) completed the intervention. Patients who were younger were more likely to enroll in the study (p = 0.04) whereas there were no significant differences by gender (p = 0.35). Twenty-three of the 24 (95.8%) participants' contacted post-test recommended the intervention for others. Nearly equal numbers of participants chose the website, (n = 16, 50%) vs. print (n = 14, 44%). **CONCLUSION:** The intervention was feasible and acceptable in patients with lung cancer. Recruitment rates were higher and completion rates were similar as compared to previous home-based lifestyle interventions for patients with other types of cancer. Strategies to enhance recruitment of older adults are important for future research.

The Effects of smoking status and smoking history on patients with brain metastases from lung cancer. Shenker RF1, McTyre ER1, Ruiz J2, et al. Cancer Med. 2017 Apr 12. doi: 10.1002/cam4.1058. [Epub ahead of print]
There is limited data on the effects of smoking on lung cancer patients with brain metastases. This single institution retrospective study of patients with brain metastases from lung cancer who received stereotactic radiosurgery assessed whether smoking history is associated with overall survival, local control, rate of new brain metastases (brain metastasis velocity), and likelihood of neurologic death after brain metastases. Patients were stratified by adenocarcinoma versus nonadenocarcinoma histologies. Kaplan-Meier analysis was performed for survival endpoints. Competing risk analysis was performed for neurologic death analysis to account for risk of nonneurologic death. Separate linear regression and multivariate analyses were performed to estimate the brain metastasis velocity. Of 366 patients included in the analysis, the median age was 63, 54% were male and, 60% were diagnosed with adenocarcinoma. Current smoking was reported by 37% and 91% had a smoking history. Current smoking status and pack-year history of smoking had no effect on overall survival. There was a trend for an increased risk of neurologic death in nonadenocarcinoma patients who continued to smoke (14%, 35%, and 46% at 6/12/24 months) compared with patients who did not smoke (12%, 23%, and 30%, P = 0.053). Cumulative pack years smoking was associated with an increase in neurologic death for nonadenocarcinoma patients (HR = 1.01, CI: 1.00-1.02, P = 0.046). Increased pack-year history increased brain metastasis velocity in multivariate analysis for overall patients (P = 0.026). Current smokers with nonadenocarcinoma lung cancers had a trend toward greater neurologic death than nonsmokers. Cumulative pack years smoking is associated with a greater brain metastasis velocity.

COMPLEMENTARY & ALTERNATIVE THERAPY

Chinese medicine Bu-Fei decoction attenuates epithelial-mesenchymal transition of non-small cell lung cancer via inhibition of transforming growth factor β1 signaling pathway in vitro and in vivo. He XR1, Han SY2, Li XH3, Zheng WX4, Pang LN5, Jiang ST6, Li PP7. J Ethnopharmacol. 2017 Apr 12. pii: S0378-8741(17)30181-2. doi: 10.1016/j.jep.2017.04.008. [Epub ahead of print]
ETHNOPHARMACOLOGICAL RELEVANCE: Traditional Chinese medicine Bu-Fei decoction (BFD) has been utilized to treat patients with Qi deficiency for decades, with the advantages of invigorating vital energy, clearing heat-toxin and moistening lung, etc. According to previous clinical experience and trials, BFD has been found to indeed improve life quality of lung cancer patients and prolong survival time. Nevertheless, little is known on its potential mechanisms so far. Being regarded as a pivotal cytokine in the tumor microenvironment, transforming growth factor β (TGF-β) stands out as a

robust regulator of epithelial-mesenchymal transition (EMT), which is closely linked to tumor progression. **AIM OF THE STUDY:** The present study was designed to explore whether BFD antagonized EMT via blocking TGF-β1-induced signaling pathway, and then help contribute to create a relatively steady microenvironment for confining lung cancer. **MATERIALS AND METHODS:** This experiment was performed in lung adenocarcinoma A549 cells both in vitro and in vivo. In detail, the influences mediated by TGF-β1 alone or in combination with different concentrations of BFD on migration were detected by wound healing and transwell assays, and the effects of BFD on cell viability were determined by cell counting kit-8 (CCK-8) assay. TGF-β1, EMT relevant proteins and genes were evaluated by western blotting, confocal microscopy, quantitative real-time polymerase chain reaction (qRT-PCR), immunohistochemistry (IHC) and enzyme-linked immuno sorbent assay (ELISA). Female BALB/C nude mice were subcutaneously implanted A549 cells and given BFD by gavage twice daily for 28 days. The tumor volume was monitored every 4 days to draw growth curve. The tumor weight, expression levels of EMT-related protein in tumor tissues and TGF-β1 serum level were evaluated, respectively. **RESULTS:** BFD only exerted minor effects on A549 cell proliferation and this was in accordance with the in vivo result, which showed that the tumor growth and weight were not be restrained by BFD administration. However, the data elucidated that BFD could dose-dependently suppress EMT induced by TGF-β1 in vitro via attenuating canonical Smad signaling pathway. In the A549 xenograft mouse model, BFD also inhibited protein markers that are associated with EMT and TGF-β1 secretion into serum. **CONCLUSIONS:** Based on these above data, the conclusion could be put forward that BFD probably attenuated TGF-β1 mediated EMT in A549 cells via decreasing canonical Smad signaling pathway both in vitro and in vivo, which may help restrain the malignant phenotype induced by TGF-β1 in A549 cells to some extent.

Effects of Chinese Medicine as Adjunct Medication for Adjuvant Chemotherapy Treatments of Non-Small Cell Lung Cancer Patients. Jiao L1,2, Dong C1,2, Liu J1,2, et al. Sci Rep. 2017 Apr 24;7:46524. doi: 10.1038/srep46524.

The aim was to evaluate the effects of traditional Chinese medicine (TCM) as a combination medication with adjuvant chemotherapy on postoperative early stage non-small cell lung cancer (NSCLC) patients. The 314 patients with completely resected stage IB, II or IIIA cancers were assigned into vinorelbine plus cisplatin/carboplatin (NP/NC) (control, n = 158) and NP/NC with additional TCM (intervention, n = 156) groups. The primary endpoint was QOL scores; secondary endpoints were the toxicity and safety of the regimens. The NP/NC regimen caused mild (grade 1 or 2) non-hematologic toxic effects in the patients comprising vomiting (43.6%), fatigue (36.9%), pain (23%), dry mouth (27.6%) and diarrhea (7.9%). The incidence of adverse events was significantly lower in the intervention group than in the control group (0.57% vs 4.02%, P = 0.037). Transient severe (grade 3 or 4) hematological toxic effects occurred less often (hemoglobin reduction (11.9 vs 22.5 percent) and total bilirubin increased (to 42.1 vs 46.2%) in the intervention compared to the control group during the 2nd chemotherapy cycle. When combined with adjuvant chemotherapy, TCM led to partial relief of symptoms in addition to a reduction of side-effects and adverse events caused by the NP/NC regimens.

Modified Panax ginseng extract regulates autophagy by AMPK signaling in A549 human lung cancer cells. Yoo HS1, Kim JM2, Jo E3, et al. Oncol Rep. 2017 Apr 20. doi: 10.3892/or.2017.5590. [Epub ahead of print]

Panax ginseng has been used worldwide as a traditional medicine for the treatment of cancer and other diseases. The antiproliferative activity of ginseng has been increased after enzymatic processing of ginseng saponin, which may result in the accumulation of minor saponins, such as Rh2, Rg3, compound K and protopanaxatriol type (PPT) in modified regular ginseng extract (MRGX). In the present study, the anticancer activity and the associated mechanisms of MRGX were investigated using A549 human lung

cancer cells. To elucidate the mechanisms underlying the effects of MRGX, we performed a microarray analysis of gene expression in the A549 cells. Molecular mechanisms that were associated with the anticancer activity of MRGX were studied, with a special focus on the autophagy-related multiple signaling pathways in lung cancer cells. Microarray analyses elucidated autophagy-related genes affected by MRGX. Administration of MRGX at 100 μg/ml induced punctate cytoplasmic expression of LC3, Beclin-1 and ATG5 and increased expression of endogenous LC3-II whereas 50 μg/ml did not inhibit the proliferation of A549 cells. Compared to the control cells, in cells treated with MRGX at 100 μg/ml, the level of p-Akt was increased, while that of mTOR-4EBP1 was decreased. Downregulation of mTOR and 4EBP1 in the MRGX-treated cells was found not to be a p-Ulk (S757)-dependent pathway, but a p-Ulk (S317)-dependent autophagic pathway, using AMPK. These data suggest that MRGX regulates AMPK and induces autophagy in lung cancer cells.

MISCELLANEOUS WORKS

Characterizing 18 Years of the Death With Dignity Act in Oregon. Blanke C1, LeBlanc M2, Hershman D2, Ellis L2, Meyskens F2. JAMA Oncol. 2017 Apr 6. doi: 10.1001/jamaoncol.2017.0243. [Epub ahead of print]

IMPORTANCE: Numerous states have pending physician-aided dying (PAD) legislation. Little research has been done regarding use of PAD, or ways to improve the process and/or results. **OBJECTIVES:** To evaluate results of Oregon PAD, the longest running US program; to disseminate results; and to determine promising PAD research areas. **DESIGN, SETTING, AND PARTICIPANTS:** A retrospective observational cohort study of 991 Oregon residents who had prescriptions written as part of the state's Death with Dignity Act. We reviewed publicly available data from Oregon Health Authority reports from 1998 to 2015, and made a supplemental information request to the Oregon Health Authority. **MAIN OUTCOMES AND MEASURES:** Number of deaths from self-administration of lethal medication versus number of prescriptions written. **RESULTS:** A total of 1545 prescriptions were written, and 991 patients died by using legally prescribed lethal medication. Of the 991 patients, 509 (51.4%) were men and 482 (48.6%) were women. The median age was 71 years (range, 25-102 years). The number of prescriptions written increased annually (from 24 in 1998 to 218 in 2015), and the percentage of prescription recipients dying by this method per year averaged 64%. Of the 991 patients using lethal self-medication, 762 (77%) recipients had cancer, 79 (8%) had amyotrophic lateral sclerosis, 44 (4.5%) had lung disease, 26 (2.6%) had heart disease, and 9 (0.9%) had HIV. Of 991 patients, 52 (5.3%) were sent for psychiatric evaluation to assess competence. Most (953; 96.6%) patients were white and 92.2% were in hospice care. Most (118, 92.2%) patients had insurance and 92 (70.8%) had at least some college education. Most (94%) died at home. The estimated median time between medication intake and coma was 5 minutes (range, 1-38 minutes); to death it was 25 minutes (range, 1-6240 minutes). Thirty-three (3.3%) patients had known complications. The most common reasons cited for desiring PAD were activities of daily living were not enjoyable (89.7%) and losses of autonomy (91.6%) and dignity (78.7%); inadequate pain control contributed in 25.2% of cases. **CONCLUSIONS AND RELEVANCE:** The number of PAD prescriptions written in Oregon has increased annually since legislation enactment. Patients use PAD for reasons related to quality of life, autonomy, and dignity, and rarely for uncontrolled pain. Many questions remain regarding usage and results, making this area suitable for cancer care delivery research.

Big Data Science: Opportunities and Challenges to Address Minority Health and Health Disparities in the 21st Century. Zhang X1, Pérez-Stable EJ1, Bourne PE2, et al. Ethn Dis. 2017 Apr 20;27(2):95-106. doi: 10.18865/ed.27.2.95. eCollection 2017.

Addressing minority health and health disparities has been a missing piece of the puzzle in Big Data science. This article focuses on three priority opportunities that Big Data science may offer to the reduction of health and health care disparities. One opportunity is to incorporate standardized information on demographic and social determinants in electronic health records in order to target ways to improve quality of care for the most disadvantaged populations over time. A second opportunity is to enhance public health surveillance by linking geographical variables and social determinants of health for geographically defined populations to clinical data and health outcomes. Third and most importantly, Big Data science may lead to a better understanding of the etiology of health disparities and understanding of minority health in order to guide intervention development. However, the promise of Big Data needs to be considered in light of significant challenges that threaten to widen health disparities. Care must be taken to incorporate diverse populations to realize the potential benefits. Specific recommendations include investing in data collection on small sample populations, building a diverse workforce pipeline for data science, actively seeking to reduce digital divides, developing novel ways to assure digital data privacy for small populations, and promoting widespread data sharing to benefit under-resourced minority-serving institutions and minority researchers. With deliberate efforts, Big Data presents a dramatic opportunity for reducing health disparities but without active engagement, it risks further widening them.

Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Cohen AJ1, Brauer M2, Burnett R3, et al. Lancet. 2017 Apr 10. pii: S0140-6736(17)30505-6. doi: 10.1016/S0140-6736(17)30505-6. [Epub ahead of print]

BACKGROUND: Exposure to ambient air pollution increases morbidity and mortality, and is a leading contributor to global disease burden. We explored spatial and temporal trends in mortality and burden of disease attributable to ambient air pollution from 1990 to 2015 at global, regional, and country levels. **METHODS:** We estimated global population-weighted mean concentrations of particle mass with aerodynamic diameter less than 2·5 μm (PM2·5) and ozone at an approximate 11 km × 11 km resolution with satellite-based estimates, chemical transport models, and ground-level measurements. Using integrated exposure-response functions for each cause of death, we estimated the relative risk of mortality from ischaemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, lung cancer, and lower respiratory infections from epidemiological studies using non-linear exposure-response functions spanning the global range of exposure. **FINDINGS:** Ambient PM2·5 was the fifth-ranking mortality risk factor in 2015. Exposure to PM2·5 caused 4·2 million (95% uncertainty interval [UI] 3·7 million to 4·8 million) deaths and 103·1 million (90·8 million 115·1 million) disability-adjusted life-years (DALYs) in 2015, representing 7·6% of total global deaths and 4·2% of global DALYs, 59% of these in east and south Asia. Deaths attributable to ambient PM2·5 increased from 3·5 million (95% UI 3·0 million to 4·0 million) in 1990 to 4·2 million (3·7 million to 4·8 million) in 2015. Exposure to ozone caused an additional 254 000 (95% UI 97 000-422 000) deaths and a loss of 4·1 million (1·6 million to 6·8 million) DALYs from chronic obstructive pulmonary disease in 2015. **INTERPRETATION:** Ambient air pollution contributed substantially to the global burden of disease in 2015, which increased over the past 25 years, due to population ageing, changes in non-communicable disease rates, and increasing air pollution in low-income and middle-income countries. Modest reductions in burden will occur in the most polluted countries unless PM2·5 values are decreased substantially, but there is potential for substantial health benefits from exposure reduction. **FUNDING:** Bill & Melinda Gates oundation and Health Effects Institute.

Evaluating Progress in Radon Control Activities for Lung Cancer Prevention in National Comprehensive Cancer Control Program Plans, 2011-2015. Acree P1, Puckett M2, Neri A3. J Community Health. 2017 Apr 4. doi: 10.1007/s10900-017-0342-7. [Epub ahead of print]

Radon is the second leading cause of lung cancer among smokers and the leading cause among nonsmokers. The Centers for Disease Control and Prevention's National Comprehensive Cancer Control Program (NCCCP) funds every state, seven tribes, seven territories and the District of Columbia to develop formal cancer plans that focus efforts in cancer control. A 2010 review of cancer plans identified radon-related activities in 27 (42%) plans. Since then, 37 coalitions have updated their plans with new or revised cancer control objectives. There has also been recent efforts to increase awareness about radon among cancer coalitions. This study assesses NCCCP grantees current radon activities and changes since the 2010 review. We reviewed all 65 NCCCP grantee cancer plans created from 2005 to 2015 for radon related search terms and categorized plans by radon activities. The program's most recent annual progress report to CDC was also reviewed. We then compared the results from the updated plans with the findings from the 2010 review to assess changes in radon activities among cancer coalitions. Changes in state radon laws between 2010 and 2015 were also assessed. While a number of cancer plans have added or expanded radon-specific activities since 2010, approximately one-third of NCCCP grantees still do not include radon in their cancer plans. Cancer programs can consider addressing radon through partnership with existing radon control programs to further reduce the risk of lung cancer, especially among non-smokers.

Treatment Paradigms for Advanced Non-Small Cell Lung Cancer at Academic Medical Centers: Involvement in Clinical Trial Endpoint Design. Aggarwal C1, Borghaei H2. Oncologist. 2017 Apr 13. pii: theoncologist.2016-0345. doi: 10.1634/theoncologist.2016-0345. [Epub ahead of print]
Based on the positive results of various clinical trials, treatment options for non-small cell lung cancer (NSCLC) have expanded greatly over the last 25 years. While regulatory approvals of chemotherapeutic agents for NSCLC have largely been based on improvements in overall survival, recent approvals of many targeted agents for NSCLC (afatinib, crizotinib, ceritinib, osimertinib) have been based on surrogate endpoints such as progression-free survival and objective response. As such, selection of appropriate clinical endpoints for examining the efficacy of investigational agents for NSCLC is of vital importance in clinical trial design. This review provides an overview of clinical trial endpoints previously utilized for approved agents for NSCLC and highlights the key efficacy results for these trials. Trends for more recent approvals in NSCLC, including those for the immunotherapeutic agents nivolumab and pembrolizumab, are also discussed. The results of a correlative analysis of endpoints from 18 clinical trials that supported approvals of investigational agents in clinical trials for NSCLC are also presented. The Oncologist 2017;22:1-9Implications for Practice While improving survival remains the ultimate goal of oncology clinical trials, overall survival may not always be the most feasible or appropriate endpoint to assess patient response. Recently, several investigational agents, both targeted agents and immunotherapies, have gained U.S. Food and Drug Administration approval in non-small cell lung cancer based on alternate endpoints such as progression-free survival or response rate. An understanding of the assessment of response and trial endpoint choice is important for future oncology clinical trial design.

Treatment Satisfaction and Adherence to Oral Chemotherapy in Patients With Cancer.
Jacobs JM1, Pensak NA1, Sporn NJ1, MacDonald JJ1, Lennes IT1, Safren SA1, Pirl WF1, Temel JS1, Greer JA1. J Oncol Pract. 2017 Apr 11:JOP2016019729. doi: 10.1200/JOP.2016.019729. [Epub ahead of print]
PURPOSE: Although patients with cancer overwhelming prefer oral to intravenous chemotherapy, little is known about adherence to oral agents. We aimed to identify the rates and correlates of adherence in patients with diverse malignancies. **MATERIALS AND METHODS:** Ninety patients with chronic myeloid leukemia or metastatic renal cell carcinoma, non-small-cell lung cancer, or breast cancer enrolled in this prospective, single-group, observational study of medication-taking behaviors. Adherence was measured via self-report and with an electronic pill cap (Medication Event Monitoring System cap).

Patients completed surveys regarding symptom distress, mood, quality of life, cancer-specific distress, and satisfaction with clinician communication and treatment at baseline and 12-week follow-up. **RESULTS:** As measured by the Medication Event Monitoring System, patients took, on average, 89.3% of their prescribed oral chemotherapy over the 12 weeks. One quarter of the sample was less than 90% adherent, and women were more adherent than men (mean difference, 9.59%; SE difference, 4.50%; 95% CI, -18.65 to -0.52; P = .039). Improvements in patient symptom distress (B = -0.79; 95% CI, -1.41 to -0.18), depressive symptoms (B = -1.57; 95% CI, -2.86 to -0.29), quality of life (B = 0.38; 95% CI ,0.07 to 0.68), satisfaction with clinician communication and treatment (B = 0.73; 95% CI, 0.49 to 0.98), and perceived burden to others (B = -1.28; 95% CI, -2.20 to -0.37) were associated with better adherence. In a multivariate model, improved treatment satisfaction (B = 0.71; 95% CI, 0.48 to 0.94) and reduced perceived burden (B = -0.92; 95% CI, -1.76 to -0.09) were the strongest indicators of better adherence. **CONCLUSION:** Women and patients who reported increased treatment satisfaction and reduced burden to others were more adherent to oral chemotherapy. Interventions that help patients improve communication with clinicians and reduce burden may optimize oral chemotherapy adherence.