



Caring Ambassadors Lung Cancer Program Literature Review, August, 2018

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BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Hexokinase 2 is dispensable for T cell-dependent immunity.](#) Mehta MM¹, Weinberg SE¹, Steinert EM¹, et al. *Cancer Metab.* 2018 Aug 17;6:10. doi: 10.1186/s40170-018-0184-5. eCollection 2018.

BACKGROUND: T cells and cancer cells utilize glycolysis for proliferation. The hexokinase (1-4) family of enzymes catalyze the first step of glycolysis. Hexokinase 2 (HK2) is one of the most highly upregulated metabolic enzymes in both cancer and activated T cells. HK2 is required for the development and/or growth of cancer in several cancer models, but the necessity of HK2 in T cells is not fully understood. The clinical applicability of HK2 inhibition in cancer may be significantly limited by any potential negative effects of HK2 inhibition on T cells. Therefore, we investigated the necessity of HK2 for T cell function. In order to identify additional therapeutic cancer targets, we performed RNA-seq to compare in vivo proliferating T cells to T cell leukemia. **METHODS:** HK2 was genetically ablated in mouse T cells using a floxed Hk2 allele crossed to CD4-Cre. CD4⁺ and CD8⁺ cells from mice were characterized metabolically and tested in vitro. T cell function in vivo was tested in a mouse model of colitis, Th2-mediated lung inflammation, and viral infection. Treg function was tested by crossing Hk2-floxed mice to FoxP3-Cre mice. Hematopoietic function was tested by deleting HK2 from bone marrow with Vav1-iCre. RNA-seq was used to compare T cells proliferating in response to virus with primary T-ALL leukemia induced with mutant Notch1 expression. **RESULTS:** We unexpectedly report that HK2 is largely dispensable for in vitro T cell activation, proliferation, and differentiation. Loss of HK2 does not impair in vivo viral immunity and causes only a small impairment in the development of pathological inflammation. HK2 is not required for Treg function or hematopoiesis in vivo. One hundred sixty-seven metabolic genes were identified as being differentially expressed between T cells and leukemia. **CONCLUSIONS:** HK2 is a highly upregulated enzyme in cancer and in T cells. The requirement for HK2 in various cancer models has been described previously. Our finding that T cells are able to withstand the loss of HK2 indicates that HK2 may be a promising candidate for cancer therapy. Furthermore, we identify several other potential metabolic targets in T-ALL leukemia that could spare T cell function.

[Neuropilin-1 upregulation elicits adaptive resistance to oncogene-targeted therapies.](#) Rizzolio S1,2, Cagnoni G1,2, Battistini C1,2, et al. *J Clin Invest.* 2018 Aug 31;128(9):3976-3990. doi: 10.1172/JCI99257. Epub 2018 Aug 13.

Cancer cell dependence on activated oncogenes is therapeutically targeted, but acquired resistance is virtually unavoidable. Here we show that the treatment of addicted melanoma cells with BRAF inhibitors, and of breast cancer cells with HER2-targeted drugs, led to an adaptive rise in neuropilin-1 (NRP1) expression, which is crucial for the onset of acquired resistance to therapy. Moreover, NRP1 levels dictated the efficacy of MET oncogene inhibitors in addicted stomach and lung carcinoma cells. Mechanistically, NRP1 induced a JNK-dependent signaling cascade leading to the upregulation of alternative effector kinases EGFR or IGF1R, which in turn sustained cancer cell growth and mediated acquired resistance to BRAF, HER2, or MET inhibitors. Notably, the combination with NRP1-interfering molecules improved the efficacy of oncogene-targeted drugs and prevented or even reversed the onset of resistance in cancer cells and tumor models. Our study provides the rationale for targeting the NRP1-dependent upregulation of tyrosine kinases, which are responsible for loss of responsiveness to oncogene-targeted therapies.

SCREENING, DIAGNOSIS, AND STAGING

[A Multicenter Study to Assess EGFR Mutational Status in Plasma: Focus on an Optimized Workflow for Liquid Biopsy in a Clinical Setting.](#) Sorber L1,2, Zwaenepoel K3,4, De Winne K5, et al. *Cancers (Basel).* 2018 Aug 27;10(9). pii: E290. doi: 10.3390/cancers10090290.

A multicenter study was performed to determine an optimal workflow for liquid biopsy in a clinical setting. In total, 549 plasma samples from 234 non-small cell lung cancer (NSCLC) patients were collected. Epidermal Growth Factor Receptor (EGFR) circulating cell-free tumor DNA (ctDNA) mutational analysis was performed using digital droplet PCR (ddPCR). The influence of (pre-) analytical variables on ctDNA analysis was investigated. Sensitivity of ctDNA analysis was influenced by an interplay between increased plasma volume ($p < 0.001$) and short transit time ($p = 0.018$). Multistep, high-speed centrifugation both increased plasma generation ($p < 0.001$) and reduced genomic DNA (gDNA) contamination. Longer transit time increased the risk of hemolysis ($p < 0.001$) and low temperatures were shown to have a negative effect. Metastatic sites were found to be strongly associated with ctDNA detection ($p < 0.001$), as well as allele frequency ($p = 0.034$). Activating mutations were detected in a higher concentration and allele frequency compared to the T790M mutation ($p = 0.003$, and $p = 0.002$, respectively). Optimization of (pre-) analytical variables is key to successful ctDNA analysis. Sufficient plasma volumes without hemolysis or gDNA contamination can be achieved by using multistep, high-speed centrifugation, coupled with short transit time and temperature regulation. Metastatic site location influenced ctDNA detection. Finally, ctDNA levels might have further value in detecting resistance mechanisms.

[Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration Use for Subclassification and Genotyping of Lung Non-Small-Cell Carcinoma.](#) Raad S1, Hanna N1, Jalal S1, Bendaly E1, Zhang C1, Nuguru S1, Oueini H1, Diab K1. *South Med J.* 2018 Aug;111(8):484-488. doi: 10.14423/SMJ.0000000000000846.

OBJECTIVES: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is the primary method for the diagnosis and staging of lung cancer. The purpose of this study was to assess the yield of EBUS-TBNA in the subtyping and genotyping of lung adenocarcinoma. **METHODS:** Sixty-nine patients at Indiana University Hospital and Sidney and Lois Eskenazi Hospital with possible or confirmed lung adenocarcinoma underwent EBUS-TBNA using a 21-gauge Olympus needle without suction. Samples were sent for molecular testing after rapid onsite specimen evaluation. A total of 6 to 10 passes

were placed in a cell block. **RESULTS:** Sixty-nine samples from patients with non-small-cell lung cancer were sent for molecular testing for epidermal growth factor receptor. Results were obtained in all of the patients. Mutations were found in three patients (4.3%). Fifty-eight samples were sent for V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (100% yield), 10 of which had mutations (17.2%). Fifty-one samples were sent for proto-oncogene tyrosine-protein kinase ROS testing (1 [7.8%] mutant). Tissue samples were inadequate in three patients (94.1% yield). Sixty-three samples were sent for anaplastic lymphoma receptor tyrosine kinase testing (3 [4.8%] mutant, 6 [9.5%] inadequate, 90.5% yield). **CONCLUSIONS:** EBUS-TBNA with a 21-gauge needle is appropriate for the analysis of multiple mutations and the genotyping of lung adenocarcinoma.

[Attitudes towards lung cancer screening in a population sample.](#) Smits SE1, McCutchan GM1, Hanson JA2, Brain KE1. Health Expect. 2018 Aug 7. doi: 10.1111/hex.12819. [Epub ahead of print]

BACKGROUND: Lung cancer is the leading cause of cancer death worldwide. Routine UK lung cancer screening is not yet available, thus understanding barriers to participation in lung screening could help maximize effectiveness if introduced. **METHODS:** Population-based survey of 1007 adults aged 16 and over in Wales using random quota sampling. Computer-assisted face-to-face interviews included demographic variables (age, gender, smoking, social group), four lung cancer belief statements and three lung screening attitudinal items. Determinants of lung screening attitudes were examined using multivariable regression adjusted for age, gender, social group and previous exposure to lung campaign messages. **RESULTS:** Avoidance of lung screening due to fear of what might be found was statistically significantly associated with negative lung cancer beliefs including fatalism (aOR = 8.8, 95% CI = 5.6-13.9, $P \leq 0.001$), low perceived value of symptomatic presentation (aOR = 2.4, 95% CI = 1.5-3.9, $P \leq 0.001$) and low treatment efficacy (aOR = 0.3, CI = 0.2-0.7, $P \leq 0.01$). Low perceived effectiveness of lung screening was significantly associated with fatalism (aOR = 6.4, 95% CI = 3.5-11.7, $P \leq 0.001$), low perceived value of symptom presentation (aOR = 4.9, 95% CI = 2.7-8.9, $P \leq 0.001$) and low treatment efficacy (aOR = 0.1, 95% CI = 0.1-0.3, $P \leq 0.001$). In contrast, respondents who thought lung screening could reduce cancer deaths had positive beliefs about lung cancer (aOR = 0.4, 95% CI = 0.2-0.7, $P \leq 0.001$) and its treatment (aOR = 6.1, 95% CI = 3.0-12.6, $P \leq 0.001$). **CONCLUSION:** People with negative beliefs about lung cancer may be more likely to avoid lung screening. Alongside the introduction of effective early detection strategies, interventions are needed to modify public perceptions of lung cancer, particularly for fatalism.

[Association of Broad-Based Genomic Sequencing With Survival Among Patients With Advanced Non-Small Cell Lung Cancer in the Community Oncology Setting.](#) Presley CJ1, Tang D2, Soulos PR3, et al. JAMA. 2018 Aug 7;320(5):469-477. doi: 10.1001/jama.2018.9824.

IMPORTANCE: Broad-based genomic sequencing is being used more frequently for patients with advanced non-small cell lung cancer (NSCLC). However, little is known about the association between broad-based genomic sequencing and treatment selection or survival among patients with advanced NSCLC in a community oncology setting. **OBJECTIVE:** To compare clinical outcomes between patients with advanced NSCLC who received broad-based genomic sequencing vs a control group of patients who received routine testing for EGFR mutations and/or ALK rearrangements alone. **DESIGN, SETTING, AND PARTICIPANTS:** Retrospective cohort study of patients with chart-confirmed advanced NSCLC between January 1, 2011, and July 31, 2016, and who received care at 1 of 191 oncology practices across the United States using the Flatiron Health Database. Patients were diagnosed with stage IIIB/IV or unresectable nonsquamous NSCLC who received at least 1 line of antineoplastic treatment. **EXPOSURES:** Receipt of either broad-based genomic sequencing or routine testing (EGFR and/or ALK only). Broad-based genomic sequencing included any multigene panel sequencing assay examining more than 30 genes prior to third-line treatment. **MAIN OUTCOMES AND MEASURES:** Primary outcomes

were 12-month mortality and overall survival from the start of first-line treatment. Secondary outcomes included frequency of genetic alterations and treatments received. **RESULTS:** Among 5688 individuals with advanced NSCLC (median age, 67 years [interquartile range, 41-85], 63.6% white, 80% with a history of smoking); 875 (15.4%) received broad-based genomic sequencing and 4813 (84.6%) received routine testing. Among patients who received broad-based genomic sequencing, 4.5% received targeted treatment based on testing results, 9.8% received routine EGFR/ALK targeted treatment, and 85.1% received no targeted treatment. Unadjusted mortality rates at 12 months were 49.2% for patients undergoing broad-based genomic sequencing and 35.9% for patients undergoing routine testing. Using an instrumental variable analysis, there was no significant association between broad-based genomic sequencing and 12-month mortality (predicted probability of death at 12 months, 41.1% for broad-based genomic sequencing vs 44.4% for routine testing; difference -3.6% [95% CI, -18.4% to 11.1%]; P = .63). The results were consistent in the propensity score-matched survival analysis (42.0% vs 45.1%; hazard ratio, 0.92 [95% CI, 0.73 to 1.11]; P = .40) vs unmatched cohort (hazard ratio, 0.69 [95% CI, 0.62 to 0.77]; log-rank P < .001). **CONCLUSIONS AND RELEVANCE:** Among patients with advanced non-small cell lung cancer receiving care in the community oncology setting, broad-based genomic sequencing directly informed treatment in a minority of patients and was not independently associated with better survival.

Molecular testing and treatment patterns for patients with advanced non-small cell lung cancer: PivOTAL observational study. Lee DH1, Tsao MS2, Kambartel KO3, et al. PLoS One. 2018 Aug 27;13(8):e0202865. doi: 10.1371/journal.pone.0202865. eCollection 2018.

BACKGROUND: The goals of this multinational retrospective study were to describe treatment patterns and survival outcomes by receipt of molecular testing and molecular status of patients with advanced non-small cell lung cancer (NSCLC). **METHODS:** This chart review study, conducted in Italy, Spain, Germany, Australia, Japan, Korea, Taiwan, and Brazil, included 1440 patients with newly diagnosed advanced (stage IIIB/IV) NSCLC initiating systemic therapy from January 2011 through June 2013, with follow-up until July 2016. We evaluated treatment patterns and survival by histology, line of therapy, molecular testing, and test results for epidermal growth factor receptor (EGFR) mutation and/or anaplastic lymphoma kinase (ALK) rearrangement. Country-specific data were analyzed descriptively and presented as ranges (lowest to highest country). Overall survival (OS) was estimated using Kaplan-Meier method. **RESULTS:** Patients with ≥ 1 molecular test varied from 43% (Brazil) to 85% (Taiwan). Numerically greater proportions of patients who were female, Asian, or never/former-smokers, and those with nonsquamous histology or stage-IV NSCLC, received a test. Testing was common for nonsquamous NSCLC (54%, Brazil, to 91%, Taiwan), with positive EGFR and ALK tests from 17% (Brazil and Spain) to 67% (Taiwan) and from 0% (Brazil) to 60% (Taiwan), respectively. First-line treatment regimens for nonsquamous NSCLC with positive EGFR/ALK tests included targeted therapy for 30% (Germany) to 89% (Japan); with negative/inconclusive test results, platinum-based combinations for 88% (Japan) to 98% (Brazil); and if not tested, platinum-based combinations for 80% (Australia) to 95% (Japan), except in Taiwan, where 44% received single agents. Median OS from first-line therapy initiation was 10.0 (Japan) to 26.7 (Taiwan) months for those tested and 7.6 (Australia/Brazil) to 19.3 (Taiwan) months for those not tested. **CONCLUSIONS:** We observed substantial variation among countries in testing percentages, treatment patterns, and survival outcomes. Efforts to optimize molecular testing rates should be implemented in the context of each country's health care scenario.

Effectiveness of Lung-RADS in Reducing False-Positive Results in a Diverse, Underserved, Urban Lung Cancer Screening Cohort. Kaminetzky M1, Milch HS2, Shmukler A1, et al. J Am Coll Radiol. 2018 Aug 23. pii: S1546-1440(18)30858-5. doi: 10.1016/j.jacr.2018.07.011. [Epub ahead of print]

PURPOSE: The Lung CT Screening Reporting and Data System™ (Lung-RADSTM) was created to standardize lung cancer screening CT reporting and recommendations but has not been well validated prospectively in clinical practice. The aim of this study was to determine the effectiveness of lung cancer screening using Lung-RADS in a diverse, underserved, academic clinical screening program, focusing on whether Lung-RADS would successfully reduce the 23.3% false-positive rate found in the National Lung Screening Trial. **METHODS:** Institutional review board approval was obtained to study the clinical lung cancer screening cohort. Low-dose CT results were prospectively assigned a Lung-RADS or equivalent score. The proportion of examinations in each Lung-RADS category and the corresponding lung cancer rate, subsequent imaging, interventions, mortality, and compliance were tracked. The National Death Index was queried for follow-up losses. **RESULTS:** The cohort comprised 1,181 patients with 2,270 person-years of follow-up from December 2012 to December 2016. The mean age was 64 ± 16.2 years, with 51% women, 63% nonwhite, 71% current smokers, 69% overweight and obese, and multiple comorbidities. The Lung-RADS false-positive rate was 10.4% (95% confidence interval, 8.8%-12.3%). Baseline CT results were negative in 87% (n = 1,031): for Lung-RADS 1, the lung cancer rate was 0.2%, and for Lung-RADS 2, the cancer rate was 0.5%. Positive baseline examinations were Lung-RADS 3 in 10% (n = 119), 4a in 1.2% (n = 14), and 4b in 1.5% (n = 18). Corresponding cancer rates were 3.4%, 43%, and 83%, respectively. Lung cancer prevalence was 2.1%. Mortality was 40% in patients with lung cancer versus 2.5% in the remaining cohort (P < .001). Fifty-four percent of patients were overdue for first annual examinations. Eighty-four percent of patients (n = 989) had follow-up verified via electronic records or personal contact, and the remainder had vital status ascertained via the National Death Index. **CONCLUSIONS:** Lung cancer screening using Lung-RADS was effective in reducing the false-positive rate compared with the National Lung Screening Trial in a diverse and underserved urban population.

[Yield of Low-Dose Computerized Tomography Screening for Lung Cancer in High-Risk Workers: The Case of 7189 US Nuclear Weapons Workers.](#) Markowitz SB1, Manowitz A1, Miller JA1, Frederick JS1, Onyekelu-Eze AC1, Widman SA1, Pepper LD1, Miller A1. Am J Public Health. 2018 Aug 23:e1-e7. doi: 10.2105/AJPH.2018.304518. [Epub ahead of print]

OBJECTIVES: To determine the lung cancer screening yield and stages in a union-sponsored low-dose computerized tomography scan program for nuclear weapons workers with diverse ages, smoking histories, and occupations. **METHODS:** We implemented a low-dose computerized tomography program among 7189 nuclear weapons workers in 9 nonmetropolitan US communities during 2000 to 2013. Eligibility criteria included age, smoking, occupation, radiographic asbestos-related fibrosis, and a positive beryllium lymphocyte proliferation test. **RESULTS:** The proportion with screen-detected lung cancer among smokers aged 50 years or older was 0.83% at baseline and 0.51% on annual scan. Of 80 lung cancers, 59% (n = 47) were stage I, and 10% (n = 8) were stage II. Screening yields of study subpopulations who met the National Lung Screening Trial or the National Comprehensive Cancer Network Group 2 eligibility criteria were similar to those found in the National Lung Screening Trial. **CONCLUSIONS:** Computerized tomography screening for lung cancer among high-risk workers leads to a favorable yield of early-stage lung cancers. Public Health Implications. Health equity and efficiency dictate that screening high-risk workers for lung cancer should be an important public health priority. (Am J Public Health. Published online ahead of print August 23, 2018; e1-e7. doi:10.2105/AJPH.2018.304518).

[Influence of Extent of Lymph Node Evaluation on Survival for Pathologically Lymph Node Negative Non-Small Cell Lung Cancer.](#) Becker DJ1, Levy BP2, Gold HT1, Sherman SE1, Makarov DV1, Schreiber D3, Wisnivesky JP2, Pass HI1. Am J Clin Oncol. 2018 Aug;41(8):820-825. doi: 10.1097/COC.0000000000000379.

OBJECTIVES: Despite previous retrospective reports that the number of lymph nodes resected at curative intent surgery for lung cancer correlates with overall survival (OS), no consensus exists regarding the minimal nor optimal number of lymph nodes to resect at curative lung cancer surgery. **METHODS:** We studied subjects in the Surveillance Epidemiology and End Results Database (SEER) diagnosed with non-small cell lung cancer between 2000 and 2011 who underwent either lobectomy or pneumonectomy and had pathologic negative nodal evaluation. We excluded patients with sublobar resection and/or no lymph node evaluation. We examined associations between number of lymph nodes evaluated and OS/lung cancer-specific survival by multivariable Cox regression; and predictors of evaluation of more lymph nodes. **RESULTS:** Among the 33,463 patients in our sample, a median of 7 lymph nodes were evaluated. We found that lung cancer-specific survival and OS improved with increasing lymph node evaluation up to 16 to 18 lymph nodes (hazard ratio, 0.77 [95% confidence interval, 0.70-0.85] and 0.78 [95% confidence interval, 0.72-0.86], respectively). There was little additional improvement in outcomes with evaluation of >16 to 18 lymph nodes. Blacks, Hispanics, females, and patients from distinct geographical regions were less likely to have 16 or more lymph nodes evaluated. **CONCLUSIONS:** There was a consistently increasing survival benefit associated with a more extensive lymph node evaluation at lung cancer resection, up to 16 to 18 lymph nodes removed. The median number of nodes evaluated was, however, only 7, suggesting that setting a goal of ≥ 16 examined lymph nodes may lead to improved survival outcomes, and reduce disparities in care.

[Evaluating Shared Decision Making for Lung Cancer Screening.](#) Brenner AT1,2, Malo TL2, Margolis M3, et al. JAMA Intern Med. 2018 Aug 13. doi: 10.1001/jamainternmed.2018.3054. [Epub ahead of print]

IMPORTANCE: The US Preventive Services Task Force recommends that shared decision making (SDM) involving a thorough discussion of benefits and harms should occur between clinicians and patients before initiating lung cancer screening (LCS) with low-dose computed tomography. The Centers for Medicare & Medicaid Services require an SDM visit using a decision aid as a prerequisite for LCS coverage. However, little is known about how SDM about LCS occurs in practice. **OBJECTIVE:** To assess the quality of SDM about the initiation of LCS in clinical practice. **DESIGN, SETTING, AND PARTICIPANTS:** A qualitative content analysis was performed of transcribed conversations between primary care or pulmonary care physicians and 14 patients presumed to be eligible for LCS, recorded between April 1, 2014, and March 1, 2018, that were identified within a large database. **MAIN OUTCOMES AND MEASURES:** Independent observer ratings of communication behaviors of physicians using the OPTION (Observing Patient Involvement in Decision Making) scale, a validated 12-item measure of SDM (total score, 0-100 points, where 0 indicates no evidence of SDM and 100 indicates evidence of SDM at the highest skill level); time spent discussing LCS during visits; and evidence of decision aid use. **RESULTS:** A total of 14 conversations about initiating LCS were identified; 9 patients were women, and 5 patients were men; the mean (SD) patient age was 63.9 (5.1) years; 7 patients had Medicare, and 8 patients were current smokers. Half the conversations were conducted by primary care physicians. The mean total OPTION score for the 14 LCS conversations was 6 on a scale of 0 to 100 (range, 0-17). None of the conversations met the minimum skill criteria for 8 of the 12 SDM behaviors. Physicians universally recommended LCS. Discussion of harms (such as false positives and their sequelae or overdiagnosis) was virtually absent. The mean total visit length of a discussion was 13:07 minutes (range, 3:48-27:09 minutes). The mean time spent discussing LCS was 0:59 minute (range, 0:16-2:19 minutes), or 8% of the total visit time (range, 1%-18%). There was no evidence that decision aids or other patient education materials for LCS were used. **CONCLUSIONS AND RELEVANCE:** In this small sample of recorded encounters about initiating LCS, the observed quality of SDM was poor and explanation of potential harms of screening was virtually nonexistent. Time spent discussing LCS was

minimal, and there was no evidence that decision aids were used. Although these findings are preliminary, they raise concerns that SDM for LCS in practice may be far from what is intended by guidelines.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[The assessment of correlation and prognosis among 18F-FDG uptake parameters, Glut1, pStat1 and pStat3 in surgically resected non-small cell lung cancer patients.](#) Kaida H1, Azuma K2, Kawahara A3, et al. *Oncotarget*. 2018 Aug 10;9(62):31971-31984. doi: 10.18632/oncotarget.25865. eCollection 2018 Aug 10.

INTRODUCTION: To assess the correlation among 18F-FDG uptake, Glut1, pStat1 and pStat3, and to investigate the relationship between the prognosis and 18F-FDG uptake and these molecular markers in surgically resected non-small cell lung cancer (NSCLC) patients. **RESULTS:** Knockdown of Glut1 led to a significant increase in pStat1 expression. Glut1 expression positively correlated with the SUVmax, SUVmean, and TLG significantly (P<0.001). pStat3 expression negatively correlated with all PET parameters significantly (P<0.001). pStat1 had positive weak correlations with the SUVmax and SUVmean. All PET parameters and Glut1 were significantly associated with DFS (P<0.05). TLG, MTV, Glut1 and pStat1 were significantly associated with OS (P<0.05). **CONCLUSION:** pStat3 and Glut1 may be associated with 18F-FDG uptake mechanism. TLG, MTV, and Glut1 may be independent prognostic factors. **METHODS:** The SUVmax, SUVmean, MTV and TLG of primary lesions were calculated in 140 patients. The expressions of Glut1 and Stat pathway proteins in NSCLC cell lines were examined by immune blots. Excised tumor tissue was analyzed by immunohistochemistry. OS and DFS were evaluated by the Kaplan-Meier method. The difference in survival between subgroups was analyzed by log-rank test. The prognostic significance of clinicopathological, molecular and PET parameters was assessed by Cox proportional hazard regression analysis.

[Impact of insurance status on receipt of definitive surgical therapy and posttreatment outcomes in early stage lung cancer.](#) Stokes SM1, Wakeam E2, Swords DS3, Stringham JR4, Varghese TK Jr4. *Surgery*. 2018 Aug 28. pii: S0039-6060(18)30471-9. doi: 10.1016/j.surg.2018.07.020. [Epub ahead of print]

BACKGROUND: The impact of insurance on outcomes in the modern era of evidence-based guidelines is unclear. We sought to examine differences in receipt of therapy and outcomes for early stage, non-small cell lung cancer patients by insurance coverage. **METHOD:** Clinical T1-3 N0-1 non-small cell lung cancer cases were identified in the 2004 to 2014 National Cancer Database and compared across 4 groups: private, Medicare, Medicaid, and uninsured. A multivariable, linear regression model was used to examine the effects of insurance status on time to curative surgical therapy, adjusting for patient and facility characteristics. Receipt of different therapies was examined with multivariable logistic regression. Survival analysis was conducted with Cox regression. **RESULTS:** A total of 240,361 patients presented with early stage non-small cell lung cancer (60,532 private, 164,377 Medicare, 11,001 Medicaid, and 4,451 uninsured). After adjustment, Medicaid and uninsured patients received surgical therapy later than privately insured patients (9.5 days and 7.0 days, respectively, P < .001), were more likely to be delayed > 8 weeks (odds ratio 1.64, 95% confidence interval 1.55-1.73 and odds ratio 1.46, 95% confidence interval 1.34-1.58), and were significantly less likely to receive surgery (odds ratio 0.53, 95% confidence interval 0.50-0.56 and odds ratio 0.50, 95% confidence interval 0.47-0.55). Uninsured patients were more likely to receive no treatment (odds ratio 2.15, 95% confidence interval 1.92-2.41), followed by Medicaid patients (odds ratio 1.66, 95% confidence interval 1.53-1.80). The 5-year overall survival was significantly worse

in the Medicaid and uninsured populations. **CONCLUSION:** Even in the modern era, uninsured and Medicaid early stage non-small cell lung cancer patients have decreased odds of receiving a potentially curative operation and experience inferior outcomes. Given substantial expenditures on the Medicaid program, strategies for increasing utilization of curative surgery in Medicaid patients with lung cancer are needed.

[Comparison between computed tomography-guided percutaneous microwave ablation and thoracoscopic lobectomy for stage I non-small cell lung cancer.](#) Wang Y1,2, Liu B1,2, Cao P3, et al. Thorac Cancer. 2018 Aug 28. doi: 10.1111/1759-7714.12842. [Epub ahead of print]

BACKGROUND: The study was conducted to investigate the effectiveness and cost of computed tomography (CT)-guided percutaneous microwave ablation (MWA) and thoracoscopic lobectomy for stage I non-small cell lung cancer (NSCLC). **METHODS:** We retrospectively analyzed the data of 46 and 85 patients with stage I NSCLC treated with CT-guided percutaneous MWA or thoracoscopic lobectomy, respectively, at our center from July 2013 to June 2015. Overall survival (OS), disease-free survival (DFS), local control rate, hospital stay, and cost were evaluated. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. **RESULTS:** The one and two-year OS rates were 97.82% and 91.30% and 97.65% and 90.59% in the MWA and lobectomy groups, respectively. The one and two-year DFS rates were 95.65% and 76.09% and 95.29% and 75.29%, respectively. No significant differences were observed in log-rank analysis between the groups ($P = 0.169$). The hospital stays in the MWA and lobectomy groups were 6.62 ± 2.31 and 9.57 ± 3.19 days, respectively. The costs of MWA and lobectomy were $\text{US}\$3274.50 \pm \text{US}\233.91 and $\text{US}\$4678.87 \pm \text{US}\155.96 , respectively. The differences were all significant ($P = 0.003$). **CONCLUSION:** MWA and thoracoscopic lobectomy for stage I NSCLC demonstrate similar one and two-year OS and DFS, with no significant differences between the two groups. MWA involved a shorter hospital stay and lower cost, thus should be considered a better option for patients with severe cardiopulmonary comorbidity and patients unwilling to undergo surgery.

[Perioperative Outcomes for Stage I Non-Small Cell Lung Cancer: Differences between Men and Women.](#) Nelson DB1, Lapid DJ1, Mitchell KG1, et al. Ann Thorac Surg. 2018 Aug 14. pii: S0003-4975(18)31140-8. doi: 10.1016/j.athoracsur.2018.06.070. [Epub ahead of print]

BACKGROUND: Previous studies have highlighted important biologic and survival-related differences among men and women with non-small cell lung cancer (NSCLC). However, differences in perioperative or short term outcomes have not been as well characterized. In this study, we investigated differences in the perioperative period and postoperative emergency room visits among men and women after lobectomy for stage I NSCLC. **METHODS:** A retrospective review was performed of patients who underwent a lobectomy for clinical stage I NSCLC at a single institution from 2010 to 2015. **RESULTS:** We identified 559 patients for inclusion, including 293 (52%) women and 266 (48%) men. Women were more likely to present with cT1 status ($p=0.005$) and to undergo minimally invasive surgery ($p=0.058$). To reduce confounding, 206 case-matched pairs were identified. After matching, there were no differences in length of stay ($p=0.551$), or pulmonary complications ($p=0.509$); however, men experienced more cardiac complications (18% versus 7%), $p=0.001$. Importantly, while rates of 30- and 90-day emergency department (ED) visits between sexes were similar ($p=0.531$, $p=0.890$, respectively), and there were no sex-related differences in presenting symptom upon return to ED ($p=0.478$), women were more likely to be re-admitted after presenting to the ED within 30-days ($p=0.038$). **CONCLUSIONS:** Women demonstrated an increased likelihood of being admitted after presenting to the emergency department within 30-days after discharge, indicating important differences between men and women in the short term period after lobectomy. Further research will be required to further understand the etiology for these differences.

[Needlescopic-assisted thoracoscopic pulmonary anatomical lobectomy and segmentectomy for lung cancer: a bridge between multiportal and uniportal thoracoscopic surgery.](#) Ko HJ1, Chiang XH2, Yang SM3,4, Yang MC1. Surg Today. 2018 Aug 27. doi: 10.1007/s00595-018-1707-y. [Epub ahead of print]

PURPOSE: Needlescopic instruments allow us to perform complex laparoscopic procedures, which are almost painless and scarless postoperatively; however, their utilization in thoracoscopic surgery has been limited to minor procedures, including bullectomy and sympathectomy. We present our initial experience of performing thoracoscopic anatomical lung resection via a single utility incision with additional needlescopic working ports and compare the operative results with those of uniportal video-assisted thoracoscopic surgery (VATS). **METHODS:** We reviewed data on 75 consecutive patients with lung cancer, who underwent anatomical lung resections, including lobectomy and segmentectomy, between February 2015 and September 2017. Of the 75 patients, 39 underwent uniportal VATS (uniportal group), and 36 underwent needlescopic-assisted VATS (n-VATS group). We compared the peri- and postoperative outcomes of the two groups. **RESULTS:** The clinical characteristics did not differ significantly between the groups, except in the ages of the patients. The n-VATS group had a shorter operation time (mean 159.3 min vs. 198.8 min, $P = 0.023$) and lower intraoperative blood loss (mean 40.9 mL vs. 143.2 mL, $P = 0.047$). Two major pulmonary arterial bleeding events and one conversion to thoracotomy occurred in the uniportal group. **CONCLUSION:** Uniportal VATS can be performed more efficiently and safely with the assistance of additional needlescopic ports and instruments, without compromising the benefits of less postoperative pain and early recovery.

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

[Safety and Efficacy of Bevacizumab Plus Standard-of-Care Treatment Beyond Disease Progression in Patients With Advanced Non-Small Cell Lung Cancer: The AvaALL Randomized Clinical Trial.](#)

Gridelli C1, de Castro Carpeno J2, Dingemans AC3, et al. JAMA Oncol. 2018 Aug 30:e183486. doi: 10.1001/jamaoncol.2018.3486. [Epub ahead of print]

IMPORTANCE: Bevacizumab treatment beyond progression has been investigated in breast and metastatic colorectal cancers. Avastin in All Lines Lung (AvaALL) is the first randomized phase 3 study of bevacizumab across multiple lines of treatment beyond progression in non-small cell lung cancer (NSCLC). **OBJECTIVE:** To assess the efficacy and safety of continuous bevacizumab treatment beyond first progression in NSCLC. **DESIGN, SETTING, AND PARTICIPANTS:** AvaALL was a randomized, open-label, phase 3b trial, conducted from 2011 to 2015 in 123 centers worldwide. Patients with nonsquamous NSCLC previously treated with first-line bevacizumab plus platinum-doublet chemotherapy and at least 2 cycles of bevacizumab maintenance were randomized (1:1) at first progression to receive bevacizumab plus standard of care (SOC) or SOC alone. **INTERVENTIONS:** Patients received bevacizumab (7.5 or 15 mg/kg intravenously every 21 days) and/or investigator's choice of SOC. For subsequent lines, patients treated with bevacizumab received SOC with or without bevacizumab; the SOC arm received SOC only. **MAIN OUTCOMES AND MEASURES:** The primary outcome was overall survival (OS). Secondary outcomes included progression-free survival from first to second (PFS2) and third progression (PFS3), time to second (TTP2) and third progression (TTP3), and safety. **RESULTS:** Between June 2011 and January 2015, 485 patients (median age, 63.0 years [range, 26-84 years]; 293 [60.4%] male) were randomized. Median OS was not significantly longer with bevacizumab plus SOC vs SOC alone: 11.9 (90% CI, 10.2-13.7) vs 10.2 (90% CI, 8.6-11.9) months (hazard ratio [HR], 0.84; 90% CI, 0.71-1.00; $P = .104$). Median PFS2 was numerically longer with bevacizumab plus SOC vs SOC alone: 5.5 (90% CI, 4.2-5.7) vs 4.0 (90% CI, 3.4-4.3) months (HR, 0.83; 90% CI, 0.70-0.98; $P = .06$). Median PFS3 appeared longer with bevacizumab plus SOC vs SOC alone:

4.0 (90% CI, 2.9-4.5) vs 2.6 (90% CI, 2.3-2.9) months (HR, 0.63; 90% CI, 0.49-0.83), as did TTP2 and TTP3. Grade 3/4 adverse events were more frequent with bevacizumab plus SOC (186 [76.5%]) vs SOC alone (140 [60.3%]). No new safety signals were observed. **CONCLUSIONS AND RELEVANCE:** The primary end point was not met; however, OS was underpowered according to initial statistical assumptions. Continued therapy beyond first progression led to improved PFS3 (but not PFS2), TTP2, and TTP3. Although a result with $P = .06$ for PFS2 would conventionally be considered significant at a specified 2-sided α of .10, in the absence of adjustments for multiplicity, this result could be a chance finding. No new safety signals were identified with bevacizumab treatment beyond progression.

Results of PROFILE 1029, a Phase III Comparison of First-Line Crizotinib versus Chemotherapy in East Asian Patients with ALK-Positive Advanced Non-Small Cell Lung Cancer. Wu YL1, Lu S2, Lu Y3, et al. *J Thorac Oncol.* 2018 Aug 14. pii: S1556-0864(18)30721-4. doi: 10.1016/j.jtho.2018.06.012. [Epub ahead of print]

INTRODUCTION: The phase III randomized PROFILE 1014 study demonstrated superiority of crizotinib to first-line chemotherapy in prolonging progression-free survival (PFS) in previously untreated patients with ALK receptor tyrosine kinase gene (ALK)-positive advanced nonsquamous non-small cell lung cancer. This result was consistent with that in the smaller subset of East Asian patients in PROFILE 1014. The subsequent study reported here prospectively evaluated crizotinib in a larger East Asian patient population. **METHODS:** In this open-label phase III study (PROFILE 1029), patients were randomized 1:1 to receive orally administered crizotinib 250 mg twice daily continuously (3-week cycles) or intravenously administered chemotherapy (pemetrexed 500 mg/m², plus cisplatin 75 mg/m², or carboplatin [at a dose to produce area under the concentration-time curve of 5-6 mg·min/mL]) every 3 weeks for a maximum of six cycles. PFS confirmed by independent radiology review was the primary end point. **RESULTS:** Crizotinib significantly prolonged PFS (hazard ratio, 0.402; 95% confidence interval [CI]: 0.286-0.565; $p < 0.001$). The median PFS was 11.1 months with crizotinib and 6.8 months with chemotherapy. The objective response rate was 87.5% (95% CI: 79.6-93.2%) with crizotinib versus 45.6% (95% CI: 35.8-55.7%) with chemotherapy ($p < 0.001$). The most common adverse events were increased transaminase levels, diarrhea, and vision disorders with crizotinib and leukopenia, neutropenia, and anemia with chemotherapy. Significantly greater improvements from baseline in patient-reported outcomes were seen in crizotinib-treated versus chemotherapy-treated patients. **CONCLUSIONS:** First-line crizotinib significantly improved PFS, objective response rate, and patient-reported outcomes compared with standard platinum-based chemotherapy in East Asian patients with ALK-positive advanced NSCLC, which is similar to the results from PROFILE 1014. The safety profiles of crizotinib and chemotherapy were consistent with those previously published.

Phase 1B Study of Mometinib Combined With Trametinib in Metastatic, Kirsten Rat Sarcoma Viral Oncogene Homolog-Mutated Non-Small-Cell Lung Cancer After Platinum-Based Chemotherapy Treatment Failure. Barbie DA1, Spira A2, Kelly K3, Humeniuk R4, Kawashima J4, Kong S4, Koczywas M5. *Clin Lung Cancer.* 2018 Aug 4. pii: S1525-7304(18)30171-2. doi: 10.1016/j.clcc.2018.07.004. [Epub ahead of print]

INTRODUCTION: Specific treatment options are lacking for Kirsten rat sarcoma viral oncogene homolog (KRAS)-mutated non-small-cell lung cancer (NSCLC) despite treatment advances in other mutation-driven subgroups. **PATIENTS AND METHODS:** In this study we evaluated the multitargeted Janus kinase/TANK-binding kinase 1 (TBK1) inhibitor mometinib combined with the mitogen/extracellular signal-related kinase (MEK)1/MEK2 inhibitor trametinib in patients with platinum-treated, refractory, metastatic, KRAS-mutated NSCLC. Dose escalations (3 + 3 design) were conducted with mometinib in combination with trametinib 1.0 mg once daily, then with trametinib in combination with the maximum tolerated dose (MTD) of mometinib. MTD was determined from dose-limiting

toxicity (DLT) during patients' first 28-day cycle. Safety was the primary end point, and efficacy parameters, including disease control rate (DCR) at 8 weeks, were secondary end points. **RESULTS:** Twenty-one patients were enrolled (median age: 68 years; 14 [66.7%] female). The MTD was momelotinib 150 mg twice daily in combination with trametinib 1.0 mg once daily. DLTs that determined the MTD were increased alanine aminotransferase and fatigue. The most common adverse events of any grade were nausea (n = 14 [66.7%]), diarrhea (n = 11 [52.4%]), and fatigue (n = 11 [52.4%]). The most common Grade ≥ 3 event was hypoxia (n = 3 [14.3%]). No patients achieved objective response. DCR at 8 weeks was 12 patients (57.1%) (90% confidence interval [CI], 37.2%-75.5%). Median progression-free and overall survival were 3.6 months (90% CI, 2.2-5.6 months) and 7.4 months (90% CI, 4.0-15.3 months), respectively. Maximum momelotinib plasma concentrations were reached 1 to 2 hours after dosing, but were insufficient to achieve significant TBK1 inhibition. **CONCLUSION:** The additional use of momelotinib with trametinib does not improve on the activity of single-agent trametinib in KRAS-mutated NSCLC on the basis of historic data.

[Phase Ib/II Study of Capmatinib \(INC280\) Plus Gefitinib After Failure of Endothelial Growth Factor Receptor \(EGFR\) Inhibitor Therapy in Patients With EGFR-Mutated, MET Factor-Dysregulated Non-Small-Cell Lung Cancer.](#)

Wu YL1, Zhang L1, Kim DW1, et al. J Clin Oncol. 2018 Aug 29;JCO2018777326. doi: 10.1200/JCO.2018.77.7326. [Epub ahead of print]

PURPOSE: Mesenchymal-epithelial transition factor (MET) dysregulation occurs in up to 26% of non-small-cell lung cancers (NSCLCs) after epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) treatment. Capmatinib (INC280) is a potent and selective MET inhibitor with preclinical activity in combination with gefitinib in EGFR-mutant, MET-amplified/overexpressing models of acquired EGFR-TKI resistance. This phase Ib/II study investigated the safety and efficacy of capmatinib plus gefitinib in patients with EGFR-mutated, MET-dysregulated (amplified/overexpressing) NSCLC who experienced disease progression while receiving EGFR-TKI treatment. **Methods** Patients in phase Ib received capmatinib 100- to 800-mg capsules once per day or 200- to 600-mg capsules or tablets twice per day, plus gefitinib 250 mg once per day. Patients in phase II received the recommended phase II dose. The primary end point was the overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. **Results** Sixty-one patients were treated in phase Ib, and 100 were treated in phase II. The recommended phase II dose was capmatinib 400 mg twice per day plus gefitinib 250 mg once per day. Preliminary clinical activity was observed, with an ORR across phase Ib/II of 27%. Increased activity was seen in patients with high MET-amplified tumors, with a phase II ORR of 47% in patients with a MET gene copy number ≥ 6 . Across phases Ib and II, the most common drug-related adverse events were nausea (28%), peripheral edema (22%), decreased appetite (21%), and rash (20%); the most common drug-related grade 3/4 adverse events were increased amylase and lipase levels (both 6%). No significant drug-drug interactions between capmatinib and gefitinib were evident. **Conclusion** This study, focused on a predominant EGFR-TKI resistance mechanism in patients with EGFR-mutated NSCLC, shows that the combination of capmatinib with gefitinib is a promising treatment for patients with EGFR-mutated, MET-dysregulated NSCLC, particularly MET-amplified disease.

[Erlotinib versus vinorelbine plus cisplatin as adjuvant therapy in Chinese patients with stage IIIA EGFR mutation-positive non-small-cell lung cancer \(EVAN\): a randomised, open-label, phase 2 trial.](#)

Yue D1, Xu S2, Wang Q3, et al. Lancet Respir Med. 2018 Aug 24. pii: S2213-2600(18)30277-7. doi: 10.1016/S2213-2600(18)30277-7. [Epub ahead of print]

BACKGROUND: Adjuvant chemotherapy after radical resection of stage IIIA non-small-cell lung cancer (NSCLC) has quite poor outcomes. We aimed to investigate whether adjuvant erlotinib therapy improves 2-year disease-free survival compared with chemotherapy in epidermal growth factor receptor (EGFR) mutation-positive stage IIIA NSCLC. **METHODS:** In this randomised, open-label, phase 2 trial,

eligible patients aged 18-75 years who had undergone complete (R0) resection of histologically or pathologically confirmed stage IIIA EGFR mutation-positive NSCLC and had not received any previous anticancer therapies were enrolled. Patients were randomly assigned (1:1) to receive either adjuvant erlotinib (150 mg once daily administered orally) or vinorelbine and cisplatin chemotherapy (four cycles of vinorelbine [25 mg/m² intravenously on days 1 and 8 of each 21-day cycle] plus cisplatin [75 mg/m² intravenously on day 1 of each 21-day cycle]). Randomisation was done by Simon's minimisation with a random element and was stratified by EGFR activating mutation type (exon 19 vs 21), histology (adenocarcinoma vs non-adenocarcinoma), and smoking status (smoker vs non-smoker). The primary endpoint in the unblinded intention-to-treat analysis was 2-year disease-free survival. This ongoing study is registered with ClinicalTrials.gov, number NCT01683175. **FINDINGS:** Between Sept 8, 2012, and May 21, 2015, 102 patients from 16 centres across China were enrolled and randomly assigned to receive erlotinib (n=51) or chemotherapy (n=51). Median follow-up was 33.0 months (IQR 17.8-43.1). 2-year disease-free survival was 81.4% (95% CI 69.6-93.1) in the erlotinib group and 44.6% (26.9-62.4) in the chemotherapy group (relative risk 1.823 [95% CI 1.194-2.784; p=0.0054]). The difference in 2-year disease-free survival between the groups was 36.7% (95% CI 15.5-58.0; p=0.0007). Adverse events of any grade occurred in 29 (58%) of 50 patients in the erlotinib group and 28 (65%) of 43 patients in the chemotherapy group. Grade 3 or worse adverse events occurred in six (12%) of 50 patients in the erlotinib group versus 11 (26%) of 43 in the chemotherapy group; the most common of these in the erlotinib group was rash (in two [4%] of 50 patients) and in the chemotherapy group were decreased neutrophil count (in seven [16%] of 43 patients) and myelosuppression (in four [9%]). No treatment-related deaths were reported. **INTERPRETATION:** Adjuvant erlotinib improved 2-year disease-free survival in patients with EGFR mutation-positive stage IIIA NSCLC compared with chemotherapy, with a better tolerability profile. This study suggests that tyrosine kinase inhibitors could have a potentially important role as adjuvant therapy in EGFR mutation-positive stage IIIA NSCLC. However, this trial was a phase 2 study. Mature overall survival data are also needed. Ongoing studies will hopefully confirm the role of adjuvant EGFR tyrosine kinase inhibitor therapy in patients with NSCLC. **FUNDING:** National Key Research and Development Program of China and Shanghai Roche Pharmaceuticals Ltd.

[Erlotinib as Neoadjuvant Therapy in Stage IIIA \(N2\) EGFR Mutation-Positive Non-Small Cell Lung Cancer: A Prospective, Single-Arm, Phase II Study.](#)

Xiong L1, Li R1, Sun J1, et al. *Oncologist*. 2018 Aug 29. pii: theoncologist.2018-0120. doi: 10.1634/theoncologist.2018-0120. [Epub ahead of print]

LESSONS LEARNED: The findings of this prospective, single-arm, phase II study showed that neoadjuvant erlotinib was well tolerated and might improve the radical resection rate in patients with stage IIIA-N2 epidermal growth factor receptor mutation-positive non-small cell lung cancer (NSCLC). Erlotinib shows promise as a neoadjuvant therapy option in this patient population. Next-generation sequencing may be useful for predicting outcomes with preoperative tyrosine kinase inhibitors (TKIs) in patients with NSCLC. Large-scale randomized controlled trials investigating the role of TKIs in perioperative therapy, combining neoadjuvant and adjuvant treatments to enhance personalized therapy for patients in this precision medicine era, are warranted. **BACKGROUND:** Information on epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) as neoadjuvant therapy in non-small cell lung cancer (NSCLC) is scarce. We evaluated whether neoadjuvant erlotinib improves operability and survival in patients with stage IIIA-N2 EGFR mutation-positive NSCLC. **METHODS:** We conducted a prospective, single-arm, phase II study. Patients received erlotinib 150 mg per day for 56 days in the neoadjuvant period. The primary endpoint was the radical resection rate. **RESULTS:** Nineteen patients were included in the final analysis. After erlotinib treatment, 14 patients underwent surgery. The radical resection rate was 68.4% (13/19) with a 21.1% (4/19) rate of pathological downstaging. The objective response rate was 42.1%; 89.5% (17/19) of patients achieved disease control, with a 10.3-month median disease-free survival among patients who underwent surgery. Among all 19 patients who received

neoadjuvant therapy, median progression-free survival (PFS) and overall survival were 11.2 and 51.6 months, respectively. Adverse events (AEs) occurred in 36.8% (7/19) of patients, with the most common AE being rash (26.3%); 15.8% experienced grade 3/4 AEs. Quality of life (QoL) improvements were observed after treatment with erlotinib for almost all QoL assessments. Effects of TP53 mutation on prognosis were evaluated in eight patients with adequate tissue samples. Next-generation sequencing revealed that most patients had a TP53 gene mutation (7/8) in addition to an EGFR mutation. No TP53 mutation, or very low abundance, was associated with longer PFS (36 and 38 months, respectively), whereas high abundance was associated with short PFS (8 months). **CONCLUSION:** Neoadjuvant erlotinib was well tolerated and may improve the radical resection rate in this patient population. Next-generation sequencing may predict outcomes with preoperative TKIs.

Organ-specific response to nivolumab in patients with non-small cell lung cancer (NSCLC).

Schmid S1,2, Diem S3,4,5, Li Q6, et al. Cancer Immunol Immunother. 2018 Aug 31. doi: 10.1007/s00262-018-2239-4. [Epub ahead of print]

BACKGROUND: Response to immune checkpoint inhibitors depends on tumor intrinsic properties and also on host factors in the tumour microenvironment including the presence of immune cells (IC). We hypothesized that nivolumab efficacy varies across different metastatic sites. **METHODS:** We retrospectively analyzed computed tomography scans of patients with metastatic non-small cell lung carcinoma (NSCLC) receiving nivolumab. RECIST 1.1 criteria were applied to assess the overall response rate (ORR) and organ-specific response rate (OSRR). **RESULTS:** We analyzed 52 patients including 44% females, 58% adenocarcinoma and 8% never smokers. Involved organs had target-lesions in the lung (42%), liver (25%), lymph nodes (56%) and soft tissue (13%) and non-target lesions in the bones (23%). ORR and disease control rate (DCR) were 20% and 45%, respectively. Median overall survival, progression-free survival and duration of response were 11.9, 2.3 and 10.3 months. OSRR and organ-specific DCR (OSDCR) were 28% and 90% in lymph nodes, 8% and 54 in the liver, and 9% and 55% in lung metastases. Nine out of 12 patients with bone metastases had progressive lesions. The cumulative incidence probability of organ-specific progression at 6 months was 14% in lymph nodes, 42% in the liver, 36% in lung metastases and 26% in the primary tumor, 29% in soft tissue and 33% in adrenal metastases. **CONCLUSION:** In conclusion, the efficacy of immunotherapy is dependent on the metastatic location. Treatment appears more active in lymph nodes compared to other organ sites such as liver, adrenals and bone. Future strategies may include additional local treatment in case of oligoprogression in these organs in patients with otherwise sustained treatment benefit.

Oral fluorouracil vs vinorelbine plus cisplatin as adjuvant chemotherapy for stage II-IIIa non-small cell lung cancer: Propensity score-matched and instrumental variable analyses.

Urushiyama H1, Jo T1,2, Yasunaga H3, et al. Cancer Med. 2018 Aug 27. doi: 10.1002/cam4.1725. [Epub ahead of print]

BACKGROUND: Adjuvant chemotherapy with vinorelbine plus cisplatin (VNR/CDDP) is a standard regimen for treatment of postoperative stage II-IIIa non-small cell lung cancer (NSCLC). However, oral fluorouracil offers a feasible alternative adjuvant chemotherapeutic regimen. We compared the prognoses of patients with NSCLC treated with adjuvant chemotherapy with either VNR/CDDP or oral fluorouracil. **METHODS:** We identified patients with stage II-IIIa NSCLC who underwent lung surgery followed by adjuvant chemotherapy with VNR/CDDP (n = 384) or oral fluorouracil (n = 268) between July 2010 and March 2015, using the national Japanese inpatient and outpatient Diagnosis Procedure Combination database. We compared recurrence-free survival between the groups by multivariable Cox regression analysis for one-to-one propensity score-matched patients and by instrumental variable analysis. **RESULTS:** Younger patients and patients with positive N2 nodes were more likely to receive VNR/CDDP, while older patients and those with T3N0 classification were more likely to receive oral

fluorouracil. Among 172 pairs of propensity-matched patients, time to adjuvant chemotherapy was shorter for oral fluorouracil compared with VNR/CDDP. Oral fluorouracil was also significantly associated with improved recurrence-free survival compared with VNR/CDDP, according to multivariable Cox regression analysis (hazard ratio, 0.41; 95% confidence interval, 0.26-0.64). Instrumental variable analysis showed a similar relationship (hazard ratio, 0.19; 95% confidence interval, 0.038-0.92). **CONCLUSIONS:** On a large nationwide cohort, adjuvant chemotherapy with oral fluorouracil prolonged recurrence-free survival in patients with postoperative stage II-IIIa NSCLC, compared with VNR/CDDP. Oral fluorouracil may thus be a useful alternative to VNR/CDDP for the adjuvant treatment of these patients.

Association of Target Volume Margins with Locoregional Control and Acute Toxicities for Non-Small Cell Lung Cancer Treated with Concurrent Chemoradiation Therapy. Yegya-Raman N1, Reyhan M1, Kim S2, Deek MP1, Yue N1, Zou W3, Malhotra J4, Aisner J4, Jabbour SK5. *Pract Radiat Oncol.* 2018 Aug 22. pii: S1879-8500(18)30253-4. doi: 10.1016/j.prro.2018.08.007. [Epub ahead of print]

PURPOSE: To investigate the association between target volume margins and clinical outcomes for patients with inoperable non-small cell lung cancer (NSCLC) treated with concurrent chemoradiation therapy. **METHODS:** /Materials: We reviewed records of 82 patients with inoperable NSCLC treated from 2009-2016 with concurrent chemoradiation. All patients received positron emission tomography-based treatment planning, 4-dimensional computed tomography simulation to define an internal target volume, and daily cone beam computed tomography. We quantified variations in target volume margins with a margin deviation index (MDI), calculated as the percentage change in equivalent uniform dose between the original planning target volume (PTV) and a standard reference PTV 10mm beyond the original gross tumor volume (GTV), consistent with the minimum margins mandated by recent NSCLC trials. Greater MDIs equated to smaller effective target volume margins. We dichotomized patients by the upper tercile MDI value (5.8%). Endpoints included time to locoregional progression and time to grade ≥ 3 radiation esophagitis (RE3) or radiation pneumonitis (RP3), modelled with the Fine-Gray method. **RESULTS:** Median follow-up was 37.8 months (range, 5.9-58.1 months). Larger MDIs correlated with smaller clinical target volume (CTV)+PTV margins, larger GTVs, later treatment year, and intensity-modulated radiation therapy use. The risk of locoregional progression did not differ for MDI $\geq 5.8\%$ versus $< 5.8\%$ (aHR 0.88, P=.76), while the risk of RE3 or RP3 was decreased for MDI $\geq 5.8\%$ (aHR 0.27, P=.027). Patients with MDI $\geq 5.8\%$ were treated with smaller CTV+PTV margins (median, 5.6mm versus 8mm, P<.0001) and a marginally lower volume of esophagus receiving ≥ 50 Gy (median, 31.1% versus 35.3%, P=.069). **CONCLUSIONS:** Smaller margins were used for larger tumors, yet were not associated with an increase in locoregional failures. Additional studies could clarify whether smaller margins, when used alongside modern radiotherapy techniques, decrease treatment-related toxicity for inoperable NSCLC.

24-Month Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin With or Without Pembrolizumab As First-Line Therapy for Advanced Nonsquamous Non-Small-Cell Lung Cancer. Borghaei H1, Langer CJ2, Gadgeel S3, et al. *J Thorac Oncol.* 2018 Aug 20. pii: S1556-0864(18)30942-0. doi: 10.1016/j.jtho.2018.08.004. [Epub ahead of print]

INTRODUCTION: Cohort G of KEYNOTE-021 (NCT02039674) evaluated the efficacy and safety of pembrolizumab plus pemetrexed-carboplatin (PC) versus PC alone as first-line therapy for advanced nonsquamous NSCLC. At the primary analysis (median follow-up, 10.6 months), pembrolizumab significantly improved objective response rate (ORR) and progression-free survival (PFS); hazard ratio (HR) for overall survival (OS) was 0.90 (95% CI, 0.42-1.91). Herein, we present an updated analysis. **METHODS:** 123 patients with previously untreated stage IIIB/IV nonsquamous NSCLC without EGFR/ALK aberrations were randomized 1:1 to 4 cycles of PC with/without pembrolizumab 200 mg Q3W. Pembrolizumab treatment continued for 2 years; maintenance pemetrexed was permitted in both

groups. Eligible patients in the PC alone group with radiologic progression could cross over to pembrolizumab monotherapy. P values are nominal (one-sided $P < 0.025$). **RESULTS:** As of December 1, 2017, median follow-up was 23.9 mo. ORR was 56.7% with pembrolizumab plus PC versus 30.2% with PC alone (estimated difference, 26.4%; 95% CI, 8.9%–42.4%; $P = 0.0016$). PFS was significantly improved with pembrolizumab plus PC versus PC alone (HR, 0.53; 95% CI, 0.33–0.86; $P = 0.0049$). 41 patients in the PC alone group received subsequent anti-PD-1/anti-PD-L1 therapy. The HR for OS was 0.56 (95% CI, 0.32–0.95; $P = 0.0151$). 41% of patients in the pembrolizumab plus PC group and 27% in the PC alone group had grade 3–5 treatment-related adverse events. **CONCLUSIONS:** Significant improvements in PFS and ORR with pembrolizumab plus PC versus PC alone observed in the primary analysis were maintained and the HR for OS with 24-month median follow-up was 0.56, favoring pembrolizumab plus PC.

Assessment of Resistance Mechanisms and Clinical Implications in Patients With EGFR T790M-Positive Lung Cancer and Acquired Resistance to Osimertinib. Oxnard GR^{1,2}, Hu Y¹, Mileham KF³, et al. *AMA Oncol.* 2018 Aug 2. doi: 10.1001/jamaoncol.2018.2969. [Epub ahead of print]

IMPORTANCE: Osimertinib mesylate is used globally to treat EGFR-mutant non-small cell lung cancer (NSCLC) with tyrosine kinase inhibitor resistance mediated by the EGFR T790M mutation. Acquired resistance to osimertinib is a growing clinical challenge that is poorly understood. **OBJECTIVE:** To understand the molecular mechanisms of acquired resistance to osimertinib and their clinical behavior. **DESIGN, SETTING, AND PARTICIPANTS:** Patients with advanced NSCLC who received osimertinib for T790M-positive acquired resistance to prior EGFR tyrosine kinase inhibitor were identified from a multi-institutional cohort ($n = 143$) and a confirmatory trial cohort (NCT01802632) ($n = 110$). Next-generation sequencing of tumor biopsies after osimertinib resistance was performed. Genotyping of plasma cell-free DNA was studied as an orthogonal approach, including serial plasma samples when available. The study and analysis were finalized on November 9, 2017. **MAIN OUTCOMES AND MEASURES:** Mechanisms of resistance and their association with time to treatment discontinuation on osimertinib. **RESULTS:** Of the 143 patients evaluated, 41 (28 [68%] women) had tumor next-generation sequencing after acquired resistance to osimertinib. Among 13 patients (32%) with maintained T790M at the time of resistance, EGFR C797S was seen in 9 patients (22%). Among 28 individuals (68%) with loss of T790M, a range of competing resistance mechanisms was detected, including novel mechanisms such as acquired KRAS mutations and targetable gene fusions. Time to treatment discontinuation was shorter in patients with T790M loss (6.1 vs 15.2 months), suggesting emergence of pre-existing resistant clones; this finding was confirmed in a validation cohort of 110 patients with plasma cell-free DNA genotyping performed after osimertinib resistance. In studies of serial plasma levels of mutant EGFR, loss of T790M at resistance was associated with a smaller decrease in levels of the EGFR driver mutation after 1 to 3 weeks of therapy (100% vs 83% decrease; $P = .01$). **CONCLUSIONS AND RELEVANCE:** Acquired resistance to osimertinib mediated by loss of the T790M mutation is associated with early resistance and a range of competing resistance mechanisms. These data provide clinical evidence of the heterogeneity of resistance in advanced NSCLC and a need for clinical trial strategies that can overcome multiple concomitant resistance mechanisms or strategies for preventing such resistance.

Clinical Impact of Post-Progression Survival on Overall Survival in Elderly Patients with Non-Small-Cell Lung Cancer Harboring Sensitive EGFR Mutations Treated with First-Line EGFR Tyrosine Kinase Inhibitors. Imai H¹, Yamada Y², Sugiyama T³, et al. *Chemotherapy.* 2018;63(3):181-189. doi: 10.1159/000490949. Epub 2018 Aug 14.

BACKGROUND/AIMS: More than 50% of patients with lung cancer are aged > 65 years, and non-small-cell lung cancer (NSCLC) accounts for 85% of all cases of lung cancer among both elderly and

adult patients. Subsequent therapies confound the capability to discern the effect of first-line chemotherapy on overall survival (OS). Therefore, using individual-level data, our study aimed to determine the relationships of progression-free survival (PFS) and post-progression survival (PPS) with OS after first-line epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) treatment in elderly patients with NSCLC harboring sensitive EGFR mutations. **METHODS:** Between April 2008 and December 2015, we analyzed 68 elderly patients with NSCLC harboring sensitive EGFR mutations and treated with first-line EGFR-TKI. The relationships of PFS and PPS with OS were analyzed at an individual level. **RESULTS:** Linear regression analysis showed that PPS was more closely associated with OS ($R^2 = 0.54$) than PFS was ($R^2 = 0.48$). Best response at first-line treatment, performance status at the end of first-line treatment, and administration of EGFR-TKI rechallenge were significantly correlated with PPS. **CONCLUSIONS:** PPS has a stronger impact on OS than PFS does in elderly patients with NSCLC harboring sensitive EGFR mutations and treated with first-line EGFR-TKI. These results indicate that OS in this patient population may be influenced by treatments subsequent to first-line chemotherapy; however, this remains to be verified in prospective studies.

NSCLC - RADIOTHERAPY

[Subgroup Survival Analysis In Stage I-II NSCLC Patients With a Central Tumor Partly Treated With Risk-Adapted SBRT.](#) Stam B1, Kwint M1, Guckenberger M2, et al. Int J Radiat Oncol Biol Phys. 2018 Aug 31. pii: S0360-3016(18)33682-4. doi: 10.1016/j.ijrobp.2018.08.040. [Epub ahead of print] **PURPOSE:** Stereotactic body radiation therapy (SBRT) has been associated with increased toxicity when delivered to early stage non-small cell lung cancer (NSCLC) patients with a tumor within 2cm of the proximal bronchial tree (PBT). We investigated non-cancer death for these patients as it relates to GTV-proximity to the PBT compared to peripheral tumors. **METHODS AND MATERIALS:** We included 765 early stage NSCLC patients treated with SBRT to a median of 3x18Gy. Patients with central tumors were treated with a risk-adapted (less intense) schedule (mostly 8 fractions) in 55% of the patients in the first cm group, and 27% of the patients in the second cm group. An average anatomy with PBT and organs at risk (OARs) contoured was deformed onto each patient to obtain distance of the GTV to the PBT and doses to OARs. Log-rank, one-way Anova and Cox regressions were performed to assess differences between the first cm, second cm and peripheral groups, and associations with non-cancer death. **RESULTS:** Median overall survival was 42.7 months, median non-cancer death was 57.3 months and median follow-up 34.8 months. Non-cancer death in the first cm group (31 patients) was significantly different from non-cancer death in the other groups with hazard ratio (HR) 3.175 ($p < 0.001$). Non-cancer death in the second cm group (71 patients) was not different from non-cancer death in the peripheral group ($p = 0.53$). Doses to OARs were higher in the first and second cm groups than the peripheral group for all OARs. High dose to the PBT was associated with non-cancer death: D1%, HR:1.006Gy-1 ($p = 0.003$). **CONCLUSION:** Patients with a GTV in the first cm surrounding the PBT died more often from other causes than cancer. Non-cancer death in patients with a GTV in the second cm, who partly received a risk-adapted schedule, was comparable to patients with a peripheral tumor.

[Initial Results of a Multicenter Phase II Trial of Stereotactic Ablative Radiation Therapy for Oligometastatic Cancer.](#) Suter P1, Clump DA1, Kalash R1, D'Ambrosio D2, Mihai A3, Wang H4, Petro DP5, Burton SA1, Heron DE6. Int J Radiat Oncol Biol Phys. 2018 Aug 24. pii: S0360-3016(18)33573-9. doi:

BACKGROUND: Oligometastatic disease has emerged as a potentially curable state in the spectrum of cancer progression. Aggressive local therapy such as stereotactic ablative radiation therapy (SABR) may

improve oncologic outcomes. Herein, we report the initial oncologic outcomes and patient-reported quality of life (PR-QoL) from a phase II multi-center trial for patients with oligometastatic disease. **METHODS:** Patients with oligometastatic disease (1-5 metastases) were prospectively recruited between 2011-2017. SABR dose and fractionation was dependent upon the lesion size and location. Patient follow-up occurred within 6 weeks of completion of SABR and at 3-month intervals. Patients received FACT-G questionnaire at baseline and at each follow-up to assess for PR-QoL. Median follow-up was calculated by reverse Kaplan-Meier method. Overall survival (OS), local progression-free survival (LPFS), and distant progression-free survival (DPFS) were calculated using Kaplan-Meier. **RESULTS:** We enrolled 147 patients with oligometastatic cancer with a median age of 66.4 years (IQR: 59.9-74.6). The most common primary tumors included: lung (21.8%, non-small cell: n=29, small cell: n=3), colorectal adenocarcinoma (21.1%), and head & neck (10.9%, squamous cell carcinoma: n=11). In a median follow-up of 41.3 months (IQR: 14.6-59.0), the median OS was 42.3 months (95% CI: 27.4-NE) with 5-year OS of 43%. 5-year LPFS and DPFS were 74% and 17%, respectively. Acute grade 2+ and 3+ toxicity were 7.5% and 2.0%, respectively and late grade 2+ and 3+ toxicity were both 1.4%. There was no significant change in quality of life at completion, 6 weeks, 3 months, and 9 months after treatment. At 6 and 12 months patients were found to have statistically significant improvement in PR-QoL. **CONCLUSION:** This multi-center prospective phase II study demonstrates SABR for recurrent oligometastatic cancer is a feasible and tolerable treatment option with minimal acute and late grade 3 toxicity. Additionally, PR-QoL was not adversely affected.

Inverse-Planned Deliverable 4D-IMRT for Lung SBRT. Hamzeei M1, Modiri A1, Kazemzadeh N1, Hagan A1, Sawant A1. Med Phys. 2018 Aug 28. doi: 10.1002/mp.13157. [Epub ahead of print]

PURPOSE: We present a particle swarm optimization (PSO)-based technique to create deliverable four-dimensional (4D=3D+time) intensity-modulated radiation therapy (IMRT) plans for lung stereotactic body radiotherapy (SBRT). The 4D planning concept uses respiratory motion as an additional degree of freedom to achieve further sparing of organs at risk (OARs). The 4D-IMRT plan involves the delivery of an order of magnitude more IMRT apertures (~15,000 - 20,000), with potentially large inter-aperture variations in the delivered fluence, compared to conventional (i.e., 3D) IMRT. In order to deliver the 4D plan in an efficient manner, we present an optimization-based aperture sequencing technique. **METHOD:** A graphic processing unit (GPU)-enabled PSO-based inverse-planning engine, developed and integrated with a research version of the Eclipse (Varian, Palo Alto, CA) treatment planning system (TPS), was employed to create 4D-IMRT plans as follows. 4D computed tomography scans (4DCTs) and beam configurations from clinical treatment plans of seven lung cancer patients were retrospectively collected, and in each case, the PSO engine iteratively adjusted aperture monitor unit (MU) weights for all beam apertures across all respiratory phases to optimize OAR dose sparing while maintaining planning target volume (PTV) coverage. We calculated the transition times from each aperture to all other apertures for each beam, taking into account the maximum leaf velocity of the multileaf collimator (MLC), and developed a mixed-integer optimization technique for aperture sequencing. The goal of sequencing was to maximize delivery efficiency (i.e., minimize the time required to deliver the dose map) by accounting for leaf velocity, aperture MUs and duration of each respiratory phase. The efficiency of the proposed delivery method was compared with that of a greedy algorithm which chose only from neighboring apertures for the subsequent steps in the sequence. **RESULTS:** The 4D-IMRT optimized plans achieved PTV coverage comparable to clinical plans while improving OAR sparing by an average of 39.7% for Dmax heart, 20.5% for Dmax esophagus, 25.6% for Dmax spinal cord, and 2.1% for V13 lung (with Dmax standing for maximum dose and V13 standing for volume receiving ≥ 13 Gy). Our mixed-integer optimization-based aperture sequencing enabled the delivery to be performed in fewer cycles compared to the greedy method. This reduction was 89 ± 79 cycles corresponding to an improvement of $15.94 \pm 8.01\%$, when considering respiratory cycle duration of four seconds, and, 55 ± 33 cycles corresponding to an

improvement of 15.14±4.45%, when considering respiratory cycle duration of six seconds.

CONCLUSION: PSO-based 4D-IMRT represents an attractive technique to further improve OAR sparing in lung SBRT. Efficient delivery of a large number of sparse apertures (control points) introduces a challenge in 4D-IMRT treatment planning and delivery. Through judicious optimization of the aperture sequence across all phases, such delivery can be performed on a clinically feasible time scale. This article is protected by copyright. All rights reserved.

Radiofrequency ablation of stage IA non-small cell lung cancer in patients ineligible for surgery: results of a prospective multicenter phase II trial. Palussière J1, Chomy F2, Savina M3, et al. J Cardiothorac Surg. 2018 Aug 24;13(1):91. doi: 10.1186/s13019-018-0773-y.

BACKGROUND: A prospective multicenter phase II trial to evaluate the survival outcomes of percutaneous radiofrequency ablation (RFA) for patients with stage IA non-small cell lung cancer (NSCLC), ineligible for surgery. **METHODS:** Patients with a biopsy-proven stage IA NSCLC, staging established by a positron emission tomography-computed tomography (PET-CT), were eligible. The primary objective was to evaluate the local control of RFA at 1-year. Secondary objectives were 1- and 3-year overall survival (OS), 3-year local control, lung function (prior to and 3 months after RFA) and quality of life (prior to and 1 month after RFA). **RESULTS:** Of the 42 patients (mean age 71.7 y) that were enrolled at six French cancer centers, 32 were eligible and assessable. Twenty-seven patients did not recur at 1 year corresponding to a local control rate of 84.38% (95% CI, [67.21-95.72]). The local control rate at 3 years was 81.25% (95% CI, [54.35-95.95]). The OS rate was 91.67% (95% CI, [77.53-98.25]) at 1 year and 58.33% (95% CI, [40.76-74.49]) at 3 years. The forced expiratory volume was stable in most patients apart from two, in whom we observed a 10% decrease. There was no significant change in the global health status or in the quality of life following RFA. **CONCLUSION:** RFA is an efficient treatment for medically inoperable stage IA NSCLC patients. RFA is well tolerated, does not adversely affect pulmonary function and the 3-year OS rate is comparable to that of stereotactic body radiotherapy, in similar patients.

Targeted Sequencing and Intracranial Outcomes of Patients With Lung Adenocarcinoma Brain Metastases Treated With Radiotherapy. Press RH1, Zhang C2, Cassidy RJ1, et al. Cancer. 2018 Aug 18. doi: 10.1002/cncr.31589. [Epub ahead of print]

BACKGROUND: Treatment for advanced lung adenocarcinoma (AC) has become increasingly personalized based on molecular results. However, for patients with AC brain metastases (BMs), intracranial outcomes based on molecular subtype and the frequency of molecular aberrations are less well defined. This study sought to report targeted next-generation sequencing results and investigate molecularly based outcomes for patients with AC-BMs treated with radiotherapy. **METHODS:** The records of 132 patients with AC-BMs treated at Emory University from September 2008 to August 2016 with successful next-generation sequencing were reviewed. Rates of local disease recurrence, distant brain failure (DBF), and salvage whole-brain radiotherapy (WBRT) were estimated using cumulative incidence with competing risk analysis. Univariate and multivariate analyses were performed. **RESULTS:** The most common aberrations included tumor protein 53 (TP53) (60%), KRAS (29%), epidermal growth factor receptor (EGFR) (20.5%), phosphatase and tensin homolog (PTEN) loss (15.5%), and MET amplification (13%). The majority of patients (62%) were treated with stereotactic radiosurgery alone. In these patients, KRAS mutation, anaplastic lymphoma kinase (ALK) rearrangement, and having ≥ 6 BMs were associated with an increased risk of salvage WBRT ($P < .05$). KRAS mutation remained significant for an increased risk of salvage WBRT when compared with EGFR/ALK/KRAS-negative patients (hazard ratio, 5.17; $P < .05$), despite a similar risk of DBF. PTEN loss was associated with increased risk of DBF ($P < .05$), whereas EGFR and ALK aberrations were associated with a decreased risk of local disease recurrence ($P < .05$). **CONCLUSIONS:** The results of the current study quantified the frequency

of genetic aberrations in patients with AC-BMs and demonstrated their association with intracranial outcomes. In particular, a cohort of patients with KRAS mutations and ≥ 6 BMs were identified to be at high risk of requiring salvage WBRT after undergoing upfront stereotactic radiosurgery. Cancer 2018;000:000-000. © 2018 American Cancer Society.

Knowledge-based planning for identifying high-risk stereotactic ablative radiotherapy treatment plans for lung tumors larger than 5cm. Hof SVT1, Delaney AR1, Tekatli H1, Twisk J2, Slotman BJ1, Senan S1, Dahele M1, Verbakel WF3. Int J Radiat Oncol Biol Phys. 2018 Aug 13. pii: S0360-3016(18)33543-0. doi: 10.1016/j.ijrobp.2018.08.013. [Epub ahead of print]

PURPOSE: Stereotactic ablative body radiotherapy (SABR) for lung tumors ≥ 5 cm, can be associated with more toxicity. We investigated the relationship between dosimetry and toxicity and used a knowledge-based planning solution to retrospectively perform individualized treatment plan quality assurance (QA) with the aim of identifying where planning could have been improved. **MATERIAL AND METHODS:** Prior retrospective analysis of 53 patients with primary or recurrent non-small cell lung cancer ≥ 5 cm, treated with 5 or 8-fraction volumetric modulated arc therapy SABR, between 2008-2014, showed 30% \geq grade (G) 3 toxicity. During this period, several improvements were made to departmental planning protocols. RapidPlan was used to compare dosimetry of patients with/without G ≥ 3 toxicity and a model comprising plans from patients without toxicity and compliant with the current planning protocol, was used to quality assure the plans from patients who had toxicity. **RESULTS:** 16/53 patients had G ≥ 3 toxicity, including 10 radiation pneumonitis (RP), 3 lung hemorrhage (LH) (1 also had RP) and one airway stenosis/atelectasis. RP was again shown to be significantly correlated with contralateral and total-lung V5 and mean lung dose. The 4 highest contralateral-lung doses belonged to patients with RP. 5/10 clinical plans in patients with RP had a contralateral-lung mean dose up to 2.5x higher than the knowledge-based plan. For 2/3 patients with LH and one with airway stenosis/atelectasis, the clinical plans had the highest proximal bronchial tree doses, which was also higher than in plans from the model. In 8 patients with G ≥ 3 toxicity, clinical plans had similar dosimetry as the predictions from the model. **CONCLUSION:** A "no-toxicity" RapidPlan model identified the potential for dosimetric improvement in nearly 50% of historical treatment plans from patients with G ≥ 3 toxicity after SABR for lung tumors ≥ 5 cm. Model-based QA may be useful for benchmarking treatment planning protocols in routine practice and in clinical studies.

SMALL CELL LUNG CANCER - SCLC

The effects of prophylactic cranial irradiation versus control on survival of patients with extensive-stage small-cell lung cancer: a meta-analysis of 14 trials. Ge W1, Xu H2, Yan Y1, Cao D3. Radiat Oncol. 2018 Aug 23;13(1):155. doi: 10.1186/s13014-018-1101-3.

BACKGROUND: A recent Japanese study suggested prophylactic cranial irradiation (PCI) failed to improve survival of extensive-stage small-cell lung cancer (SCLC). However, previous studies showed that PCI was beneficial in reducing the rate of mortality for extensive-stage SCLC. In this study, we aimed to evaluate the impact of PCI on the survival of patients diagnosed with extensive-stage SCLC by meta-analysis. **METHODS:** PubMed, Embase, the Cochrane library and Chinese Biomedical Literature database (CBM) were systematically searched to identify eligible clinical studies assessing the efficacy of PCI in extensive-stage SCLC patients. After extracting survival data, brain metastasis, and response rates, the pooled estimates were calculated. **RESULTS:** A total of 14 clinical studies were included, involving 1221 cases in the PCI group and 5074 in the control group. The results showed that PCI significantly improved overall survival (Hazard ratio (HR) = 0.57; 95% confidence interval (CI): 0.47, 0.69; $p < 0.001$) and brain metastasis (risk ratio (RR) = 0.47, 95%CI: 0.33, 0.69; $p < 0.01$). Subgroup analysis along with sensitivity analysis suggested that PCI effects on overall survival were independent of region, pre-PCI

brain metastasis status and PCI administration timing. **CONCLUSION:** PCI improves overall survival in extensive-stage SCLC. More randomized controlled trials are needed to verify our findings.

Impact of prophylactic cranial irradiation on pattern of brain metastases as a first recurrence site for limited-disease small-cell lung cancer. Nakamura M1, Onozawa M1, Motegi A1, et al. J Radiat Res. 2018 Aug 9. doi: 10.1093/jrr/rry066. [Epub ahead of print]

This study sought to evaluate the impact of prophylactic cranial irradiation (PCI) on the pattern of brain recurrence after radical treatment in patients with limited-disease small-cell lung cancer (LD-SCLC). Patients treated with radiotherapy and chemotherapy between January 2006 and December 2014 at a single institution were retrospectively examined. Radiotherapy was performed using accelerated hyperfractionated radiotherapy (twice daily, 45 Gy in 30 fractions) or conventional fractionated radiotherapy (once daily, 50 Gy in 25 fractions). The chemotherapy regimen consisted of intravenous platinum-etoposide. A total of 162 patients were included and the median follow-up duration was 38 months. Ninety-three patients underwent PCI, and the 3-year overall survival (OS) rates were 14% among patients without PCI and 41% among those with PCI ($P < 0.001$). The frequency of brain metastases as a first recurrence site (BMFR) was significantly lower among patients who underwent PCI, compared with those who did not ($P = 0.002$). The median time to the 1 of BMFR was significantly shorter among patients without PCI than among those with PCI ($P = 0.012$). In addition, 68% of the BMFR patients who did not undergo PCI exhibited five or more lesions, while only 12% of BMFR patients who did undergo PCI exhibited five or more lesions ($P < 0.001$). PCI had a significant positive impact on patient prognosis after radical treatment for LD-SCLC, and the difference in the number of, and time to the appearance of, BMFR between patients treated with PCI and those treated without PCI might affect the clinical outcomes.

Barriers to Combined-Modality Therapy for Limited-Stage Small Cell Lung Cancer. Pezzi TA1, Schwartz DL1,2, Mohamed ASR1,3, et al. JAMA Oncol. 2018 Aug 1;4(8):e174504. doi: 10.1001/jamaoncol.2017.4504. Epub 2018 Aug 9.

IMPORTANCE: Combined-modality therapy with chemotherapy and radiation therapy plays a crucial role in the upfront treatment of patients with limited-stage small cell lung cancer (SCLC), but there may be barriers to utilization in the United States. **OBJECTIVE:** To estimate utilization rates and factors associated with chemotherapy and radiation therapy delivery for limited-stage SCLC using the National Cancer Database. **DESIGN, SETTING, AND PARTICIPANTS:** Analysis of initial management of all limited-stage SCLC cases from 2004 through 2013 in the National Cancer Database. **MAIN OUTCOMES AND MEASURES:** Utilization rates of chemotherapy and radiation therapy at time of initial treatment. Multivariable analysis identified independent clinical and socioeconomic factors associated with utilization and overall survival. **RESULTS:** A total of 70 247 cases met inclusion criteria (55.3% female; median age, 68 y [range, 19-90 y]). Initial treatment was 55.5% chemotherapy and radiation therapy, 20.5% chemotherapy alone, 3.5% radiation therapy alone, and 20.0% neither (0.5% not reported). Median survival was 18.2 (95% CI, 17.9-18.4), 10.5 (95% CI, 10.3-10.7), 8.3 (95% CI, 7.7-8.8), and 3.7 (95% CI, 3.5-3.8) months, respectively. Being uninsured was associated with a lower likelihood of both chemotherapy (odds ratio [OR], 0.65; 95% CI, 0.56-0.75; $P < .001$) and radiation therapy (OR, 0.75; 95% CI, 0.67-0.85; $P < .001$) administration on multivariable analysis. Medicare/Medicaid insurance had no impact on chemotherapy use, whereas Medicaid (OR, 0.79; 95% CI, 0.72-0.87; $P < .001$) and Medicare (OR, 0.86; 95% CI, 0.82-0.91; $P < .001$) were independently associated with a lower likelihood of radiation therapy delivery. Lack of health insurance (HR, 1.19; 95% CI, 1.13-1.26; $P < .001$), Medicaid (HR, 1.27; 95% CI, 1.21-1.32; $P < .001$), and Medicare (HR, 1.12; 95% CI, 1.09-1.15; $P < .001$) coverage were independently associated with shorter survival on adjusted analysis,

while chemotherapy (HR, 0.55; 95% CI, 0.54-0.57; $P < .001$) and radiation therapy (HR, 0.62; 95% CI, 0.60-0.63; $P < .001$) were associated with a survival benefit. **CONCLUSIONS AND RELEVANCE:** Substantial proportions of patients documented in a major US cancer registry did not receive radiation therapy or chemotherapy as part of initial treatment for limited-stage SCLC, which, in turn, was associated with poor survival. Lack of radiation therapy delivery was uniquely associated with government insurance coverage, suggesting a need for targeted access improvement in this population. Additional work will be necessary to conclusively define exact population patterns, specific treatment deficiencies, and causative factors leading to heterogeneous care delivery.

[Impact of coexistent chronic obstructive pulmonary disease on the survival of patients with small cell lung cancer receiving chemotherapy.](#) Ju S1, Lee HR1, Kim JY2, et al. Thorac Cancer. 2018 Aug 14. doi: 10.1111/1759-7714.12832. [Epub ahead of print]

BACKGROUND: While there is growing interest in the correlation between chronic obstructive pulmonary disease (COPD) and non-small cell lung cancer, very few studies have examined the interaction between COPD and small cell lung cancer (SCLC). Therefore, the aim of this study was to examine the impact of COPD on the survival of patients with SCLC. **METHODS:** The medical records of 110 patients with SCLC who received chemotherapy from July 2006 until April 2014 were retrospectively examined. The overall survival (OS) and progression-free survival (PFS) rates of spirometry-diagnosed COPD and non-COPD groups were compared. Predictors for poorer survival were analyzed using Cox proportional hazards regression. **RESULTS:** Of the 110 SCLC patients, 57 (51.8%) had coexistent COPD. The median OS for the COPD group was 11.6 months and for the non-COPD group was 11.2 months (log-rank test, $P = 0.581$), whereas the median PFS rates were 6.65 and 6.57 months, respectively (log-rank test, $P = 0.559$). Multivariate analysis identified Eastern Cooperative Oncology Group performance status ≥ 2 and extensive-stage SCLC as independent risk factors for shorter OS; however, coexisting COPD was not a predictor of survival. **CONCLUSIONS:** Although over half of the SCLC patients receiving chemotherapy had COPD, coexisting COPD had no impact on the survival of patients with SCLC.

[Barriers to Combined-Modality Therapy for Limited-Stage Small Cell Lung Cancer.](#) Pezzi TA1, Schwartz DL1,2, Mohamed ASR1,3, et al. JAMA Oncol. 2018 Aug 1;4(8):e174504. doi: 10.1001/jamaoncol.2017.4504. Epub 2018 Aug 9.

IMPORTANCE: Combined-modality therapy with chemotherapy and radiation therapy plays a crucial role in the upfront treatment of patients with limited-stage small cell lung cancer (SCLC), but there may be barriers to utilization in the United States. **OBJECTIVE:** To estimate utilization rates and factors associated with chemotherapy and radiation therapy delivery for limited-stage SCLC using the National Cancer Database. **DESIGN, SETTING, AND PARTICIPANTS:** Analysis of initial management of all limited-stage SCLC cases from 2004 through 2013 in the National Cancer Database. **MAIN OUTCOMES AND MEASURES:** Utilization rates of chemotherapy and radiation therapy at time of initial treatment. Multivariable analysis identified independent clinical and socioeconomic factors associated with utilization and overall survival. **RESULTS:** A total of 70 247 cases met inclusion criteria (55.3% female; median age, 68 y [range, 19-90 y]). Initial treatment was 55.5% chemotherapy and radiation therapy, 20.5% chemotherapy alone, 3.5% radiation therapy alone, and 20.0% neither (0.5% not reported). Median survival was 18.2 (95% CI, 17.9-18.4), 10.5 (95% CI, 10.3-10.7), 8.3 (95% CI, 7.7-8.8), and 3.7 (95% CI, 3.5-3.8) months, respectively. Being uninsured was associated with a lower likelihood of both chemotherapy (odds ratio [OR], 0.65; 95% CI, 0.56-0.75; $P < .001$) and radiation therapy (OR, 0.75; 95% CI, 0.67-0.85; $P < .001$) administration on multivariable analysis. Medicare/Medicaid insurance had no impact on chemotherapy use, whereas Medicaid (OR, 0.79; 95% CI, 0.72-0.87; $P < .001$) and Medicare (OR, 0.86; 95% CI, 0.82-0.91; $P < .001$) were independently associated

with a lower likelihood of radiation therapy delivery. Lack of health insurance (HR, 1.19; 95% CI, 1.13-1.26; P < .001), Medicaid (HR, 1.27; 95% CI, 1.21-1.32; P < .001), and Medicare (HR, 1.12; 95% CI, 1.09-1.15; P < .001) coverage were independently associated with shorter survival on adjusted analysis, while chemotherapy (HR, 0.55; 95% CI, 0.54-0.57; P < .001) and radiation therapy (HR, 0.62; 95% CI, 0.60-0.63; P < .001) were associated with a survival benefit. **CONCLUSIONS AND RELEVANCE:** Substantial proportions of patients documented in a major US cancer registry did not receive radiation therapy or chemotherapy as part of initial treatment for limited-stage SCLC, which, in turn, was associated with poor survival. Lack of radiation therapy delivery was uniquely associated with government insurance coverage, suggesting a need for targeted access improvement in this population. Additional work will be necessary to conclusively define exact population patterns, specific treatment deficiencies, and causative factors leading to heterogeneous care delivery.

[Impact of Baseline Characteristics on Extensive-stage SCLC Patients Treated with Etoposide/Carboplatin; a Secondary Analysis of a Phase III Study.](#) Abdel-Rahman O1,2. Clin Respir J. 2018 Aug 3. doi: 10.1111/crj.12950. [Epub ahead of print]

BACKGROUND: The purpose of the current study is to investigate the impact of baseline characteristics on the outcomes of extensive-stage small cell lung cancer (SCLC) patients recruited into a clinical trial.

METHODS: This is a secondary analysis of the control arm (etoposide/carboplatin arm) of the "NCT00363415" study which is a phase III study conducted between 2006 and 2007. Univariate analysis of factors affecting overall and progression-free survival was conducted through Cox regression analysis [including age, race, gender, ECOG performance score, body mass index, LDH, number of metastatic sites and brain metastases]. Factors with P < 0.05 in the univariate analysis were then included in the multivariate analysis. **RESULTS:** All patients within the control arm (etoposide/carboplatin) were included in the analysis (N= 455 patients). The following factors were predictive of worse overall survival in univariate analysis (P<0.05): performance score=2, LDH > upper limit of normal and ≥ 3 metastatic sites. Multivariate Cox regression analysis incorporating these three factors showed that only number of metastatic sites predicts worse overall survival (P<0.0001). Likewise, the following factors were associated with worse progression-free survival in univariate analysis (P<0.05): performance score=2 and ≥ 3 metastatic sites predict worse progression-free survival (P<0.05). Multivariate analysis incorporating these two factors showed that only number of metastatic sites predicts worse progression-free survival (P<0.0001). **CONCLUSION:** Number of metastatic sites is the most important predictive factor for overall and progression-free survival among patients with extensive-stage SCLC treated with systemic chemotherapy within a clinical trial. This article is protected by copyright. All rights reserved.

[Immunotherapeutic maintenance treatment with toll-like receptor 9 agonist lefitolimod in patients with extensive-stage small-cell lung cancer: Results from the exploratory, controlled, randomized, international phase 2 IMPULSE study.](#) Thomas M1, Ponce-Aix S2, Navarro A3, et al. Ann Oncol. 2018 Aug 20. doi: 10.1093/annonc/mdy326. [Epub ahead of print]

BACKGROUND: The immune surveillance reactivator lefitolimod (MGN1703), a DNA-based TLR9 agonist, might foster innate and adaptive immune response and thus improve immune-mediated control of residual cancer disease. The IMPULSE phase 2 study evaluated the efficacy and safety of lefitolimod as maintenance treatment in extensive-stage small-cell lung cancer (ES-SCLC) after objective response to first-line chemotherapy, an indication with a high unmet medical need and stagnant treatment improvement in the last decades. **PATIENTS AND METHODS:** 103 patients with ES-SCLC and objective tumor response (as per RECIST 1.1) following 4 cycles of platinum-based first-line induction therapy were randomized to receive either lefitolimod maintenance therapy or local standard of care at a ratio of 3:2 until progression or unacceptable toxicity. **RESULTS:** From 103 patients enrolled, 62 were randomized to lefitolimod, 41 to the control arm. Patient demographics and response patterns to first-line

therapy were balanced. Lefitolimod exhibited a favorable safety profile and pharmacodynamic assessment confirmed the mode-of-action showing a clear activation of monocytes and production of interferon-gamma-induced protein 10 (IP-10). While in the ITT population no relevant effect of lefitolimod on progression-free and overall survival (OS) could be observed, two pre-defined patient subgroups indicated promising results, favoring lefitolimod with respect to OS: in patients with a low frequency of activated CD86+ B cells (hazard ratio, HR 0.53, 95%CI 0.26-1.08; n = 38 of 88 analyzed) and in patients with reported chronic obstructive pulmonary disease (COPD) (HR 0.48, 95%CI 0.20-1.17, n = 25 of 103). **CONCLUSIONS:** The IMPULSE study showed no relevant effect of lefitolimod on the main efficacy endpoint OS in the ITT, but (1) the expected pharmacodynamic response to lefitolimod, (2) positive OS efficacy signals in two pre-defined subgroups and (3) a favorable safety profile. These data support further exploration of lefitolimod in SCLC.

[Application of prophylactic cranial irradiation in limited-stage small-cell lung cancer: which patients could benefit?](#)

Kou P1, Wang H2, Yang D1, Zhang Y3, Yu J1. *Future Oncol.* 2018 Aug 9. doi: 10.2217/fon-2018-0481. [Epub ahead of print]

AIM: To analyze the role of prophylactic cranial irradiation (PCI) on the survival for patients with limited-stage small-cell lung cancer (LS-SCLC). **PATIENTS & METHODS:** We screened patients from Surveillance, Epidemiology and End Results database. Kaplan-Meier analysis and Cox proportional hazard model were used to evaluate factors influencing survival. **RESULTS:** LS-SCLC patients who receiving PCI were associated with better overall survival (OS) ($p < 0.001$) and cancer-specific survival (CSS) ($p < 0.001$). Multivariable Cox analysis revealed PCI was an independent prognostic factor for OS ($p < 0.001$) and CSS ($p < 0.001$). In subgroup analysis, there were no OS and CSS differences between PCI and no PCI groups in black patients and patient with a tumor size < 5 cm (all $p > 0.05$).

CONCLUSION: PCI remains an effective method for most LS-SCLC patients. However, caution should be taken in recommending PCI for black patients and patients with a tumor size < 5 cm. Further clinical trials are necessary to validate our results and identify the most suitable patients for PCI in the modern era.

[Pilot Study: Regional Changes in Brain 18F-FDG Uptake After Prophylactic Cranial Irradiation and Chemotherapy in small cell lung cancer May Reflect Functional Changes.](#)

Eshghi N1, Garland L1, Choudhary G2, Hsu CC1, Eshghi A3, Han J1, Hamilton RJ1, Krupinski E4, Kuo PH1. *J Nucl Med Technol.* 2018 Aug 3. pii: jnmt.118.212316. doi: 10.2967/jnmt.118.212316. [Epub ahead of print]

OBJECTIVE: Chemotherapy followed by prophylactic cranial irradiation (PCI) is associated with increased survival in patients with small cell lung cancer (SCLC) but is associated with fatigue and cognitive impairment. This retrospective study evaluated regional differences in fluorodeoxyglucose (18F-FDG) uptake of the brain before and after PCI. The null hypothesis was that direct toxic effects on the brain from PCI and chemotherapy are symmetric, thus asymmetric deviations may reflect functional changes due to therapy. **MATERIALS AND METHODS:** Electronic medical records from 2013-2016 were reviewed for patients with SCLC, MRI of brain negative for metastasis, and 18F-FDG-positron emission tomography/computed tomography (PET/CT) scans pre- and post PCI. As standard of care, patients received first-line chemotherapy or chemoradiation to the thorax followed by PCI. The 18F-FDGPET/CT scans closest in temporal proximity before and after PCI were selected. Sixteen patients met these initial criteria. Commercially available PET software (MIM) was utilized to register and subtract the PET scans pre-and post PCI to obtain difference maps. Occipital and cerebellar regions were excluded from the final statistical analysis given known high variability and misregistration. The Chi-square test was used to analyze the data. **RESULTS:** Two patients had 18F-FDG uptake differences only in occipital and cerebellar regions. The software registration failed on one patient's scans. Therefore, thirteen patients were included in the final analysis. Nine of thirteen patients demonstrated significant unilateral changes in

only one region of the brain, and three of thirteen showed significant changes unilaterally in two regions. The Chi-square test revealed a significant unilateral regional difference on the patient level ($X^2 = 6.24$, $P = 0.025$). The most commonly affected brain region was the frontal lobe. **CONCLUSION:** Significantly more patients had unilateral rather than bilateral regional differences (both increases and decreases) in 18F-FDG uptake in the brain pre-and post PCI. This suggests that differences in unilateral distribution are related to functional changes, since direct toxicity alone from PCI and chemotherapy would be symmetric. The frontal region was the most commonly affected, suggesting a potential contributing etiology for cognitive impairment and decreased executive function after therapy.

PALLIATIVE AND SUPPORTIVE CARE

[Lung cancer patients have the highest malignancy-associated suicide rate in USA: a population-based analysis.](#) Rahouma M1, Kamel M1, Abouarab A1, et al. *Ecancermedicalsecience*. 2018 Aug 16;12:859. doi: 10.3332/ecancer.2018.859. eCollection 2018.

PURPOSE: Previous studies have reported that psychological and social distresses associated with a cancer diagnosis have led to an increase in suicides compared to the general population. We sought to explore lung cancer-associated suicide rates in a large national database compared to the general population, and to the three most prevalent non-skin cancers [breast, prostate and colorectal cancer (CRC)]. **METHODS:** The Surveillance, Epidemiology and End Results (SEER) database (1973-2013) was retrospectively reviewed to identify cancer-associated suicide deaths in all cancers combined, as well as for each of lung, prostate, breast or CRCs. Suicide incidence and standardised mortality ratio (SMR) were estimated using SEER*Stat-8.3.2 program. Suicidal trends over time and timing from cancer diagnosis to suicide were estimated for each cancer type. **RESULTS:** Among 3,640,229 cancer patients, 6,661 committed suicide. The cancer-associated suicide rate was 27.5/100,000 person years (SMR = 1.57). The highest suicide risk was observed in patients with lung cancer (SMR = 4.17) followed by CRC (SMR = 1.41), breast cancer (SMR = 1.40) and prostate cancer (SMR = 1.18). Median time to suicide was 7 months in lung cancer, 56 months in prostate cancer, 52 months in breast cancer and 37 months in CRC ($p < 0.001$). We noticed a decreasing trend in suicide SMR over time, which is most notable for lung cancer compared to the other three cancers. In lung cancer, suicide SMR was higher in elderly patients (70-75 years; SMR = 12), males (SMR = 8.8), Asians (SMR = 13.7), widowed patients (SMR = 11.6), undifferentiated tumours (SMR = 8.6), small-cell lung cancer (SMR = 11.2) or metastatic disease (SMR = 13.9) and in patients who refused surgery (SMR = 13). **CONCLUSION:** The cancer-associated suicide rate is nearly twice that of the general population of the United States of America. The suicide risk is highest among the patients with lung cancer, particularly elderly, widowed, male patients and patients with unfavourable tumour characteristics. The identification of high-risk patients is of extreme importance to provide proper psychological assessment, support and counselling to reduce these rates.

[The Perceived Facilitators and Challenges of Translating a Lung Cancer Palliative Care Intervention Into Community-Based Settings.](#) Siler S1, Mamier I, Winslow B. *J Hosp Palliat Nurs*. 2018 Aug;20(4):407-415. doi: 10.1097/NJH.0000000000000470.

Despite significant progress in implementing palliative care interventions for patients with cancer, few intervention studies seek health care clinicians' input before implementation of these into the community. The purpose of this study was to explore palliative care and oncology clinicians' perspectives on the perceived facilitators and challenges in meeting the quality-of-life needs of patients with lung cancer and family caregivers in community-based settings. The Reach Effectiveness Adoption Implementation Maintenance model for implementation research was used as a framework. This was a multisite qualitative study using focus group and key informant interviews. Nineteen clinicians addressed useful practices and challenges in the following areas: (a) early palliative care, (b) interdisciplinary care

planning, (c) symptom management, (d) addressing psychological and social needs, and (e) providing culturally respectful care, including spiritual care. In preparation for the intervention, specific education needs and organizational challenges were revealed. Challenges included timing and staffing constraints, the need for clinician education on palliative care services to increase organizational buy-in, and education in providing spiritual support for patients and family caregivers. This research allowed investigators to understand perceptions of clinicians as they prepared to integrate palliative care in their settings. Hospice and palliative care nurses can be instrumental in implementing palliative care into community practice.

Outcomes of a Dignity Therapy/Life Plan Intervention for Patients With Advanced Cancer

Undergoing Chemotherapy. Dose AM1, McCabe PJ, Krecke CA, Sloan JA. *J Hosp Palliat Nurs.* 2018 Aug;20(4):400-406. doi: 10.1097/NJH.0000000000000461.

Dignity therapy is a psychosocial intervention provided at the end of life to improve patient outcomes, but many persons cannot complete it because of health decline. Patients also reprioritize their life plans as death becomes imminent. As part of meeting standards to provide psychosocial palliative care simultaneously with cancer treatment, we provided a dignity therapy/life plan intervention to 18 patients with advanced pancreatic or lung cancer receiving cancer treatment. The study aim was to evaluate patient-reported outcomes of dignity therapy/life plan. Dignity therapy entailed interviews during 3 outpatient oncology encounters, which then became a legacy document for family. Participants documented life goals as their life plan. Distress, quality of life, spirituality, dignity, and purpose in life were measured at baseline, immediately after intervention, and 3 months later. No variables were significantly different from baseline to postintervention and 3 months later, except for less distress between baseline and 3 months ($P = .04$). Although this intervention did not show improvements in outcomes, patients with advanced disease receiving active treatment typically experience worsening symptoms overall. Maintaining psychosocial outcomes may be preventing further morbidity in an advanced cancer population during treatment and bears further exploration. Given our small sample size, further research is warranted.

Translation and Evaluation of a Lung Cancer, Palliative Care Intervention for Community

Practice. Nguyen HQ1, Ruel N2, Macias M3, Borneman T2, Alian M4, Becher M5, Lee K6, Ferrell B7. *J Pain Symptom Manage.* 2018 Aug 2. pii: S0885-3924(18)30392-0. doi: 10.1016/j.jpainsymman.2018.07.018. [Epub ahead of print]

CONTEXT: A notable gap in the evidence base for palliative care (PC) for cancer is that most trials were conducted in specialized centers with limited translation and further evaluation in "real-world" settings. Health systems are desperate for guidance on effective, scalable models. **OBJECTIVES:** The objective of this study was to determine the effects of a nurse-led PC intervention for patients with non-small-cell lung cancer and their family caregivers (FCGs) in a community-based setting. **METHODS:** Two-group, sequential, quasi-experimental design with Phase 1 (usual care [UC]) followed by Phase 2 (intervention) was conducted at three Kaiser Permanente Southern California sites. Participants included patients with Stage 2-4 non-small-cell lung cancer and their FCG. Standard measures of quality of life (QOL) included Functional Assessment of Cancer Therapy-Lung, Functional Assessment of Chronic Illness Therapy-Spirituality Subscale, City of Hope Family QOL; other outcomes were distress, health care utilization, caregiver preparedness, and burden. **RESULTS:** Patients in the intervention cohort had significant improvements in three (physical, emotional, and functional well-being) of the five QOL domains at one month that were sustained through three month compared to UC ($P < 0.01$). Caregivers in the intervention cohort had improvements in physical ($P = 0.04$) and spiritual well-being ($P = 0.03$) and preparedness ($P = 0.04$) compared to UC. There were no differences in distress or health care utilization between cohorts.

CONCLUSION: Our findings suggest that a research-based PC intervention can be successfully adapted to community settings to achieve similar, if not better, QOL outcomes for patients and FCGs compared to UC. Nonetheless, additional modifications to ensure consistent referrals to PC and streamlining routine assessments and patient/FCG education are needed to sustain and disseminate the PC intervention. Copyright © 2018 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.

Characteristics associated with physical function trajectories in older adults with cancer during

chemotherapy. Wong ML1, Paul SM2, Mastick J2, Ritchie C3, Steinman MA3, Walter LC3, Miaskowski C2. *J Pain Symptom Manage.* 2018 Aug 22. pii: S0885-3924(18)30436-6. doi: 10.1016/j.jpainsymman.2018.08.006. [Epub ahead of print]

CONTEXT: Studies on physical function trajectories in older adults during chemotherapy remain limited. **OBJECTIVES:** Determine demographic, clinical, and symptom characteristics associated with initial levels as well as trajectories of physical function over two cycles of chemotherapy in adults age >65 with breast, gastrointestinal, gynecological, or lung cancer. **METHODS:** Older adults with cancer (n=363) who had received chemotherapy within the preceding four weeks were assessed six times over two cycles of chemotherapy using the Short Form-12 Physical Component Summary (PCS) score. Hierarchical linear modeling was used to evaluate for inter-individual variability in initial levels and trajectories of PCS scores. **RESULTS:** Mean age was 71.4 years (SD 5.5). Mean PCS score at enrollment was 40.5 (SD 0.45). On average, PCS scores decreased slightly (i.e., 0.21 points) at each subsequent assessment. Lower PCS scores at enrollment were associated with older age, greater comorbidity, being unemployed, lack of regular exercise, higher morning fatigue, lower evening energy, occurrence of pain, lower trait anxiety, and lower attentional function. Only higher morning fatigue and lower enrollment PCS scores were associated with decrements in physical function over time. **CONCLUSION:** While several symptoms were associated with decrements in PCS scores at enrollment in older adults with cancer receiving chemotherapy, morning fatigue was the only symptom associated with decreases in physical function over time. Regular assessments of symptoms and implementation of evidence-based interventions should be considered to maintain physical function in older adults during chemotherapy.

Effects of shared decision making on distress and healthcare utilization among patients with lung cancer: a systematic review.

Geerse OP1, Stegmann ME2, Kerstjens HAM2, et al. *Pain Symptom Manage.* 2018 Aug 23. pii: S0885-3924(18)30441-X. doi: 10.1016/j.jpainsymman.2018.08.011. [Epub ahead of print]

CONTEXT: Lung cancer is associated with significant distress, poor quality of life, and a median prognosis of less than one year. Benefits of shared decision making (SDM) have been described for multiple diseases, either by the use of decisions aids or as part of supportive care interventions. **OBJECTIVES:** To summarize the effects of interventions facilitating SDM on distress and healthcare utilization among patients with lung cancer. **METHODS:** We performed a systematic literature search in the CINAHL, Cochrane, EMBASE, MEDLINE, and PsychINFO databases. Studies were eligible when conducted in a population of patients with lung cancer, evaluated the effects of an intervention that facilitated SDM, and measured distress and/or health care utilization as outcomes. **RESULTS:** A total of 12 studies, detailed in 13 publications, were included: nine randomized trials and three retrospective cohort studies. All studies reported on a supportive care intervention facilitating SDM as part of their intervention. Eight studies described effects on distress and eight studies measured effects on healthcare utilization. No effect was found in studies measuring generic distress. Positive effects, in favor of the intervention groups, were observed in studies using anxiety-specific measures (n=1) or depression-specific measures (n=3). Evidence for reductions in healthcare utilization was found in five studies.

CONCLUSION: Although not supported by all studies, our findings suggest that facilitating SDM in the context of lung cancer may lead to improved emotional outcomes and less aggressive therapies. Future studies, explicitly studying the effects of SDM by using decision aids, are needed to better elucidate potential benefits.

Factors Associated with Family Caregivers' Confidence in Future Surrogate Decision Making for Persons with Cancer. Dionne-Odom JN1,2, Ejem D1, Azuero A1, et al. *J Palliat Med.* 2018 Aug 21. doi: 10.1089/jpm.2018.0148. [Epub ahead of print]

BACKGROUND: Improving family caregiver preparation for surrogate decision making is a critical priority. **OBJECTIVE:** Determine a parsimonious set of intrapersonal factors associated with family caregivers' confidence in making future medical decisions for their relatives with cancer. **METHODS:** Cross-sectional mail survey. Family caregivers of Medicare beneficiaries with pancreatic, lung, brain, ovarian, head and neck, hematologic, and stage IV cancers from communities of eight U.S. cancer centers. Participants completed validated measures of their social and mental health, self-care behaviors, coping styles, and surrogate decision-making confidence. Using linear modeling, the Bayesian information criterion was used to identify factors associated with decision-making confidence. A bootstrap approach was used to conduct penalized inference on the selected model coefficients. Model fit validation was assessed with a random forest ensemble. **RESULTS:** Caregivers (n = 294) were on average 65.5 years old, mostly female (72.8%), and care recipients' spouse/partner (60.2%). The parsimonious set of factors associated with low caregiver decision-making confidence included less engagement in spiritual growth self-care, more use of avoidant coping, low emotional social support, and younger care recipient age (in-sample R² = 0.22). These factors were also identified by a random forest approach. After overfitting adjustment (shrunken R² = 0.09), the strongest associations with low surrogate decision-making confidence were low spiritual growth self-care (adjusted standardized B = 0.17, p = 0.005) and high use of avoidant coping (adjusted standardized B = -0.12, p = 0.049). **DISCUSSION:** Identifying strategies to enhance spiritual growth and reduce avoidant coping may be promising targets for interventions to improve family caregivers' confidence in future surrogate decision making.

Depression and healthcare utilization at end of life among older adults with advanced non-small cell lung cancer. McDermott C1, Bansal A2, Ramsey SD2, Lyman GH2, Sullivan SD2. *J Pain Symptom Manage.* 2018 Aug 16. pii: S0885-3924(18)30401-9. doi: 10.1016/j.jpainsymman.2018.08.004. [Epub ahead of print]

CONTEXT: Limited data exist regarding how depression diagnosed at different times relative to a cancer diagnosis may affect healthcare utilization at end of life (EOL). **OBJECTIVES:** To assess the relationship between depression and health care utilization at EOL among older adults (ages >=67) diagnosed with advanced non-small cell lung cancer (NSCLC) from 2009-2011. **METHODS:** Using the SEER-Medicare database, we fit multivariable logistic regression models to explore the association of depression with duration of hospice stay plus high-intensity care, e.g. inpatient admissions, in-hospital death, emergency department visits, and chemotherapy at EOL. We used a regression model to evaluate hospice enrollment, accounting for the competing risk of death. **RESULTS:** Among 13,827 subjects, pre-cancer depression was associated with hospice enrollment (sub-hazard ratio 1.19, 95% confidence interval (CI) 1.11-1.28), 90+ hospice days (adjusted odds ratio (aOR) 1.29, 95% CI 1.06-1.58), and lower odds of most utilization; we found no association with EOL chemotherapy. Diagnosis-time depression was associated with hospice enrollment (SHR 1.16, 95% CI 1.05-1.29) but not high-intensity utilization. Post-diagnosis depression was associated with lower hospice enrollment (SHR 0.80, 95% CI 0.74-0.85) and higher odds of ICU admission (aOR 1.18, 95% CI 1.01-1.37). **CONCLUSION:** EOL healthcare utilization varied by timing of depression diagnosis. Those with pre-cancer depression had lower odds of high-intensity healthcare, were more likely to utilize hospice, and have longer hospice stays. Regular

depression screening and treatment may help patients optimize decision-making for EOL care. Additionally, hospice providers may need additional resources to attend to mental health needs in this population.

COMPLEMENTARY & ALTERNATIVE THERAPY

[6-Gingerol as an arginase inhibitor prevents urethane-induced lung carcinogenesis by reprogramming tumor supporting M2 macrophages to M1 phenotype.](#) Yao J1, Du Z1, Li Z1, et al.

Food Funct. 2018 Aug 28. doi: 10.1039/c8fo01147h. [Epub ahead of print]

6-Gingerol (6-G) is the main bioactive component in Ginger (*Zingiber officinale* Roscoe). The aim of this study was to explore the contribution of macrophage polarization in 6-G-associated anti-cancer effects. In a urethane-induced lung carcinogenic model, lung carcinogenesis was positively correlated with macrophage (F4/80+) infiltration in lung interstitial in the control group. Furthermore, higher numbers of arginase+/F4/80+ M2 cells than iNOS+/F4/80+ M1 cells were observed in interstitial macrophages. Moreover, macrophage depletion by liposome-encapsulated clodronate (LEC) could significantly prevent lung carcinogenesis, whereas pexidartinib promoted lung carcinogenesis. After 6-G treatment, lung carcinogenesis was ameliorated with increased M1 macrophages and decreased M2 macrophages in the lung interstitial. ELISA showed that the levels of IFN- γ and IL-12 increased and the levels of IL-10 and TGF- β 1 decreased in the alveolar cavity compared to those in the control group. Unexpectedly, the carcinogenesis-preventing efficacy of 6-G was promoted in LEC-treated mice, but completely aborted in pexidartinib-treated mice. In the in vitro experiment, 6-G reset the IL-4-induced arginase+ M2 cells toward iNOS+ M1 cells and exhibited reduced levels of arginase 1 and ROS and elevated levels of L-arginine and NO. LEC and nor-NOHA selectively suppressed M2 macrophages but had a negligible effect on M1 macrophages, whereas pexidartinib decreased both M2 and M1 macrophages. The iNOS+ macrophage-promoting efficacy of 6-G was increased by LEC, but was completely eliminated by pretreatment with pexidartinib or nor-NOHA. M2 macrophage-resetting efficacy of 6-G was confirmed in a Lewis lung cancer allograft model. This study indicated a reprogramming effect of 6-G as an arginase inhibitor on tumor supporting macrophages.

[Therapeutic efficacy and safety of Kang-ai injection combined with platinum-based doublet chemotherapy in advanced NSCLC: A meta-analysis.](#) Lu Q1, Li CL2. Life Sci. 2018 Aug 23. pii: S0024-3205(18)30516-2. doi: 10.1016/j.lfs.2018.08.055. [Epub ahead of print]

AIMS: Kang-ai injection (KA) is a famous Chinese patent medicine authorized by China Food and Drug Administration, which is widely used to treat advanced non-small cell lung cancer (NSCLC) in China. This meta-analysis is aimed to evaluate the therapeutic efficacy and safety of KA on advanced NSCLC.

METHODS: Seven databases were examined for related studies until January 15, 2018. Odds ratio (OR) was used to evaluate tumor response, Karnofsky Performance Scale (KPS) improvement and adverse reactions, and mean difference (MD) was used to estimate immune functions. **KEY FINDINGS:** Thirty randomized controlled trials involving 1956 patients with advanced NSCLC were included. The results showed that compared with the platinum-based doublet chemotherapy (PBDC) alone, KA combined with PBDC could significantly enhance tumor response (OR = 1.69, 95% CI [1.40, 2.04], $P < 0.00001$), KPS improvement (OR = 3.01, 95% CI [2.36, 3.84], $P < 0.00001$) and immune functions including the percentages of CD3+ (MD = 8.90, 95% CI [3.06, 14.73], $P = 0.003$), CD4+ (MD = 9.43, 95% CI [6.32, 12.53], $P < 0.00001$) and NK (MD = 4.81, 95% CI [1.95, 7.68], $P = 0.001$) and the ratio of CD4+/CD8+ (MD = 0.29, 95% CI [0.04, 0.53], $P = 0.02$). Moreover, KA combined with PBDC markedly decreased the incidences of adverse reactions including gastrointestinal reaction (OR = 0.38, 95% CI [0.30, 0.47], $P < 0.00001$), myelosuppression (OR = 0.32, 95% CI [0.23, 0.45], $P < 0.00001$) and hair loss (OR = 0.53, 95% CI [0.36, 0.76], $P < 0.00001$). However, there was no significant difference between the combination

treatment group and the control group in the percentage of CD8+ (MD = -2.93, 95% CI [-6.68, 0.82], P = 0.13). **SIGNIFICANCE:** Despite the small sample size and study limitations, the results of this meta-analysis indicated that the combination therapy of KA and PBDC (especially NP regimen) might be a beneficial therapeutic method for advanced NSCLC patients.

MISCELLANEOUS WORKS

[Racial and Ethnic Differences in the Relationship Between Aspirin Use and Non-Small Cell Lung Cancer Risk and Survival.](#)

Erickson PI, Gardner LD2, Loffredo CA3, et al. *Cancer Epidemiol Biomarkers Prev.* 2018 Aug 31. pii: cebp.0366.2018. doi: 10.1158/1055-9965.EPI-18-0366. [Epub ahead of print]

BACKGROUND: African Americans (AA) experience higher incidence and mortality of lung cancer as compared with European Americans (EA). Inflammation is associated with lung cancer, many aspects of which differ between AA and EA. We investigated whether use, frequency, and duration of the anti-inflammatory drug aspirin was associated with lung cancer risk and survival, separately among AA and EA populations. **METHODS:** Using data from the Maryland Non-Small Cell Lung Cancer (NSCLC) Case-Control Study (1,220 cases [404 AA and 816 EA] and 1,634 controls [1,004 EA and 630 AA]), we estimated the adjusted odds ratios (OR) and hazard ratios (HR) with 95% confidence intervals (CI) of the associations between aspirin use and NSCLC risk and survival, respectively. **RESULTS:** Any aspirin use (OR: 0.66, 95% CI: 0.49 - 0.89), daily use of ≥ 1 tablet (OR: 0.68, 95% CI: 0.50 - 0.90), and use for ≥ 3 years (OR: 0.61, 95% CI: 0.44 - 0.85) was associated with lower NSCLC risk only among men, even after adjustment for covariates including BMI and global genetic ancestry. These variables were also associated with improved survival, but only among AA (HR: 0.64, 95% CI: 0.46-0.91; HR: 0.61, 95% CI: 0.42 - 0.90; and HR: 0.60, 95% CI: 0.39 - 0.92, respectively). Tylenol and other NSAIDs were either associated with elevated or no NSCLC risk. **CONCLUSIONS:** Aspirin use is associated with lower risk of NSCLC among men and improved survival among AA. **IMPACT:** Preventive regular aspirin use could be considered among men and African Americans.

[Exposure to a firefighting overhaul environment without respiratory protection increases immune dysregulation and lung disease risk.](#)

Gainey SJ1, Horn GP2, Towers AE3, et al. *PLoS One.* 2018 Aug 21;13(8):e0201830. doi: 10.1371/journal.pone.0201830. eCollection 2018. Firefighting activities appear to increase the risk of acute and chronic lung disease, including malignancy. While self-contained breathing apparatuses (SCBA) mitigate exposures to inhalable asphyxiates and carcinogens, firefighters frequently remove SCBA during overhaul when the firegrounds appear clear of visible smoke. Using a mouse model of overhaul without airway protection, the impact of fireground environment exposure on lung gene expression was assessed to identify transcripts potentially critical to firefighter-related chronic pulmonary illnesses. Lung tissue was collected 2 hrs post-overhaul and evaluated via whole genome transcriptomics by RNA-seq. Although gas metering showed that the fireground overhaul levels of carbon monoxide (CO), carbon dioxide (CO₂), hydrogen cyanine (HCN), hydrogen sulfide (H₂S) and oxygen (O₂) were within NIOSH ceiling recommendations, 3852 lung genes were differentially expressed when mice exposed to overhaul were compared to mice on the fireground but outside the overhaul environment. Importantly, overhaul exposure was associated with an up/down-regulation of 86 genes with a fold change of 1.5 or greater (p<0.5) including the immunomodulatory-linked genes S100a8 and Tnfsf9 (downregulation) and the cancer-linked genes, Capn11 and Rorc (upregulation). Taken together these findings indicate that, without respiratory protection, exposure to the fireground overhaul environment is associated with transcriptional changes impacting proteins potentially related to inflammation-associated lung disease and cancer.

[Are clinical trial eligibility criteria an accurate reflection of a real-world population of advanced non-small-cell lung cancer patients?](#) Al-Baimani K1, Jonker H1, Zhang T2, et al. *Curr Oncol*. 2018 Aug;25(4):e291-e297. doi: 10.3747/co.25.3978. Epub 2018 Aug 14.

BACKGROUND: Advanced non-small-cell lung cancer (nsclc) represents a major health issue globally. Systemic treatment decisions are informed by clinical trials, which, over years, have improved the survival of patients with advanced nsclc. The applicability of clinical trial results to the broad lung cancer population is unclear because strict eligibility criteria in trials generally select for optimal patients.

METHODS: We performed a retrospective chart review of all consecutive patients with advanced nsclc seen in outpatient consultation at our academic institution between September 2009 and September 2012, collecting data about patient demographics and cancer characteristics, treatment, and survival from hospital and pharmacy records. Two sets of arbitrary trial eligibility criteria were applied to the cohort. Scenario A stipulated Eastern Cooperative Oncology Group performance status (ecog ps) 0-1, no brain metastasis, creatinine less than 120 $\mu\text{mol/L}$, and no second malignancy. Less-strict scenario B stipulated ecog ps 0-2 and creatinine less than 120 $\mu\text{mol/L}$. We then used the two scenarios to analyze treatment and survival of patients by trial eligibility status. **RESULTS:** The 528 included patients had a median age of 67 years, with 55% being men and 58% having adenocarcinoma. Of those 528 patients, 291 received at least 1 line of palliative systemic therapy. Using the scenario A eligibility criteria, 73% were trial-ineligible. However, 46% of "ineligible" patients actually received therapy and experienced survival similar to that of the "eligible" treated patients (10.2 months vs. 11.6 months, $p = 0.10$). Using the scenario B criteria, only 35% were ineligible, but again, the survival of treated patients was similar in the ineligible and eligible groups (10.1 months vs. 10.9 months, $p = 0.57$). **CONCLUSIONS:** Current trial eligibility criteria are often strict and limit the enrolment of patients in clinical trials. Our results suggest that, depending on the chosen drug, its toxicities and tolerability, eligibility criteria could be carefully reviewed and relaxed.