



Caring Ambassadors Lung Cancer Program Literature Review, June 2016

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES	1-3
SCREENING, DIAGNOSIS AND STAGING	3-5
CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES	
NSCLC SURGERY	6-7
NSCLC CHEMOTHERAPY	8-10
NSCLC RADIOTHERAPY	10-13
SMALL CELL LUNG CANCER (SCLC)	13-16
PALLIATIVE AND SUPPORTIVE CARE	16-21
COMPLEMENTARY AND ALTERNATIVE THERAPY	21-24
MISCELLANEOUS WORKS	24-27

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Polymorphism of rs9387478 correlates with overall survival in female nonsmoking patients with lung cancer.](#) Han JF1,2, An SJ2, Su WM2, et al. Int J Biol Markers. 2016 May 28;31(2):e144-52. doi: 10.5301/jbm.5000180.

BACKGROUND: Our previous study identified rs9387478 as a new susceptibility locus associated with lung cancer in never-smoking women in Asia; however, the clinical and prognostic significance of this finding is not known. **METHODS:** We analyzed the relationship between the rs9387478 single nucleotide polymorphism and i) clinical parameters and ii) overall survival time in 505 female nonsmoking lung cancer patients, using the chi-square test and Kaplan-Meier analysis with the log-rank test, respectively. We further established the epidermal growth factor receptor (EGFR) mutation status and assessed its association with rs9387478 genotypes as well as the efficacy of EGFR tyrosine kinase inhibitors. **RESULTS:** The frequency of the AA genotype was significantly higher in the EGFR-mutation-negative group than in the EGFR-mutation-positive group (32% vs. 16%, $\chi^2 = 13.025$, $p = 0.011$). Patients with the CC genotype had a better overall survival time than patients with the AA/AC genotype (median survival time: 54.2 vs. 32.9 months, $\chi^2 = 4.593$, $p = 0.032$). The distribution of rs9387478 genotypes differed according to the clinical disease stage. **CONCLUSIONS:** This study indicates that the rs9387478 genotype was associated with overall survival in nonsmoking female patients with lung cancer, although it was not significant after adjusting for multiple testing. The identification of the location of the rs9387478 single nucleotide polymorphism in the genomic interval containing the DCBLD1 and ROS1 genes, together with the finding that the rs9387478 polymorphism correlates with EGFR mutation status, may have important implications for therapeutic approaches targeting EGFR or ROS1 in patients with lung cancer.

[High Expression of Rab-like 3 \(Rab13\) is Associated with Poor Survival of Patients with Non-Small Cell Lung Cancer via Repression of MAPK8/9/10-Mediated Autophagy.](#) Zhang W1, Sun J2, Luo J3. Med Sci Monit. 2016 May 10;22:1582-8.

BACKGROUND: Rab-like 3 (Rab13) is a member of the Rab subfamily of small GTPases which are involved in controlling proliferation and vesicular trafficking. Recent studies suggest that Rab proteins

might play a critical role in regulating cancer cell survival, but the underlying mechanisms remain largely unknown. **MATERIAL AND METHODS:** We performed a bioinformatics analysis to examine the correlation between the expression level of Rab13 and survival of non-small cell lung cancer (NSCLC) patients in three independent cohorts containing 484 patients. The function of Rab13 was examined in NSCLC cell line A549 in vitro. Following Rab13 knockdown, cells were stained with propidium iodine (PI) and Annexin V, followed by flow cytometry analysis (FACS) for cell death and autophagy induction. The activity of the MAPK signaling pathway was assessed by Western blotting of different MAPK phosphorylations, and modulated with different chemical inhibitors. **RESULTS:** High expression of Rab13 was significantly correlated with poor survival in all three independent NSCLC cohorts. In line with this result, Rab13 was frequently overexpressed in lung cancer cell lines as compared with normal lung fibroblast cell lines. Knockdown of Rab13 in lung cancer cells significantly enhanced cell death accompanied with autophagy induction, as evidenced by an increased level of autophagy marker LC3-II. Interestingly, Rab13 knockdown was associated with enhanced activation of MAPK8/9/10 but not MAPK11/12/13/14. Treatment of MAPK8/9/10-specific inhibitor SP600125, but not MAPK11/12/13/14-specific inhibitor SB203580, largely abolished Rab13 knockdown-induced LC3-I/LC3-II conversion and autophagic cell death. **CONCLUSIONS:** Together, these results suggest that high expression of Rab13 might inhibit cell death in NSCLCs via repression of MAPK8/9/10-mediated autophagy.

[Shorter telomere length of T-cells in peripheral blood of patients with lung cancer.](#) Qian Y1, Ding T1, Wei L2, Cao S3, Yang L1. *Onco Targets Ther.* 2016 May 4;9:2675-82. doi: 10.2147/OTT.S98488. eCollection 2016.

PURPOSE: Telomere shortening occurs in tumor tissues and peripheral blood lymphocytes of many common human malignancies, including lung cancer, but its variation in T-cells has never been investigated. Thus, the aim of this study was to assess telomere length in T-cells and its correlation with the clinical characteristics of patients with lung cancer. **PATIENTS AND METHODS:** A total of 40 patients with lung cancer but without prior cancer history and 25 healthy individuals were selected. T-cells were isolated and their telomere lengths were measured using quantitative real-time polymerase chain reaction methods. **RESULTS:** Telomere length in T-cells was significantly shorter in patients with lung cancer than in controls ($P < 0.001$). Shorter telomere length was significantly associated with increased clinical stage ($P = 0.008$) and distant metastasis ($P = 0.028$). Naïve T-cells from patients with lung cancer had significantly decreased telomere length when compared with those from controls ($P = 0.012$). **CONCLUSION:** The shortened telomere length in T-cells occurred in naïve T-cells and might be related to lung cancer progression.

[PAXIP1 potentiates the combination of WEE1 inhibitor AZD1775 and platinum agents in lung cancer.](#) Jhuraney A1, Woods NT1, Wright G2, et al. *Mol Cancer Ther.* 2016 May 11. pii: molcanther.0182.2015. [Epub ahead of print]

The DNA damage response (DDR) involves a complex network of signaling events mediated by modular protein domains such as the BRCT (BRCA1 C-terminal) domain. Thus, proteins that interact with BRCT domains and are a part of the DDR constitute potential targets for sensitization to DNA damaging chemotherapy agents. We performed a pharmacological screen to evaluate seventeen kinases, identified in a BRCT-mediated interaction network as targets to enhance platinum-based chemotherapy in lung cancer. Inhibition of mitotic kinase WEE1 was found to have the most effective response in combination with platinum compounds in lung cancer cell lines. In the BRCT-mediated interaction network, WEE1 was found in complex with PAXIP1, a protein containing six BRCT domains involved in transcription and in the cellular response to DNA damage. We show that PAXIP1 BRCT domains regulate WEE1-mediated phosphorylation of CDK1. Further, ectopic expression of PAXIP1 promotes enhanced caspase 3-mediated apoptosis in cells treated with WEE1 inhibitor AZD1775 (formerly, MK-1775) compared with cells

treated with AZD1775 alone. Cell lines and patient-derived xenograft models expressing both PAXIP1 and WEE1 exhibited synergistic effects of AZD1775 and cisplatin. In summary, PAXIP1 is involved in sensitizing lung cancer cells to the WEE1 inhibitor AZD1775 in combination with platinum-based treatment. We propose that WEE1 and PAXIP1 levels may be used as mechanism-based biomarkers of response when WEE1 inhibitor AZD1775 is combined with DNA damaging agents.

SCREENING, DIAGNOSIS AND STAGING

[Comprehensive Genomic Profiling Facilitates Implementation of the National Comprehensive Cancer Network Guidelines for Lung Cancer Biomarker Testing and Identifies Patients Who May Benefit From Enrollment in Mechanism-Driven Clinical Trials.](#) Suh JH1, Johnson A2, Albacker L2, et al. *Oncologist*. 2016 May 5. pii: theoncologist.2016-0030. [Epub ahead of print]

BACKGROUND: The National Comprehensive Cancer Network (NCCN) guidelines for patients with metastatic non-small cell lung cancer (NSCLC) recommend testing for EGFR, BRAF, ERBB2, and MET mutations; ALK, ROS1, and RET rearrangements; and MET amplification. We investigated the feasibility and utility of comprehensive genomic profiling (CGP), a hybrid capture-based next-generation sequencing (NGS) test, in clinical practice. **METHODS:** CGP was performed to a mean coverage depth of 576× on 6,832 consecutive cases of NSCLC (2012-2015). Genomic alterations (GAs) (point mutations, small indels, copy number changes, and rearrangements) involving EGFR, ALK, BRAF, ERBB2, MET, ROS1, RET, and KRAS were recorded. We also evaluated lung adenocarcinoma (AD) cases without GAs, involving these eight genes. **RESULTS:** The median age of the patients was 64 years (range: 13-88 years) and 53% were female. Among the patients studied, 4,876 (71%) harbored at least one GA involving EGFR (20%), ALK (4.1%), BRAF (5.7%), ERBB2 (6.0%), MET (5.6%), ROS1 (1.5%), RET (2.4%), or KRAS (32%). In the remaining cohort of lung AD without these known drivers, 273 cancer-related genes were altered in at least 0.1% of cases, including STK11 (21%), NF1 (13%), MYC (9.8%), RICTOR (6.4%), PIK3CA (5.4%), CDK4 (4.3%), CCND1 (4.0%), BRCA2 (2.5%), NRAS (2.3%), BRCA1 (1.7%), MAP2K1 (1.2%), HRAS (0.7%), NTRK1 (0.7%), and NTRK3 (0.2%).

CONCLUSION: CGP is practical and facilitates implementation of the NCCN guidelines for NSCLC by enabling simultaneous detection of GAs involving all seven driver oncogenes and KRAS. Furthermore, without additional tissue use or cost, CGP identifies patients with "pan-negative" lung AD who may benefit from enrollment in mechanism-driven clinical trials. **IMPLICATIONS FOR PRACTICE:** National Comprehensive Cancer Network guidelines for patients with metastatic non-small cell lung cancer (NSCLC) recommend testing for several genomic alterations (GAs). The feasibility and utility of comprehensive genomic profiling were studied in NSCLC and in lung adenocarcinoma (AD) without GAs. Of patients with NSCLC, 71% harbored at least one GA to a gene listed in the guidelines or KRAS; 273 cancer-related genes were altered in at least 0.1% of the AD cases. Although logistical and administrative hurdles limit the widespread use of next-generation sequencing, the data confirm the feasibility and potential utility of comprehensive genomic profiling in clinical practice.

[Liquid Biopsy in Lung Cancer: A Perspective From Members of the Pulmonary Pathology Society.](#)

Sholl LM1, Aisner DL1, Allen TC1, et al. *Arch Pathol Lab Med*. 2016 May 19. [Epub ahead of print] Liquid biopsy has received extensive media coverage and has been called the holy grail of cancer detection. Attempts at circulating tumor cell and genetic material capture have been progressing for several years, and recent financially and technically feasible improvements of cell capture devices, plasma isolation techniques, and highly sensitive polymerase chain reaction- and sequencing-based methods have advanced the possibility of liquid biopsy of solid tumors. Although practical use of circulating RNA-based testing has been hindered by the need to fractionate blood to enrich for RNAs, the detection of circulating tumor cells has profited from advances in cell capture technology. In fact, the US Food and

Drug Administration has approved one circulating tumor cell selection platform, the CellSearch System. Although the use of liquid biopsy in a patient population with a genomically defined solid tumor may potentially be clinically useful, it currently does not supersede conventional pretreatment tissue diagnosis of lung cancer. Liquid biopsy has not been validated for lung cancer diagnosis, and its lower sensitivity could lead to significant diagnostic delay if liquid biopsy were to be used in lieu of tissue biopsy. Ultimately, notwithstanding the enthusiasm encompassing liquid biopsy, its clinical utility remains unproven.

Prognostic Value of Volumetric Parameters on Staging and Posttreatment FDG PET/CT in Patients With Stage IV Non-Small Cell Lung Cancer. Lee JW1, Lee SM, Yun M, Cho A. Clin Nucl Med. 2016 May;41(5):347-53. doi: 10.1097/RLU.0000000000001126.

PURPOSE: This study aimed to evaluate the prognostic value of metabolic tumor burden as measured with metabolic tumor volume (MTV) and total lesion glycolysis (TLG), as well as SUVmax on initial staging and posttreatment F-FDG PET/CT in patients with stage IV non-small cell lung cancer (NSCLC). **METHODS:** Sixty-three NSCLC patients with stage IV who underwent staging and posttreatment FDG PET/CT after completion of the first-line chemotherapy were retrospectively enrolled. SUVmax, MTV, and TLG of primary cancer and all metastatic lesions (lymph node and distant metastases) on both PET/CT images were measured and their association with progression-free survival (PFS) and overall survival (OS) analyzed. **RESULTS:** Median PFS and OS in the patient population were 5.9 and 23.1 months, respectively. Among the PET/CT parameters, MTV and TLG of primary cancer lesions on initial PET/CT and MTV and TLG of metastatic lesions on posttreatment PET/CT were independent prognostic factors for both PFS and OS ($P < 0.05$). The median OS in patients who showed low values of those PET/CT parameters was more than 26.0 months, whereas patients with high values of those parameters had a median OS of less than 15.0 months. **CONCLUSIONS:** Metabolic tumor burdens of primary cancer lesions on staging PET/CT and metastatic lesions on posttreatment PET/CT were independent prognostic factors in patients with stage IV NSCLC. Volume-based PET parameters could further stratify the prognosis of stage IV NSCLC patients.

Electromagnetic Navigation Bronchoscopy-Guided Dye Marking for Thoracoscopic Resection of Pulmonary Nodules. Awais O1, Reidy MR1, Mehta K1, et al. Ann Thorac Surg. 2016 May 5. pii: S0003-4975(16)00224-1. doi: 10.1016/j.athoracsur.2016.02.040. [Epub ahead of print]

BACKGROUND: Computed tomography scans are increasingly used not only for lung cancer screening but also for staging and evaluation of other cancers. As a result, more patients with pulmonary nodules, many with subcentimeter lesions, are being referred to thoracic surgeons, some with concern for primary lung neoplasm and others with possible metastatic lung lesions. Obtaining a definitive diagnosis of these lesions is difficult. Electromagnetic navigational bronchoscopy (ENB)-guided pleural dye marking followed by thoracoscopic resection is a novel alternative technique for definitive diagnosis. The main objective of this study was to evaluate the feasibility and our initial experience with ENB-guided dye localization and minimally invasive resection for diagnosis of lung lesions. **METHODS:** Selected patients with lung lesions underwent ENB-guided dye marking and minimally invasive resection. The primary end points were the rate of nodule localization and definitive diagnosis of the nodule. **RESULTS:** We performed ENB-guided localization and minimally invasive resection in 29 patients. The median lesion size was 10 mm, with a median distance from pleural surface of 13 mm. The operative mortality was 0%. The median hospital stay was 3 days. The nodule was localized and resected, and a definitive diagnosis was obtained in all patients (29 of 29; 100%). The nodule was neoplastic in 19 patients. All malignant lesions were completely resected with negative microscopic margins. **CONCLUSIONS:** Our initial experience with ENB-guided dye localization and minimally invasive

resection found that the technique was feasible, safe, and successful in the diagnosis of small lung lesions. Thoracic surgeons should further investigate this method and incorporate it into their armamentarium.

[The International Association for the Study of Lung Cancer consensus statement on optimizing management of EGFR mutation positive non-small cell lung cancer: status in 2016.](#) Tan DS1, Yom SS2, Tsao MS3, et al. J Thorac Oncol. 2016 May 20. pii: S1556-0864(16)30458-0. doi: 10.1016/j.jtho.2016.05.008. [Epub ahead of print]

Mutations in the epidermal growth factor receptor (EGFR) represent one of the most common "actionable" alterations in non-small cell lung cancer (NSCLC). Typified by high response rates to targeted therapies, EGFR tyrosine kinase inhibitors (TKI) are now established first-line treatment options and have transformed the treatment paradigm for NSCLC. With the recent breakthrough designation and approval of osimertinib, a 3rd generation EGFR TKI, available systemic and local treatment options have expanded, requiring new clinical algorithms that take into account individual patient molecular and clinical profiles. In this International Association for the Study of Lung Cancer (IASLC) commissioned consensus statement, key pathologic, diagnostic and therapeutic considerations, such as optimal choice of EGFR TKI and management of brain metastasis, are discussed. In addition, recommendations are made for clinical guidelines and research priorities, such as the role of re-biopsies and use of circulating free DNA (cfDNA) for molecular studies. With the rapid pace of progress in treating EGFR mutant NSCLC, this statement provides a state-of-the-art review of the contemporary issues in managing this unique subgroup of patients.

[Shared Medical Decision Making in Lung Cancer Screening: Experienced versus Descriptive Risk Formats.](#) Fraenkel L1, Peters E2, Tyra S2, Oelberg D2. Med Decis Making. 2016 May;36(4):518-25. doi: 10.1177/0272989X15611083. Epub 2015 Oct 6.

BACKGROUND: Annual lung cancer screening using low-dose computed tomography (LDCT) scans is associated with a survival benefit, but it is also associated with potential harm. Unlike descriptive probability formats, experienced tasks have been shown to decrease perceptions of rare events. The objective of this study was to compare descriptive versus experienced probability formats on patients' knowledge, beliefs, endorsement of screening for heavy smokers, and preference (choice predisposition) to undergo screening. **METHODS:** A total of 276 patients attending an outpatient pulmonary practice were randomized to learn about screening using 1 of 3 formats: numbers only, numbers + icon arrays, numbers + a set of slides illustrating LDCT scans of 250 people in random order that displayed the number of normal scans, false-positive lung nodules, cancers found leading to a life saved, and cancers found leading to death despite treatment. **RESULTS:** Knowledge differed between the 3 formats ($P=0.001$), with participants randomized to the numbers + icon array format having the highest knowledge score. Beliefs were more favorable among participants randomized to the numbers + experienced format compared with the numbers + icon array format (difference between means [95% confidence interval]= 1.6 [0.4-2.8]). Differences in participants' endorsement of screening ($P=0.4$) and choice predisposition ($P=0.6$) across probability format mirrored those of beliefs but were not statistically significant. **DISCUSSION:** Contrary to what we expected, the experienced format increased propensity toward screening compared with the numbers + icon array format, as indicated by more favorable beliefs and nonsignificant trends toward stronger choice predisposition and endorsement. Experienced risk formats may not be a practical approach to improve risk communication for patients deciding whether or not to undergo annual lung cancer screening.

NSCLC - SURGERY

[Surgical Intervention Improves Survival for Metastatic Non-Small Cell Lung Cancer Patients.](#)

Shen H1, Cao Y, Li X, et al. *Medicine (Baltimore)*. 2016 May;95(21):e3800. doi: 10.1097/MD.0000000000003800.

Surgical intervention for stage IV non-small cell lung cancer (NSCLC) is still controversial. This study sought to evaluate the clinical effects of surgical intervention on survival in patients with stage IV NSCLCs and to identify the cohort benefitting the most from surgery. A retrospective study from the Surveillance, Epidemiology, and End Results database was performed to compare the survival of stage IV NSCLC patients who had undergone surgery with those who did not undergo surgery. Overall survival (OS) was evaluated using the Kaplan-Meier method and the log-rank test. The Cox proportional hazards model was used for multivariate analysis. The total number of eligible patients was 43,538, including 16.8% in the M1a stage and 83.2% in the M1b stage. The percentages of patients with no surgery (NONE), only metastatic tumor resection (MTR), only primary tumor resection (PTR), and both primary and metastatic tumor resection (PMTR) were 89.0%, 6.7%, 3.5%, and 0.8%, respectively; the corresponding 5-year survival rates were 2.0%, 4.0%, 13.0%, and 20.0%, respectively ($P < 0.001$); and the corresponding OS rates were 11.1 months, 14.7 months, 29.4 months, and 34.9 months, respectively ($P < 0.001$). Notably, the pairwise comparisons of 5-year survival rate and OS among the subgroups were all statistically significant. The multivariate analysis showed that surgical intervention was correlated with longer survival in patients with stage IV NSCLC. The stratified analysis showed significant differences in the OS on strata of the M1a stage and strata of the M1b stage. In the M1a stage, patients with PTR had significantly better OS than those with NONE ($P < 0.001$) or MTR ($P < 0.001$) but showed no significant differences compared with those with PMTR ($P = 0.174$); patients with MTR did not have prolonged survival compared with patients with NONE ($P = 0.185$), and they also did not have prolonged survival compared with patients with PMTR ($P = 0.052$). In the M1b stage, pairwise comparisons of OS were all statistically significant among the subgroups ($P < 0.001$). Surgical intervention can prolong survival to different degrees according to the modalities of surgery in stage IV NSCLC.

[Cell cycle progression score is a marker for five-year lung cancer-specific mortality risk in patients with resected stage I lung adenocarcinoma.](#) Eguchi T1,2, Kadota K3,4, Chaff J5, et al. *Oncotarget*.

2016 May 2. doi: 10.18632/oncotarget.9129. [Epub ahead of print]

PURPOSE: The goals of our study were (a) to validate a molecular expression signature (cell cycle progression [CCP] score and molecular prognostic score [mPS; combination of CCP and pathological stage {IA or IB}]) that identifies stage I lung adenocarcinoma (ADC) patients with a higher risk of cancer-specific death following curative-intent surgical resection, and (b) to determine whether mPS stratifies prognosis within stage I lung ADC histological subtypes. **METHODS:** Formalin-fixed, paraffin-embedded stage I lung ADC tumor samples from 1200 patients were analyzed for 31 proliferation genes by quantitative RT-PCR. Prognostic discrimination of CCP score and mPS was assessed by Cox proportional hazards regression, using 5-year lung cancer-specific mortality as the primary outcome.

RESULTS: In multivariable analysis, CCP score was a prognostic marker for 5-year lung cancer-specific mortality (HR=1.6 per interquartile range; 95% CI, 1.14-2.24; $P = 0.006$). In a multivariable model that included mPS instead of CCP, mPS was a significant prognostic marker for 5-year lung cancer-specific mortality (HR=1.77; 95% CI, 1.18-2.66; $P = 0.006$). Five-year lung cancer-specific survival differed between low-risk and high-risk mPS groups (96% vs 81%; $P < 0.001$). In patients with intermediate-grade lung ADC of acinar and papillary subtypes, high mPS was associated with worse 5-year lung cancer-specific survival ($P < 0.001$ and 0.015, respectively), compared with low mPS. **CONCLUSION:** This

study validates CCP score and mPS as independent prognostic markers for lung cancer-specific mortality and provides quantitative risk assessment, independent of known high-risk features, for stage I lung ADC patients treated with surgery alone

Early and late recurrence after intentional limited resection for cT1aN0M0, non-small cell lung cancer: from a multi-institutional, retrospective analysis in Japan. Matsumura Y1, Yano M2,

Yoshida J3, et al. *Interact Cardiovasc Thorac Surg.* 2016 May 25. pii: ivw125. [Epub ahead of print]

OBJECTIVES: In 2015, we reported the outcomes of patients undergoing intentional limited resection (ILR) for non-small-cell lung cancer (NSCLC) from a retrospective, multi-institutional large database in Japan. Here, we analyse the clinicopathological characteristics of the patients extracted from this database with late recurrence and compare them with those with early recurrence. **METHODS:** Of 1538 patients in the database with cT1aN0M0 NSCLC, 92 (6%) had recurrence. In this study, early recurrence was defined as recurrence within 5 years and late recurrence as recurrence beyond 5 years after surgery. We compared the clinicopathological characteristics and post-recurrence survival (PRS) between patients with early and late recurrence. **RESULTS:** Of the 92 patients with recurrence, 21 (23%) had late recurrence. Compared with the early recurrence group, there were significantly more adenocarcinomas and local recurrences in the late recurrence group ($P = 0.04$ for both). The 3- and 5-year PRS rates were 53 and 24%, respectively, and the median PRS period was 38 months. There were no significant differences in the PRS curves between patients with early and late recurrence ($P = 0.12$). Only 3 patients (0.2%) had recurrence more than 10 years after ILR. Of the 21 late-recurrence patients, 17 (81%) had tumours with a consolidation/tumour ratio (CTR) >0.25 . **CONCLUSIONS:** Late recurrence occurred in 21 (23%) of 92 patients with recurrence after ILR for cT1aN0M0 NSCLC. Late recurrence was more likely to involve adenocarcinoma and local recurrence. It is thus considered reasonable to follow patients with a CTR >0.25 for 10 years after ILR.

The Effects of Residential Segregation and Neighborhood Characteristics on Surgery and Survival in Patients with Early-Stage Non-Small Cell Lung Cancer. Johnson AM1, Johnson A2, Hines RB3,

Bayakly R4. *Cancer Epidemiol Biomarkers Prev.* 2016 May;25(5):750-8. doi: 10.1158/1055-9965.EPI-15-1126.

BACKGROUND: Although the negative effects of lower socioeconomic status on non-small cell lung cancer (NSCLC) treatment and survival have been widely studied, the impact of residential segregation on prognosis and the receipt of treatment has yet to be determined. **METHODS:** This is a retrospective, cohort study of NSCLC patients in Georgia (2000-2009; $n = 8,322$) using data from the Georgia Comprehensive Cancer Registry. The effects of segregation, economic deprivation, and combined segregation/deprivation on the odds of receiving surgery were examined in separate multilevel models. To determine the association for the exposures of interest on the risk of death for different racial groups, separate multilevel survival models were conducted for black and white patients. **RESULTS:** Living in areas with the highest [AOR = 0.35, 95% confidence interval (CI), 0.19-0.64] and second highest (AOR = 0.37, 95% CI, 0.20-0.68) levels of segregation was associated with decreased odds of receipt of surgery. Black patients living in areas with high residential segregation and high economic deprivation were 31% (95% CI, 1.04-1.66) more likely to die, even after surgery was controlled for. For white patients, economic deprivation was associated with decreased odds of surgery but not survival. Segregation had no effect. **CONCLUSION:** Our findings suggest how black and white individuals experience segregation and area-level poverty is likely different leading to differences in adverse health outcomes. **IMPACT:** Identifying neighborhood characteristics impacting health outcomes within different racial groups could help reduce health disparities across racial groups by implementing targeted policies and interventions.

[Management of EGFR Mutation-Positive Non-Small Cell Lung Cancer.](#) Lilenbaum RA1, Horn LA1. J Natl Compr Canc Netw. 2016 May;14(5 Suppl):672-4.

For appropriate treatment selection, the updated NCCN Guidelines for Non-Small Cell Lung Cancer (NSCLC) recommend broad molecular profiling for all patients with nonsquamous disease. Three different tyrosine kinase inhibitors (TKIs) are recommended as first-line treatment of EGFR mutation-positive NSCLC: gefitinib, erlotinib, and afatinib. Most patients whose disease responds will still experience progression, and the type of disease progression drives management. Systemic progression requires switching TKI treatment, whereas patients with oligoprogression and central nervous system progression may have their new lesions treated but continue on their TKI. A new third-generation TKI has been approved and others are currently under development, and new combinations of these drugs with a VEGFR inhibitor offer promise to improve outcomes.

[First-line treatment of advanced epidermal growth factor receptor \(EGFR\) mutation positive non-squamous non-small cell lung cancer.](#) Greenhalgh J1, Dwan K, Boland A, Bates V, Vecchio F, Dundar Y, Jain P, Green JA. Cochrane Database Syst Rev. 2016 May 25;5:CD010383. doi: 10.1002/14651858.CD010383.pub2.

BACKGROUND: Epidermal growth factor receptor (EGFR) mutation positive (M+) non-small cell lung cancer (NSCLC) is emerging as an important subtype of lung cancer comprising 10% to 15% of non-squamous tumours. This subtype is more common in women than men and is less associated with smoking. **OBJECTIVES:** To assess the clinical effectiveness of single -agent or combination EGFR therapies used in the first-line treatment of people with locally advanced or metastatic EGFR M+ NSCLC compared with other cytotoxic chemotherapy (CTX) agents used alone or in combination, or best supportive care (BSC). The primary outcome was overall survival. Secondary outcomes included progression-free survival, response rate, toxicity, and quality of life. **SEARCH METHODS:** We conducted electronic searches of the the Cochrane Register of Controlled Trials (CENTRAL) (2015, Issue 6), MEDLINE (1946 to 1 June 2015), EMBASE (1980 to 1 June 2015), and ISI Web of Science (1899 to 1 June 2015). We also searched the conference abstracts of the American Society for Clinical Oncology and the European Society for Medical Oncology (1 June 2015); Evidence Review Group submissions to the National Institute for Health and Care Excellence; and the reference lists of retrieved articles.

SELECTION CRITERIA: Parallel randomised controlled trials comparing EGFR-targeted agents (alone or in combination with cytotoxic agents or BSC) with cytotoxic chemotherapy (single or doublet) or BSC in chemotherapy-naive patients with locally advanced or metastatic (stage IIIB or IV) EGFR M+ NSCLC unsuitable for treatment with curative intent. **DATA COLLECTION AND ANALYSIS:** Two review authors independently identified articles, extracted data, and carried out the 'Risk of bias' assessment. We conducted meta-analyses using a fixed-effect model unless there was substantial heterogeneity, in which case we also performed a random-effects analysis as a sensitivity analysis.

MAIN RESULTS: Nineteen trials met the inclusion criteria. Seven of these exclusively recruited people with EGFR M+ NSCLC; the remainder recruited a mixed population and reported results for people with EGFR M+ NSCLC as subgroup analyses. The number of participants with EGFR M+ tumours totalled 2317, of whom 1700 were of Asian origin. Overall survival (OS) data showed inconsistent results between the included trials that compared EGFR-targeted treatments against cytotoxic chemotherapy or placebo. Erlotinib was the intervention treatment used in eight trials, gefitinib in seven trials, afatinib in two trials, and cetuximab in two trials. The findings of one trial (FASTACT 2) did report a statistically significant OS gain for participants treated with erlotinib plus cytotoxic chemotherapy when compared to cytotoxic chemotherapy alone, but this result was based on a small number of participants (n = 97). For progression-free survival (PFS), a pooled analysis of 3 trials (n = 378) demonstrated a statistically

significant benefit for erlotinib compared with cytotoxic chemotherapy (hazard ratio (HR) 0.30; 95% confidence interval (CI) 0.24 to 0.38). In a pooled analysis with 491 participants administered gefitinib, 2 trials (IPASS and NEJSG) demonstrated a statistically significant PFS benefit of gefitinib compared with cytotoxic chemotherapy (HR 0.39; 95% CI 0.32 to 0.48). Afatinib (n = 709) showed a statistically significant PFS benefit when compared with chemotherapy in a pooled analysis of 2 trials (HR 0.42; 95% CI 0.34 to 0.53). Commonly reported grade 3/4 adverse events for afatinib, erlotinib, and gefitinib monotherapy were rash and diarrhoea. Myelosuppression was consistently worse in the chemotherapy arms, fatigue and anorexia were also associated with some chemotherapies. No statistically significant PFS or OS benefit for cetuximab plus cytotoxic chemotherapy (n = 81) compared to chemotherapy alone was reported in either of the two trials. Six trials reported on quality of life and symptom improvement using different methodologies. For each of erlotinib, gefitinib, and afatinib, 2 trials showed improvement in one or more indices for the tyrosine-kinase inhibitor (TKI) compared to chemotherapy. The quality of evidence was high for the comparisons of erlotinib and gefitinib with cytotoxic chemotherapy and for the comparison of afatinib with cytotoxic chemotherapy. **AUTHORS' CONCLUSIONS:** Erlotinib, gefitinib, and afatinib are all active agents in EGFR M+ NSCLC patients, and demonstrate an increased tumour response rate and prolonged progression-free survival compared to cytotoxic chemotherapy. We also found a beneficial effect of the TKI compared to cytotoxic chemotherapy. However, we found no increase in overall survival for the TKI when compared with standard chemotherapy. Cytotoxic chemotherapy is less effective in EGFR M+ NSCLC than erlotinib, gefitinib, or afatinib and is associated with greater toxicity. There were no data supporting the use of monoclonal antibody therapy.

[Time is Money: Hospital Costs Associated With Video-Assisted Thoracoscopic Surgery](#)

[Lobectomies](#). Khullar OV1, Fernandez FG1, Perez S2, et al. Ann Thorac Surg. 2016 May 18. pii: S0003-4975(16)30125-4. doi: 10.1016/j.athoracsur.2016.03.024. [Epub ahead of print]

BACKGROUND: Proposed changes in health care will place an increasing burden on surgeons to care for patients more efficiently to minimize cost. We reviewed costs surrounding video-assisted thoracoscopic surgery (VATS) lobectomies to see where changes could be made to ensure maximum value. **METHODS:** We queried The Society of Thoracic Surgeons database for all VATS lobectomies performed for lung cancer from January 2011 to December 2013. Clinical data were linked with hospital financial data to determine hospital expenditures for each patient. **RESULTS:** In all, 263 VATS lobectomies were included. Mean operating room time was 236 minutes, and median length of stay was 4 days. Mean hospital cost was \$19,769. The majority of cost (58%) was attributed to operating room and floor costs (length of stay), and the majority of operating room costs were secondary to room rate and staplers. A total of 77 complications, as defined by STS, occurred in the cohort; 41 patients had only one complication, 11 patients had two complications, and 6 patients had three or more complications. The occurrence of one complication was associated with a net loss of \$496 whereas two complications in a patient led to a \$3,882 net loss. Overall, complications were independently correlated with significant cost increases. **CONCLUSIONS:** Our study shows that the most significant costs associated with VATS lobectomies relate to operating room time, stapler use, floor charges, and cost associated with complications. Cost-reducing strategies will need to concentrate on optimizing operating room times and reducing length of stay while simultaneously minimizing complications.

[PD-L1 polymorphism can predict clinical outcomes of non-small cell lung cancer patients treated with first-line paclitaxel-cisplatin chemotherapy](#)

Lee SY1,2, Jung DK3,4, Choi JE3,5, et al. Sci Rep. 2016 May 16;6:25952. doi: 10.1038/srep25952.

This study was conducted to investigate whether polymorphisms of genes involved in immune checkpoints can predict the clinical outcomes of patients with advanced stage non-small cell lung cancer (NSCLC) after 1st line paclitaxel-cisplatin chemotherapy. A total of 379 NSCLC patients were enrolled.

Twelve single nucleotide polymorphisms (SNPs) of PD-1, PD-L1, and CTLA-4 genes were selected and genotyped. The associations of SNPs with chemotherapy response and overall survival (OS) were analyzed. Among the 12 SNPs investigated, PD-L1 rs2297136T > C and rs4143815C > G were significantly associated with clinical outcomes after chemotherapy. The rs2297136T > C was significantly associated with both better chemotherapy response and better OS, and the rs4143815C > G had a significantly better response to chemotherapy. Consistent with the individual genotype analyses, rs2297136C-rs4143815G haplotype (ht4) carrying variant alleles at both loci was significantly associated with better chemotherapy response and OS compared with combined other haplotypes. Patients with at least one ht4 had significantly better chemotherapy response and OS compared to those without ht4. PD-L1 rs2297136T > C and rs4143815C > G polymorphisms may be useful for the prediction of clinical outcome of 1(st) line paclitaxel-cisplatin chemotherapy in NSCLC. Further studies are needed to confirm our findings and to understand the role of PD-L1 in the chemotherapy outcome of NSCLC patients.

NSCLC - RADIOTHERAPY

"Even if I Don't Remember, I Feel Better": A Qualitative Study of Early Stage Non-Small Cell Lung Cancer Patients Undergoing Stereotactic Body Radiotherapy or Surgery. Golden SE1, Thomas CR Jr2, Deffebach ME3,4, Sukumar MS5, Schipper PH6, Tieu BH7, Kee AY8, Tsen AC9, Slatore CG10,11; Early Stage Lung Cancer Comparative Effectiveness Research Consortium. Ann Am Thorac Soc. 2016 May 16. [Epub ahead of print]

RATIONALE: While surgical resection is recommended for most patients with early stage lung cancer according to the National Comprehensive Cancer Network (NCCN) guidelines, stereotactic body radiotherapy (SBRT) is being increasingly utilized. Provider-patient communication regarding risks/benefits of each approach may be a modifiable factor leading to improved patient-centered outcomes. **OBJECTIVES:** To qualitatively describe the experiences of patients undergoing either surgery or stereotactic body radiotherapy for early stage non-small cell lung cancer (NSCLC). **METHODS:** We qualitatively evaluated and used content analysis to describe the experiences of 13 patients in three health care systems in the Pacific Northwest with early clinical stage NSCLC before undergoing treatment, with a focus on knowledge obtained, communication, and feelings of distress. **MEASUREMENTS AND MAIN RESULTS:** Although most participants reported rarely having been told about other options for treatment, and could not readily recall many details about specific risks of recommended treatment, they were satisfied with their care. Participants paradoxically described their clinicians as displaying caring and empathy despite not explicitly addressing patient concerns and worries. We found that the communication domains that underlie shared decision making occurred infrequently, but participants were still pleased with their role in the decision making process. We did not find substantially different themes based on where the participant received care or treatment selected. **CONCLUSIONS:** Patients were satisfied with all aspects of their care despite reporting little knowledge about risks or other treatment options, no direct elicitation of worries from providers, and a lack of shared decision making. While the development of effective communication strategies to address these gaps is warranted, their effect on patient-centered outcomes, such as distress and decisional conflict, is unclear.

Establishing the feasibility of the dosimetric compliance criteria of RTOG 1308: phase III randomized trial comparing overall survival after photon versus proton radiochemotherapy for inoperable stage II-IIIb NSCLC. Giaddui T1, Chen W2, Yu J2, et al. Radiat Oncol. 2016 May 4;11(1):66. doi: 10.1186/s13014-016-0640-8.

BACKGROUND: To establish the feasibility of the dosimetric compliance criteria of the RTOG 1308 trial through testing against Intensity Modulation Radiation Therapy (IMRT) and Passive Scattering Proton Therapy (PSPT) plans. **METHODS:** Twenty-six lung IMRT and 26 proton PSPT plans were

included in the study. Dose Volume Histograms (DVHs) for targets and normal structures were analyzed. The quality of IMRT plans was assessed using a knowledge-based engineering tool. **RESULTS:** Most of the RTOG 1308 dosimetric criteria were achieved. The deviation unacceptable rates were less than 10 % for most criteria; however, a deviation unacceptable rate of more than 20 % was computed for the planning target volume minimum dose compliance criterion. Dose parameters for the target volume were very close for the IMRT and PSPT plans. However, the PSPT plans led to lower dose values for normal structures. The dose parameters in which PSPT plans resulted in lower values than IMRT plans were: lung V5Gy (%) (34.4 in PSPT and 47.2 in IMRT); maximum spinal cord dose (31.7 Gy in PSPT and 43.5 Gy in IMRT); heart V5Gy (%) (19 in PSPT and 47 in IMRT); heart V30Gy (%) (11 in PSPT and 19 in IMRT); heart V45Gy (%) (7.8 in PSPT and 12.1 in IMRT); heart V50% (Gy) (7.1 in PSPT and 9.8 in IMRT) and mean heart dose (7.7 Gy in PSPT and 14.9 Gy in IMRT). **CONCLUSIONS:** The revised RTOG 1308 dosimetric compliance criteria are feasible and achievable.

[Isolated Nodal Failure after Stereotactic Body Radiotherapy for Lung Cancer: The Role for Salvage Mediastinal Radiotherapy.](#) Ward MC1, Oh SC2, Pham YD2, Woody NM2, Marwaha G3, Videtic GM2, Stephans KL2. J Thorac Oncol. 2016 May 17. pii: S1556-0864(16)30452-X. doi: 10.1016/j.jtho.2016.05.003. [Epub ahead of print]

INTRODUCTION: Isolated nodal failure (INF) without synchronous local or distant failure is an uncommon occurrence after stereotactic body radiation therapy (SBRT) for lung cancer. Here we review the natural history and patterns of failure after post-SBRT INF with or without salvage mediastinal radiotherapy (SvRT). **METHODS:** Patients treated with SBRT for non-small cell lung cancer with definitive intent were identified. Patients who experienced hilar or mediastinal INF without synchronous distant, lobar, or local failure were included and grouped according to the use of SvRT. The rates of subsequent locoregional control, distant metastases, progression-free survival (PFS), and overall survival were assessed. **RESULTS:** Of 797 patients treated with definitive SBRT, 24 (3%) experienced INF and 15 (63%) received SvRT. The most common SvRT regimen (53%) was 45 Gy in 15 fractions. The median follow-up after INF was 11.3 months for survivors. There were no grade 3 or higher toxicities after SvRT. The 1-year Kaplan-Meier PFS and overall survival estimates were 33% and 56% for patients not receiving radiotherapy and 75% and 73% with SvRT. After SvRT, the rate of locoregional control at 1 year was 84.4%. Crude rates of distant failure were 20.0% with SvRT and 22.2% with no radiotherapy. Of the 13 deaths observed, five (38%) were related to distant progression of lung cancer, four (31%) to comorbidities, three (23%) to mediastinal progression, and one (8%) to an unknown cause. **CONCLUSIONS:** INF is uncommon after SBRT. Despite the significant comorbidities of this population, intrathoracic progression remains a contributor to morbidity and mortality. SVRT for INF is well tolerated and may improve PFS.

[Statistical Determination of the Gating Windows for Respiratory-Gated Radiotherapy Using a Visible Guiding System.](#) Oh SA1,2, Yea JW1,2,3, Kim SK1,2,3. PLoS One. 2016 May 26;11(5):e0156357. doi: 10.1371/journal.pone.0156357. eCollection 2016.

Respiratory-gated radiation therapy (RGRT) is used to minimize the radiation dose to normal tissue in lung-cancer patients. Although determining the gating window in the respiratory phase of patients is important in RGRT, it is not easy. Our aim was to determine the optimal gating window when using a visible guiding system for RGRT. Between April and October 2014, the breathing signals of 23 lung-cancer patients were recorded with a real-time position management (RPM) respiratory gating system (Varian, USA). We performed statistical analysis with breathing signals to find the optimal gating window for guided breathing in RGRT. When we compared breathing signals before and after the breathing training, 19 of the 23 patients showed statistically significant differences ($p < 0.05$). The standard deviation of the respiration signals after breathing training was lowest for phases of 30%-70%.

The results showed that the optimal gating window in RGRT is 40% (30%-70%) with respect to repeatability for breathing after respiration training with the visible guiding system. RGRT was performed with the RPM system to confirm the usefulness of the visible guiding system. The RPM system and our visible guiding system improve the respiratory regularity, which in turn should improve the accuracy and efficiency of RGRT.

[Can we predict the development of serious adverse events \(SAEs\) and early treatment termination in elderly non-small cell lung cancer \(NSCLC\) patients receiving platinum-based chemotherapy?](#)

Kato T1, Morise M2, Ando M3, et al. J Cancer Res Clin Oncol. 2016 Jul;142(7):1629-40. doi: 10.1007/s00432-016-2170-z. Epub 2016 May 11.

PURPOSE: Predicting the feasibility of platinum-based chemotherapy remains an important issue in elderly (over 70 years) patients with non-small cell lung cancer (NSCLC). The aim of this study was to identify the risk factors for the early serious adverse events (SAEs) (during cycles 1-2) in elderly receiving platinum-based chemotherapy, and to explore the clinical characteristics of patients who require early treatment termination without progressive disease (PD). **METHODS:** One hundred and ninety-eight consecutive elderly NSCLC patients receiving platinum-based chemotherapy were retrospectively reviewed. **RESULTS:** The median age was 73 years (range 70-83). 161 (81 %) were males, and 190 (95 %) were PS 0-1. Fifty-one (29 %) and 39 (19 %) patients developed early non-hematological SAEs and hematological SAEs, respectively. Multivariate analysis identified low serum albumin (<3.0 g/dl) as an independent risk factor for non-hematological SAEs, while low creatinine clearance (<45 ml/min) for hematological SAEs. In all, 24 (12 %) patients needed early treatment termination without PD. The major reason for this event was the development of non-hematological SAEs (4.5 %), followed by grade 2 non-hematological adverse events (AEs) (3 %). In multivariate analysis, age over 75 years and low serum albumin were associated with this event. The median overall survival (OS) in patients with this event was only 6.0 months, while the development of early SAE was not associated with poor OS. **CONCLUSION:** Baseline serum albumin might be useful for predicting the feasibility of platinum-based chemotherapy, and the risk estimation of early treatment termination without PD might be beneficial for the treatment selection in elderly NSCLC patients.

[Feasibility and efficacy of helical intensity-modulated radiotherapy for stage III non-small cell lung cancer in comparison with conventionally fractionated 3D-CRT.](#)

He J1, Huang Y1, Chen Y1, Shi S1, Ye L1, Hu Y1, Zhang J1, Zeng Z1. J Thorac Dis. 2016 May;8(5):862-71. doi: 10.21037/jtd.2016.03.46.

BACKGROUND: The standard treatment for stage III non-small-cell lung cancer (NSCLC) is still 60 Gy in conventional fractions combined with concurrent chemotherapy; however, the resulting local controls are disappointing. The aim of this study was to compare and assess the feasibility and efficacy of hypofractionated chemoradiotherapy using helical tomotherapy (HT) with conventional fractionation as opposed to using three-dimensional conformal radiotherapy (3D-CRT) for stage III NSCLC.

METHODS: Sixty-nine patients with stage III (AJCC 7th edition) NSCLC who underwent definitive radiation treatment at our institution between July 2011 and November 2013 were reviewed and analyzed retrospectively. A dose of 60 Gy in 20 fractions was delivered in the HT group (n=34), whereas 60 Gy in 30 fractions in the 3D-CRT group (n=35). Primary endpoints were toxicity, overall response rate, overall survival (OS) and progression-free survival (PFS). **RESULTS:** The median follow-up period was 26.4 months. V20 (P=0.005), V30 (P=0.001), V40 (P=0.004), mean lung dose (P=0.000) and max dose of spinal cord (P=0.005) were significantly lower in the HT group than in the 3D-CRT group. There was no significant difference in the incidences of acute radiation pneumonitis (RP) \geq grade 2 between the two groups, whereas the incidences of acute radiation esophagitis \geq grade 2 were significantly lower in the HT group than in the 3D-CRT group (P=0.027). Two-year overall response rate was significantly higher in the HT group than in the 3D-CRT group (P=0.015). One- and 2-year OS rates were significantly higher in

the HT group (95.0% and 68.7%, respectively) than in the 3D-CRT group (85.5% and 47.6%, respectively; P=0.0236). One- and 2-year PFS rates were significantly higher in the HT group (57.8% and 26.3%, respectively) than in the 3D-CRT group (32.7% and 11.4%, respectively; P=0.0351). Univariate analysis indicated that performance status (PS), T stage and radiotherapy technique were significant prognostic factors for both OS and PFS. Multivariate analysis indicated that PS and radiotherapy technique were independent prognostic factors of OS and PS was independent prognostic factor of PFS. **CONCLUSIONS:** Hypofractionated chemoradiotherapy via HT can shorten the radiotherapy time without increasing treatment-related toxicity. The preliminary findings are that OS and PFS can be improved by hypofractionated chemoradiotherapy via HT for patients with stage III NSCLC.

[**A feasibility study of dynamic adaptive radiotherapy for non-small cell lung cancer.**](#) Kim M1, Phillips MH2. Med Phys. 2016 May;43(5):2153. doi: 10.1118/1.4945023.

PURPOSE: The final state of the tumor at the end of a radiotherapy course is dependent on the doses given in each fraction during the treatment course. This study investigates the feasibility of using dynamic adaptive radiotherapy (DART) in treating lung cancers assuming CBCT is available to observe midtreatment tumor states. DART adapts treatment plans using a dynamic programming technique to consider the expected changes of the tumor in the optimization process. **METHODS:** DART is constructed using a stochastic control formalism framework. It minimizes the total expected number of tumor cells at the end of a treatment course, which is equivalent to maximizing tumor control probability, subject to the uncertainty inherent in the tumor response. This formulation allows for nonstationary dose distributions as well as nonstationary fractional doses as needed to achieve a series of optimal plans that are conformal to the tumor over time, i.e., spatiotemporally optimal plans. Sixteen phantom cases with various sizes and locations of tumors and organs-at-risk (OAR) were generated using in-house software. Each case was planned with DART and conventional IMRT prescribing 60 Gy in 30 fractions. The observations of the change in the tumor volume over a treatment course were simulated using a two-level cell population model. Monte Carlo simulations of the treatment course for each case were run to account for uncertainty in the tumor response. The same OAR dose constraints were applied for both methods. The frequency of replanning was varied between 1, 2, 5 (weekly), and 29 times (daily). The final average tumor dose and OAR doses have been compared to quantify the potential dosimetric benefits of DART. **RESULTS:** The average tumor max, min, mean, and D95 doses using DART relative to these using conventional IMRT were 124.0%-125.2%, 102.1%-114.7%, 113.7%-123.4%, and 102.0%-115.9% (range dependent on the frequency of replanning). The average relative maximum doses for the cord and esophagus, mean doses for the heart and lungs, and D05 for the unspecified tissue resulting 84%-102.4%, 99.8%-106.9%, 66.9%-85.6%, 58.2%-78.8%, and 85.2%-94.0%, respectively. **CONCLUSIONS:** It is feasible to apply DART to the treatment of NSCLC using CBCT to observe the midtreatment tumor state. Potential increases in the tumor dose and reductions in the OAR dose, particularly for parallel OARs with mean or dose-volume constraints, could be achieved using DART compared to nonadaptive IMRT.

SMALL CELL LUNG CANCER - SCLC

[**Patient-derived xenografts faithfully replicated clinical outcome in a phase II co-clinical trial of arsenic trioxide in relapsed small cell lung cancer.**](#) Owonikoko TK1, Zhang G2, Kim HS3, et al. J Transl Med. 2016 May 3;14(1):111. doi: 10.1186/s12967-016-0861-5.

BACKGROUND: SCLC has limited treatment options and inadequate preclinical models. Promising activity of arsenic trioxide (ASO) recorded in conventional preclinical models of SCLC supported the clinical evaluation of ASO in patients. We assessed the efficacy of ASO in relapsed SCLC patients and in corresponding patient-derived xenografts (PDX). **METHODS:** Single arm, Simon 2-stage, phase II trial to enroll patients with relapsed SCLC who have failed at least one line of therapy. ASO was administered

as an intravenous infusion over 1-2 h daily for 4 days in week 1 and for 2 days in weeks 2-6 of an 8-week cycle. Treatment continued until disease progression. Pretreatment tumor biopsy was employed for PDX generation through direct implantation into subcutaneous pockets of SCID mice without in vitro manipulation and serially propagated for five generations. Ex vivo efficacy of cisplatin (3 mg/kg i.p. weekly) and ASO (3.75 mg/kg i.p. every other day) was tested in PDX representative of platinum sensitive and platinum refractory SCLC. **RESULTS:** The best response in 17 evaluable patients was stable disease in 2 (12 %), progressive disease in 15 (88 %) patients and median time-to-progression of seven (range 1-7) weeks. PDX was successfully grown in 5 of 9 (56 %) transplanted biopsy samples. Serially-propagated PDXs preserved characteristic small cell histology and genomic stability confirmed by immunohistochemistry, short tandem repeat (STR) profiling and targeted sequencing. ASO showed in vitro cytotoxicity but lacked in vivo efficacy against SCLC PDX tumor growth. **CONCLUSIONS:** Cisplatin inhibited growth of PDX derived from platinum-sensitive SCLC but was ineffective against PDX from platinum-refractory SCLC. Strong concordance between clinical and ex vivo effects of ASO and cisplatin in SCLC supports the use of PDX models to prescreen promising anticancer agents prior to clinical testing in SCLC patients.

Prognostic impact of a 3-MicroRNA signature in cytological samples of small cell lung cancer.

Mancuso G1, Bovio E2, Rena O3, et al. Cancer Cytopathol. 2016 May 6. doi: 10.1002/cncy.21729. [Epub ahead of print]

BACKGROUND: Small cell lung cancer (SCLC) is a highly aggressive neoplasm that accounts for approximately 10% to 15% of lung cancers. In most cases, the diagnosis relies on cytology and needs to be confirmed by immunohistochemistry. Although several genetic and molecular abnormalities have been recorded, molecular markers able to predict the prognosis are still lacking. MicroRNA (miRNA) signatures have been recently proposed as useful biomarkers in lung cancer because of their high stability during standard sample processing. **METHODS:** Cytological samples for 50 patients with SCLC were collected from primary tumors (n = 25) and metastases (n = 25) by means of fine-needle aspiration (FNA) or bronchial washing (BW); they were fixed in ethanol (FNA) or Duboscq-Brazil fluid (BW). The 3-miRNA panel expression (miR-192, miR-200c, and miR-205) was quantified with a TaqMan polymerase chain reaction miRNA assay and was compared with overall survival (OS) and clinicopathological data. **RESULTS:** All samples had sufficient RNA for the miRNA expression analysis to be performed, regardless of the sample source or the fixative medium. Patients with a low expression level of the 3-miRNA panel were associated with better OS in univariate (P = .032) and multivariate analyses (P = .022). Moreover, in the group of patients older than the mean age of our cohort (65.8 years), a significant OS advantage (P = .013) was seen for patients with a low expression level of the 3-miRNA panel. **CONCLUSIONS:**

A specific 3-miRNA signature is potentially useful for predicting survival for patients with SCLC, and it may be feasible with cytological samples taken during standard diagnostic procedures.

Vismodegib or cixutumumab in combination with standard chemotherapy for patients with extensive-stage small cell lung cancer: A trial of the ECOG-ACRIN Cancer Research Group (E1508).

Belani CP1, Dahlberg SE2, Rudin CM3, et al. Cancer. 2016 May 10. doi: 10.1002/cncr.30062. [Epub ahead of print]

BACKGROUND: Preclinical targeting of the hedgehog pathway by vismodegib and of insulin-like growth factor 1 receptor by cixutumumab enhances the efficacy of chemotherapy and also demonstrates activity against the tumor cell fraction responsible for disease recurrence in small cell lung cancer. **METHODS:** Patients with newly diagnosed extensive-stage small cell lung cancer (SCLC-ED) were randomized to receive four 21-day cycles of cisplatin and etoposide alone (cisplatin at 75 mg/m² on day 1 and etoposide at 100 mg/m² on days 1-3; arm A) or in combination with either vismodegib (150 mg/d by

mouth; arm B) or cixutumumab (6 mg/kg/wk intravenously on day 1; arm C). The primary endpoint was progression-free survival (PFS). Circulating tumor cells (CTCs) were isolated/enumerated with the Veridex CellSearch platform at the baseline. **RESULTS:** One hundred fifty-two eligible patients were treated. Patient demographics and disease characteristics were well balanced between the 3 arms except for the higher rate with a performance status of 0 in arm B ($P = .03$). The median PFS times in arms A, B, and C were 4.4, 4.4, and 4.6 months, respectively; the median overall survival (OS) times were 8.8, 9.8, and 10.1 months, respectively; and the response rates were 48%, 56%, and 50%, respectively. None of the comparisons of these outcomes were statistically significant. The median OS was 10.5 months for those with low CTC counts ($\leq 100/7.5$ mL) at baseline and 7.2 months for those with high CTC counts (hazard ratio, 1.74; $P = .006$). **CONCLUSIONS:** There was no significant improvement in PFS or OS with the addition of either vismodegib or cixutumumab to chemotherapy in patients with SCLC-ED. A low baseline CTC count was associated with a favorable prognosis.

[Increased Biological Effective Dose of Radiation Correlates with Prolonged Survival of Patients with Limited-Stage Small Cell Lung Cancer: A Systematic Review.](#) Zhu L1,2, Zhang S1,2, et al. PLoS One. 2016 May 26;11(5):e0156494. doi: 10.1371/journal.pone.0156494. eCollection 2016.

OBJECTIVE: Thoracic radiotherapy (TRT) is a critical component of the treatment of limited-stage small cell lung cancer (LS-SCLC). However, the optimal radiation dose/fractionation remains elusive. This study reviewed current evidence and explored the dose-response relationship in patients with LS-SCLC who were treated with radiochemotherapy. **MATERIALS AND METHODS:** A quantitative analysis was performed through a systematic search of PubMed, Web of Science, and the Cochrane Library. The correlations between the biological effective dose (BED) and median overall survival (mOS), median progression-free survival (mPFS), 1-, 3-, and 5-year overall survival (OS) as well as local relapse (LR) were evaluated. **RESULTS:** In all, 2389 patients in 19 trials were included in this study. Among these 19 trials, seven were conducted in Europe, eight were conducted in Asia and four were conducted in the United States. The 19 trials that were included consisted of 29 arms with 24 concurrent and 5 sequential TRT arms. For all included studies, the results showed that a higher BED prolonged the mOS ($R^2 = 0.198$, $p < 0.001$) and the mPFS ($R^2 = 0.045$, $p < 0.001$). The results also showed that increased BED improved the 1-, 3-, and 5-year OS. A 10-Gy increment added a 6.3%, a 5.1% and a 3.7% benefit for the 1-, 3-, and 5-year OS, respectively. Additionally, BED was negatively correlated with LR ($R^2 = 0.09$, $p < 0.001$). A subgroup analysis of concurrent TRT showed that a high BED prolonged the mOS ($p < 0.001$) and the mPFS ($p < 0.001$), improved the 1-, 3-, and 5-year OS ($p < 0.001$) and decreased the rate of LR ($p < 0.001$). **CONCLUSION:** This study showed that an increased BED was associated with improved OS, PFS and decreased LR in patients with LS-SCLC who were treated with combined chemoradiotherapy, which indicates that the strategy of radiation dose escalation over a limited time frame is worth exploring in a prospective clinical trial.

[A New Score for Estimating Survival After Definitive Radiochemotherapy of Limited Disease Small Cell Lung Cancers.](#) Rades D1, Kaesmann L2, Janssen S2,3, Schild SE4. Lung. 2016 May 2. [Epub ahead of print]

INTRODUCTION: Most patients with limited disease small cell lung cancer (LD-SCLC) receive definitive radiochemotherapy. Some patients cannot withstand combined modality treatments. Patients with short life expectancies should receive less time-consuming programs. For patients with favorable prognoses, cure while avoiding late toxicity is important. Personalized treatment programs are required. An instrument to estimate the survival after radiochemotherapy of LD-SCLC was created. **METHODS:** Seventy-one patients receiving definitive radiochemotherapy for LD-SCLC were retrospectively analyzed. Eight factors were evaluated for survival including gender, age, Karnofsky performance score, T-stage, N-stage, tumor substage, number of pack years, and pre-radiotherapy hemoglobin level. Factors

that were significant ($p < 0.05$) or showed a trend ($p \leq 0.08$) on multivariate analyses were incorporated in the score. Scoring points were derived from 2-year survival rates divided by 10 and added to scores for individual patients. **RESULTS:** On multivariate analysis, gender ($p = 0.03$), performance score ($p < 0.001$), and pre-radiotherapy hemoglobin level ($p = 0.04$) were significant, and tumor substage showed a trend ($p = 0.08$). Taking into account the 2-year survival rates of these factors, scores for single patients ranged from 9 to 26 points. Three groups were identified: 9-13, 14-18, and 19-26 points. One-year survival rates were 8, 73, and 100 %, respectively ($p < 0.001$). Two-year survival rates were 0, 35, and 87 %, respectively ($p < 0.001$). The 3-year survival rates were 0, 19, and 75 %, respectively ($p < 0.001$). **CONCLUSION:** This score including three groups with significantly different survival rates is a helpful instrument for personalization of therapy for patients with LD-SCLC. When using this instrument, the limitations if this study must be taken into account.

PALLIATIVE AND SUPPORTIVE CARE

Palliative Care for Patients Dying in the Intensive Care Unit with Chronic Lung Disease Compared with Metastatic Cancer. Brown CE1, Engelberg RA1, Nielsen EL1, Curtis JR1. Ann Am Thorac Soc. 2016 May;13(5):684-9. doi: 10.1513/AnnalsATS.201510-667OC.

RATIONALE: Palliative care has been focused largely on patients with cancer, and yet patients with chronic lung diseases also have high morbidity and mortality. The majority of deaths in intensive care units (ICUs) follow decisions to withhold or withdraw life-sustaining treatments, suggesting that palliative care is critically important in this setting. **OBJECTIVES:** We explored differences in receipt of elements of palliative care among patients with interstitial lung disease (ILD) and chronic obstructive pulmonary disease (COPD) who die in ICUs compared with patients with cancer. **METHODS:** We identified patients with COPD, ILD, or metastatic cancer who died in the ICUs of 15 Seattle-area hospitals between 2003 and 2008. We used robust multivariable logistic and linear regression to compare differences in receipt of elements of palliative care and length of stay. **MEASUREMENTS AND MAIN RESULTS:** Compared with patients with cancer, patients with COPD were more likely to receive cardiopulmonary resuscitation before death and patients with ILD were less likely to have documentation of pain assessment in the last day of life. Patients with ILD and COPD were less likely to have a do-not-resuscitate order in place at the time of death and less likely to have documentation of discussions about prognosis than patients with cancer. Patients with COPD had longer hospital lengths of stay, and patients with COPD and ILD had longer ICU lengths of stay. **CONCLUSIONS:** Among patients who die in the ICU, patients with ILD and COPD receive fewer elements of palliative care and have longer lengths of stay than patients with cancer. These findings identify areas for improvement in caring for patients with chronic lung diseases.

Integrated Palliative Care and Oncologic Care in Non-Small-Cell Lung Cancer. Chandrasekar D1, Tribett E2, Ramchandran K3. Curr Treat Options Oncol. 2016 May;17(5):23. doi: 10.1007/s11864-016-0397-1.

OPINION STATEMENT: Palliative care integrated into standard medical oncologic care will transform the way we approach and practice oncologic care. Integration of appropriate components of palliative care into oncologic treatment using a pathway-based approach will be described in this review. Care pathways build on disease status (early, locally advanced, advanced) as well as patient and family needs. This allows for an individualized approach to care and is the best means for proactive screening, assessment, and intervention, to ensure that all palliative care needs are met throughout the continuum of care. Components of palliative care that will be discussed include assessment of physical symptoms, psychosocial distress, and spiritual distress. Specific components of these should be integrated based on disease trajectory, as well as clinical assessment. Palliative care should also include family and caregiver

education, training, and support, from diagnosis through survivorship and end of life. Effective integration of palliative care interventions have the potential to impact quality of life and longevity for patients, as well as improve caregiver outcomes.

[The Utility of Exercise Testing in Patients with Lung Cancer.](#) Ha D1, Mazzone PJ2, Ries AL3, Malhotra A3, Fuster M4. *J Thorac Oncol.* 2016 May 5. pii: S1556-0864(16)30402-6. doi: 10.1016/j.jtho.2016.04.021. [Epub ahead of print]

The harm associated with lung cancer treatment include perioperative morbidity and mortality and therapy-induced toxicities in various organs, including the heart and lungs. Optimal treatment therefore entails a need for risk assessment to weigh the probabilities of benefits versus harm. Exercise testing offers an opportunity to evaluate a patient's physical fitness/exercise capacity objectively. In lung cancer, it is most often used to risk-stratify patients undergoing evaluation for lung cancer resection. In recent years, its use outside this context has been described, including in nonsurgical candidates and lung cancer survivors. In this article we review the physiology of exercise testing and lung cancer. Then, we assess the utility of exercise testing in patients with lung cancer in four contexts (preoperative evaluation for lung cancer resection, after lung cancer resection, lung cancer prognosis, and assessment of efficiency of exercise training programs) after systematically identifying original studies involving the most common forms of exercise tests in this patient population: laboratory cardiopulmonary exercise testing and simple field testing with the 6-minute walk test, shuttle walk test, and/or stair-climbing test. Lastly, we propose a conceptual framework for risk assessment of patients with lung cancer who are being considered for therapy and identify areas for further studies in this patient population.

[Lower Pectoralis Muscle Area is Associated with a Worse Overall Survival in Non- Small Cell Lung Cancer.](#)

Kinsey CM1, San Jose Estepar R2, Van der Velden J3, Cole BF4, Christiani DC5, Washko GR6. *Cancer Epidemiol Biomarkers Prev.* 2016 May 19. pii: cebp.1067.2015. [Epub ahead of print]

BACKGROUND: Muscle wasting is a component of the diagnosis of cancer cachexia and has been associated with poor prognosis. However, recommended tools to measure sarcopenia are limited by poor sensitivity or the need to perform additional scans. We hypothesized that pectoralis muscle area (PMA) measured objectively on chest CT scan may be associated with overall survival in non-small cell lung cancer (NSCLC). **METHODS:** We evaluated two hundred fifty two cases from a prospectively enrolling lung cancer cohort. Eligible cases had CT scans performed prior to the initiation of surgery, radiation, or chemotherapy. PMA was measured in a semi-automated fashion while blinded to characteristics of the tumor, lung, and patient outcomes. **RESULTS:** Men had a significantly greater PMA than women (37.59 vs 26.19 cm², P<0.0001). In univariate analysis, PMA was associated with age and BMI. A Cox proportional hazards model was constructed to account for confounders associated with survival. Lower pectoralis area (per cm²) at diagnosis was associated with an increased hazard of death of 2% (HRadj 0.98 [0.96, 0.99], P=0.044) while adjusting for age, sex, smoking, chronic bronchitis, emphysema, histology, stage, chemotherapy, radiation, surgery, BMI, and ECOG performance status.

CONCLUSIONS: Lower pectoralis muscle area measured from chest CT scans obtained at the time of diagnosis of NSCLC is associated with a worse overall survival.

[Chronic condition clusters and functional impairment in older cancer survivors: a population-based study.](#) Kenzik KM1, Kent EE2, Martin MY3, Bhatia S4, Pisu M5. *J Cancer Surviv.* 2016 May 27. [Epub ahead of print]

PURPOSE: The purpose of the study is to identify chronic condition clusters at pre- and post-cancer diagnosis, evaluate predictors of developing clusters post-cancer, and examine the impact on functional impairment among older cancer survivors. **METHODS:** We identified 5991 survivors age 65 and older of

prostate, breast, colorectal, lung, bladder, kidney, head and neck, and gynecologic cancer and non-Hodgkin lymphoma from the Surveillance, Epidemiology and End Results-Medicare Health Outcomes Survey resource. Survivors completed surveys pre- and post-cancer diagnosis on 13 chronic conditions and functional status. Among those with ≥ 2 conditions, exploratory factor analysis identified clusters of conditions. Differences in cluster frequency from pre- to post-cancer diagnosis were evaluated across the top five cancer types using chi-square tests. Modified Poisson regression models estimated the relative risk of developing clusters post-diagnosis. Chi-square tests evaluated associations between function and clusters. **RESULTS:** Clusters included the following: cardiovascular disease cluster (pre 6.1 % and post 7.7 %), musculoskeletal cluster (28.2 % and 29.3 %), metabolic cluster (14.9 % and 17.6 %), and the major depressive disorder risk (MDDr) + gastrointestinal (GI) + pulmonary condition cluster (5.8 % and 8.7 %). Increases in MDDr + GI + Pulmonary cluster from pre- to post-cancer diagnosis were observed for prostate, lung, and colorectal cancer survivors. Functional impairment was more prevalent in survivors with defined clusters, especially in MDDr + GI + pulmonary, compared to survivors with ≥ 2 un-clustered conditions. **CONCLUSIONS:** Distinct condition clusters of two or more chronic conditions are prevalent among older cancer survivors. Cluster prevalence increases from pre- to post-cancer diagnosis and these clusters have a significant impact on functional limitations. **IMPLICATIONS FOR CANCER SURVIVORS:** Tailored management on specific multimorbidity patterns will have implications for functional outcomes among older survivors.

[Relationship between Efficacy Outcomes and Weight Gain during Treatment of Advanced, Nonsquamous, Non-small Cell Lung Cancer Patients.](#)

Patel JD1, Pereira JR2, Chen J3, et al. Ann Oncol. 2016 May 23. pii: mdw211. [Epub ahead of print]

BACKGROUND: Unintentional weight loss occurs among advanced non-small cell lung cancer (NSCLC) patients and is associated with worse survival. Small studies have suggested that weight gain during treatment is associated with superior survival. **PATIENTS AND METHODS:** A retrospective analysis analyzed data from three international phase III studies comprising 2301 advanced, nonsquamous NSCLC patients who received a platinum-based, first-line doublet, with or without bevacizumab and maintenance therapy. Body weight was recorded before and after treatment by each study's schedule. The relationship between weight gain and overall survival (OS) and progression-free survival (PFS) was assessed using log-rank test and adjusted Cox modeling. Logistic regression assessed the association between baseline covariates and post-baseline weight gain. **RESULTS:** 421 (18.3%) patients had $>5\%$ weight gain after baseline. More than half of the weight gain cohort exhibited initial weight gain by 3 weeks. Median OS was 16.7 months versus 10.7 months for the $>5\%$ versus $\leq 5\%$ weight gain subgroup (N=1880) ($p < 0.001$). PFS was 6.9 versus 4.8 months, respectively ($p < 0.001$). Differences in overall tumor response rate (50.8% versus 25.4%, respectively) and disease control rate (tumor response or stable disease) (91.5% versus 63.6%, respectively) were also significant ($p < 0.001$). Cox modeling revealed the $>5\%$ subgroup had longer survival (HR=0.54, 95%CI=0.47-0.62; $p < 0.001$) than the $<5\%$ subgroup after adjusting for baseline factors. Similar significant results were found for PFS (HR=0.59, 95%CI=0.52-0.67; $p < 0.001$). Unadjusted logistic regression indicated a significant association between weight gain ($>5\%$ versus $\leq 5\%$) and age, and BMI. **CONCLUSIONS:** Weight gain during treatment may be an early indicator of clinical benefit. If confirmed in prospective studies, monitoring weight change may provide important information regarding survival outcomes in NSCLC and may provide ideas for new therapeutic strategies.

[Cachexia among US cancer patients.](#) Arthur ST1, Van Doren BA1, Roy D1, Noone JM1, Zacherle E1, Blanchette CM1. J Med Econ. 2016 May 11:1-7. [Epub ahead of print]

BACKGROUND: Cancer cachexia is a debilitating condition and results in poor prognosis. The purpose of this study was to assess hospitalization incidence, patient characteristics, and medical cost and burden

of cancer cachexia in the US. **METHODS:** This study used a cross-sectional analysis of the Nationwide Inpatient Sample (NIS) for 2009. Five cancers reported to have the highest cachexia incidence were assessed. The hospitalization incidence related to cachexia was estimated by cancer type, cost and length of stay were compared, and descriptive statistics were reported for each cancer type, as well as differences being compared between patients with and without cachexia. **RESULTS:** Risk of inpatient death was higher for patients with cachexia in lung cancer (OR = 1.32; CI = 1.20-1.46) and in all cancers combined (OR = 1.76; CI = 1.67-1.85). The presence of cachexia increased length of stay in lung (IRR = 1.05; CI = 1.03-1.08), Kaposi's sarcoma (IRR = 1.47; CI = 1.14-1.89) and all cancers combined (IRR = 1.09; CI = 1.08-1.10). Additionally, cachectic patients in the composite category had a longer hospitalization stay compared to non-cachectic patients (3-9 days for those with cachexia and 2-7 days for those without cachexia). The cost of inpatient stay was significantly higher in cachexic than non-cachexic lung cancer patients (\$13,560 vs \$13 190; $p < 0.0001$), as well as cachexic vs non-cachexic cancer patients in general (14 751 vs 13 928; $p < 0.0001$). **CONCLUSIONS:** Cachexia increases hospitalization costs and length of stay in several cancer types. Identifying the medical burden associated with cancer cachexia will assist in developing an international consensus for recognition and coding by the medical community and ultimately an effective treatment plans for cancer cachexia.

[The Association of Chemotherapy-Induced Peripheral Neuropathy Symptoms and the Risk of Falling.](#) Kolb NA1, Smith AG1, Singleton JR1, Beck SL2, Stoddard GJ3, Brown S1, Mooney K2. JAMA Neurol. 2016 May 16. doi: 10.1001/jamaneurol.2016.0383. [Epub ahead of print]

OBJECTIVE: To determine the association between the symptoms of CIPN and the risk of falls for patients receiving neurotoxic chemotherapy. **DESIGN, SETTING, AND PARTICIPANTS:** In this secondary analysis of a prospective study, 116 patients with breast, ovarian, or lung cancer who were beginning neurotoxic chemotherapy with a taxane or platinum agent were recruited from oncology clinics. These patients would call a novel automated telephone system daily for 1 full course of chemotherapy. The telephone system (SymptomCare@Home) used a series of relevant CIPN questions to track symptoms on a 0 to 10 ordinal scale and contained a questionnaire about falls. Those reporting a numbness and tingling severity score of 3 or greater for at least 10 days were considered to have significant CIPN symptoms and were compared with those patients who did not. Data analysis was performed in November 2015. **EXPOSURE:** Chemotherapy with a neurotoxic taxane or platinum agent. **MAIN OUTCOMES AND MEASURES:** Patient-reported falls or near falls and fall-related injuries. The hypothesis was generated after data collection but prior to data analysis. **RESULTS:** Of the 116 patients who started neurotoxic chemotherapy (mean [SD] age was 55.5 [11.9] years, and 109 [94.0%] were female), 32 met the predetermined criteria for CIPN symptoms. The mean duration of follow-up was 62 days, with 51 telephone calls completed per participant. Seventy-four falls or near falls were reported. The participants with CIPN symptoms were nearly 3 times more likely to report a fall or near fall than the participants without CIPN symptoms (hazard ratio, 2.67 [95% CI, 1.62-4.41]; $P < .001$). The participants with CIPN symptoms were more likely than the participants without CIPN symptoms to obtain medical care for falls (8 of 32 participants with CIPN symptoms [25.0%] vs 6 of 84 participants without CIPN symptoms [7.1%]; $P = .01$). **CONCLUSIONS AND RELEVANCE:** These findings suggest that the sensory symptoms of CIPN are an indicator of an increased risk of falling and an increased use of health care resources. This study demonstrates the utility of a novel telephone-based system to track neuropathy symptoms. Careful monitoring and coaching of patients receiving neurotoxic chemotherapy for new sensory symptoms may facilitate more effective fall prevention strategies.

[Lower Patient Ratings of Physician Communication Are Associated With Unmet Need for Symptom Management in Patients With Lung and Colorectal Cancer.](#) Walling AM1, Keating NL2, Kahn KL2, et al. *J Oncol Pract.* 2016 Jun;12(6):e654-69. doi: 10.1200/JOP.2015.005538. Epub 2016 May 24.

PURPOSE: Little is known about factors associated with unmet needs for symptom management in patients with cancer. **METHODS:** Patients with a new diagnosis of lung and colorectal cancer from the diverse nationally representative Cancer Care Outcomes Research and Surveillance cohort completed a survey approximately 5 months after diagnosis (N = 5,422). We estimated the prevalence of unmet need for symptom management, defined as patients who report that they wanted help for at least one common symptom (pain, fatigue, depression, nausea/vomiting, cough, dyspnea, diarrhea) during the 4 weeks before the survey but did not receive it. We identified patient factors associated with unmet need by using logistic regression with random effects to account for clustering within study sites. **RESULTS:** Overall, 15% (791 of 5,422) of patients had at least one unmet need for symptom management. Adjusting for sociodemographic and clinical factors, African American race, being uninsured or poor, having early-stage lung cancer, and the presence of moderate to severe symptoms were associated with unmet need (all $P < .05$). Furthermore, patients who rated their physician's communication score < 80 (on a 0 to 100 scale) had adjusted rates of an unmet need for symptom management that were more than twice as high as patients who rated their physicians with a perfect communication score (23.1% v 10.0%; $P < .001$). **CONCLUSION:** A significant minority of patients with newly diagnosed lung and colorectal cancer report unmet needs for symptom management. Interventions to improve symptom management should consider the importance of physician communication to the patient's experience of disease.

[Factors associated with depression and anxiety symptoms in family caregivers of patients with incurable cancer.](#) Nipp RD1, El-Jawahri A2, Fishbein JN3, et al. *Ann Oncol.* 2016 May 13. pii: mdw205. [Epub ahead of print]

BACKGROUND: Family caregivers (FCs) are critically important for patients with cancer, yet they may experience psychological distress related to caregiving demands. We sought to describe rates of depression and anxiety in FCs of patients with incurable cancer and identify factors associated with these symptoms to determine those at greatest risk for psychological distress. **PATIENTS AND METHODS:** We performed a cross-sectional analysis of baseline data from a randomized trial of early palliative care. We assessed depression and anxiety using the Hospital Anxiety and Depression Scale in patients within 8 weeks of diagnosis of incurable lung or gastrointestinal cancer and their FCs. We also assessed patients' quality of life (Functional Assessment of Cancer Therapy-General), coping strategies (Brief COPE), and their report of the primary goal of their cancer treatment. We used linear regression with purposeful selection of covariates to identify factors associated with FC depression and anxiety symptoms. **RESULTS:** We enrolled 78.6% (n = 275) of potentially eligible FCs. The majority were female (69.1%) and married to the patient (66.2%). While the proportion of FCs and patients reporting depression did not differ (16.4% versus 21.5%, $P = 0.13$), FCs were more likely to report anxiety compared with patients (42.2% versus 28.4%, $P < 0.001$). Patients' use of acceptance coping was associated with lower FC depression ($B = -0.42$, $P < 0.001$), while emotional support coping was associated with higher FC depression ($B = 0.69$, $P = 0.001$) and lower FC anxiety ($B = -0.70$, $P < 0.001$). Patient report that their primary goal of their treatment was to 'cure my cancer' was associated with higher FC depression ($B = 0.72$, $P = 0.03$). **CONCLUSIONS:** Patients with incurable cancer and their FCs report high levels of depression and anxiety symptoms. We demonstrated that patients' coping strategies and prognostic understanding were associated with FC depression and anxiety symptoms, underscoring the importance of targeting these risk factors when seeking to address the psychological distress experienced by FCs.

Cost Analysis of a Randomized Trial of Early Palliative Care in Patients with Metastatic Nonsmall-Cell Lung Cancer. Greer JA1, Tramontano AC1, McMahon PM1, et al. J Palliat Med. 2016 May 11.

[Epub ahead of print]

BACKGROUND: Several trials have shown that integrated palliative and oncology care improves quality of life and mood in patients with advanced cancers. However, the degree to which early involvement of palliative care (PC) in the outpatient setting impacts the cost of care remains unknown.

METHODS: Data for this secondary analysis came from a trial of 151 patients with metastatic nonsmall-cell lung cancer (NSCLC) who were randomized to early PC integrated with standard oncology care (SC) or SC alone. We abstracted costs for hospital and outpatient care, including intravenous chemotherapy, from the hospital accounting system. Oral chemotherapy costs were estimated based on actual drug costs. To estimate hospice costs, we used Medicare reimbursement rates. We examined between-group differences in costs of care throughout the entire study period and during the last 30 days before death using the bootstrap-t method. **RESULTS:** The analytic sample includes the 138/151 patients who died by July 15, 2013. Early PC was associated with a lower mean total cost per day of \$117 ($p = 0.13$) compared to SC. In the final 30 days of life, patients in the early PC group incurred higher hospice care costs (mean difference = \$1,053; $p = 0.07$), while expenses for chemotherapy were less (mean difference = \$757; $p = 0.03$). Costs for emergency department visits and hospitalizations did not differ significantly between groups over the course of the study or at the end of life. **CONCLUSIONS:** The delivery of early PC does not appear to increase overall medical care expenses for patients with metastatic NSCLC. Larger, sufficiently powered cost studies of early PC are needed.

The effect of chemotherapy-induced anemia on dose reduction and dose delay. Family L1, Xu L1, Xu H2, Cannavale K1, Sattayapiwat O1, Page JH2, Bohac C2, Chao C3. Support Care Cancer. 2016 May 11. [Epub ahead of print]

PURPOSE: To evaluate moderate (grade 2, hemoglobin <10 g/dl) and severe (grade 3+, hemoglobin <8 g/dl) anemia as potential risk factors for DDR in the first line course of chemotherapy. While chemotherapy-induced neutropenia has been shown to be associated with dose delay/reduction (DDR) in several studies, the effect of anemia is less well studied. **METHODS:** We identified 3955 Kaiser Permanente patients diagnosed with incident non-Hodgkin's lymphoma ($n = 574$), breast ($n = 2043$), lung ($n = 463$), gastric ($n = 113$), ovarian ($n = 204$), or colorectal cancers ($n = 558$) between 2010 and 2012. Generalized linear mixed effects models were used to study the effect of anemia in subsequent cycles, adjusting for demographics, comorbidities, chemotherapy cycle, neutropenia, thrombocytopenia, and liver and renal function. **RESULTS:** We found that moderate (grade 2) to severe (grade 3-4) anemia increased the risk of DDR in subsequent chemotherapy cycles [odds ratio (OR) = 1.46, 95 % CI (1.32, 1.62) and OR = 2.02 (1.41, 2.89)], respectively, compared to grade 1 or no anemia. Both stage I-III and IV patients with grade 2 or greater anemia were at higher risk for DDR than patients with grade 1 or no anemia [ORstage IV, grade 2 = 1.94 (1.58, 2.38); ORstage IV, grade 3/4 = 2.83 (1.42, 5.62) and ORstage I-III, grade 2 = 1.33 (1.18, 1.49); ORstage I-III, grade 3-4 = 1.81 (1.18, 2.76)]. **CONCLUSIONS:** These results provide insight into novel risk factors for chemotherapy dose modification that may inform clinicians on management strategies to optimize treatment outcomes.

COMPLEMENTARY & ALTERNATIVE THERAPY

Bergamottin isolated from Citrus bergamia exerts in vitro and in vivo antitumor activity in lung adenocarcinoma through the induction of apoptosis, cell cycle arrest, mitochondrial membrane potential loss and inhibition of cell migration and invasion. Wu HJ1, Wu HB1, Zhao YQ1, Chen LJ1, Zou HZ1. Oncol Rep. 2016 May 23. doi: 10.3892/or.2016.4833. [Epub ahead of print]

The objective of the present study was to investigate the in vitro and in vivo anticancer properties of bergamottin, a natural furanocoumarin, against human non-small cell lung carcinoma (NSCLC) A549 cells. We also studied its effect on cell proliferation, cell cycle arrest, cell invasion, cell migration as well as cell apoptosis. Antiproliferative activity of bergamottin was estimated by the MTT assay. Phase contrast and fluorescence microscopy as well as flow cytometry using Annexin V-FITC assay were used to study induction of apoptosis by bergamottin in these cells. The effects of bergamottin on cell cycle phase distribution as well as on mitochondrial membrane potential were also demonstrated using flow cytometry. In vitro wound healing assay was used to study the effect of bergamottin on cell migration. The effects of bergamottin on tumor progression were also observed using a nude mouse model. The mice were divided into 4 groups and treated with bergamottin injected intraperitoneally. Bergamottin induced dose-dependent as well as time-dependent cytotoxic effects as well as inhibition of colony formation in the A549 cancer cells. Bergamottin also suppressed cancer cell invasion as well as cancer cell migration. Phase contrast microscopy and fluorescence microscopy revealed that bergamottin induced cell shrinkage, chromatin condensation and the cells became rounded and detached from each other. Bergamottin also induced a potent cell cycle arrest at the G2/M phase of the cell cycle. Experiments in mice showed that 25, 50 and 100 mg/kg bergamottin injection reduced the tumor weight from 1.61 g in the phosphate-buffered saline (PBS)-treated group (control) to 1.21, 0.42 and 0.15 g in the bergamottin-treated groups, respectively. The results of the present study revealed that bergamottin was able to inhibit lung cancer cell growth both in a cell model and a xenograft mouse model by inducing apoptosis, mitochondrial membrane potential loss, G2/M cell cycle arrest as well as inhibiting cell migration and invasion.

[Complementary and Alternative Medicine Use at a Comprehensive Cancer Center.](#) Luo Q1, Asher GN2. *Integr Cancer Ther.* 2016 May 4. pii: 1534735416643384. [Epub ahead of print]

BACKGROUND: Complementary and alternative medicine (CAM) use is common among cancer patients, but the majority of CAM studies do not specify the time periods in relation to cancer diagnoses. We sought to define CAM use by cancer patients and investigate factors that might influence changes in CAM use in relation to cancer diagnoses. **METHODS:** We conducted a cross-sectional survey of adults diagnosed with breast, prostate, lung, or colorectal cancer between 2010 and 2012 at the Lineberger Comprehensive Cancer Center. Questionnaires were sent to 1794 patients. Phone calls were made to nonrespondents. Log binomial/Poisson regressions were used to investigate the association between cancer-related changes in CAM use and conversations about CAM use with oncology providers. **RESULTS:** We received 603 (33.6 %) completed questionnaires. The mean age (SD) was 64 (11) years; 62% were female; 79% were white; and 98% were non-Hispanic. Respondents reported the following cancer types: breast (47%), prostate (27%), colorectal (14%), lung (11%). Eighty-nine percent reported lifetime CAM use. Eighty-five percent reported CAM use during or after initial cancer treatment, with category-specific use as follows: mind-body medicine 39%, dietary supplements 73%, body-based therapies 30%, and energy medicine 49%. During treatment CAM use decreased for all categories except energy medicine. After treatment CAM use returned to pretreatment levels for most CAMs except chiropractic. Initiation of CAM use after cancer diagnosis was positively associated with a patient having a conversation about CAM use with their oncology provider, mainly driven by patient-initiated conversations. **CONCLUSIONS:** Consistent with previous studies, CAM use was common among our study population. Conversations about CAM use with oncology providers appeared to influence cessation of mind-body medicine use after cancer diagnosis.

[The Efficacy of Traditional Chinese Herbal Medicine in the Treatment of EGFR Mutated Stage IV Pulmonary Adenocarcinoma Patients Who Received First-Line EGFR-TKI Treatment.](#) Hung HY1, Tseng YH2, Liao CM1, Chen SY1, Wu TP1, Lee YC3, Chen YM4. *Integr Cancer Ther.* 2016 May 5. pii: 1534735416645181. [Epub ahead of print]

BACKGROUND: Chinese herbal medicine (CHM) has been used for thousands of year in Eastern countries. First-line epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) treatment is the standard treatment in stage IV pulmonary adenocarcinoma patients who had tumor EGFR mutations. This study was to find the efficacy of CHM on lung cancer treatment. **MATERIALS AND METHODS:** We retrospectively reviewed chart records of our stage IV EGFR-mutated pulmonary adenocarcinoma patients who received first-line EGFR-TKI treatment from January 2010 to September 2014. **RESULTS:** Total, 527 patients were studied. Among them, 34 patients received CHM treatment, including 24 patients who received CHM treatment from the beginning of first-line EGFR-TKI treatment and 10 patients who started to receive CHM treatment after their disease had progressed to EGFR-TKI treatment. Median progression-free survival (PFS) of first-line EGFR-TKI treatment was numerically better in patients who also received CHM than those who did not (12.1 months vs 10.5 months, $P = .7668$). Overall survival of those 24 patient who received CHM treatment together with EGFR-TKI was 30.63 months (95% CI = 11.7 to not reached), compared to 23.67 months in the remaining patients (95% CI = 21.37-26; hazard ratio = 0.75; $P = .399$). No increase of CHM-related toxicities was found during CHM treatment, compared with EGFR-TKI treatment alone ($P > .05$). **CONCLUSION:** Alternative CHM treatment during first-line EGFR-TKI treatment did no harm to the patients and PFS and overall survival was numerically better, although not significant, than those patients who did not receive CHM treatment.

[In Vivo Anti-Cancer Mechanism of Low-Molecular-Weight Fucosylated Chondroitin Sulfate \(LFCS\) from Sea Cucumber *Cucumaria frondosa*.](#) Liu X1,2, Liu Y3,4, Hao J5,6, et al. *Molecules*. 2016 May 12;21(5). pii: E625. doi: 10.3390/molecules21050625.

The low-molecular-weight fucosylated chondroitin sulfate (LFCS) was prepared from native fucosylated chondroitin sulfate (FCS), which was extracted and isolated from sea cucumber *Cucumaria frondosa*, and the anti-cancer mechanism of LFCS on mouse Lewis lung carcinoma (LLC) was investigated. The results showed that LFCS remarkably inhibited LLC growth and metastasis in a dose-dependent manner. LFCS induced cell cycle arrest by increasing p53/p21 expression and apoptosis through activation of caspase-3 activity in LLC cells. Meanwhile, LFCS suppressed the expression of vascular endothelial growth factor (VEGF), increased the expression of tissue inhibitor of metalloproteinase-1 (TIMP-1) and downregulated the matrix metalloproteinases (MMPs) level. Furthermore, LFCS significantly suppressed the activation of ERK1/2/p38 MAPK/NF- κ B pathway, which played a prime role in expression of MMPs. All of these data indicate LFCS may be used as anti-cancer drug candidates and deserve further study.

[Potential Combinational Anti-Cancer Therapy in Non-Small Cell Lung Cancer with Traditional Chinese Medicine Sun-Bai-Pi Extract and Cisplatin.](#) Tseng CY1, Lin CH2, Wu LY3, Wang JS2, Chung MC2, Chang JF2, Chao MW2. *PLoS One*. 2016 May 12;11(5):e0155469. doi: 10.1371/journal.pone.0155469. eCollection 2016.

Traditional lung cancer treatments involve chemical or radiation therapies after surgical tumor removal; however, these procedures often kill normal cells as well. Recent studies indicate that chemotherapies, when combined with Traditional Chinese Medicines, may offer a new way to treat cancer. In vitro tests measuring the induction of autophagy and/or apoptosis were used to examine the cytotoxicity of SBPE, commonly used for lung inflammation on A549 cell line. The results indicated that intercellular levels of p62 and Atg12 were increased, LC3-I was cleaved into LC3-II, and autophagy was induced with SBPE only. After 24 hours, the apoptotic mechanism was induced. If the Cisplatin was added after cells reached the autophagy state, we observed synergistic effects of the two could achieve sufficient death of lung cancer cells. Therefore, the Cisplatin dosage used to induce apoptosis could be reduced by half, and the amount of time needed to achieve the inhibitory concentration of 50% was also half that of the original. In addition to inducing autophagy within a shortened period of time, the SBPE and chemotherapy drug combination therapy was able to achieve the objective of rapid low-dosage cancer cell elimination.

Besides, SBPE was applied with Gemcitabine or Paclitaxel, and found that the combination treatment indeed achieve improved lung cancer cell killing effects. However, SBPE may also be less toxic to normal cells.

MISCELLANEOUS WORKS

[Typical Time to Treatment of Patients With Lung Cancer in a Multisite, US-Based Study.](#) Vidaver RM1, Shershneva MB1, Hetzel SJ1, Holden TR1, Campbell TC2. *J Oncol Pract.* 2016 Jun;12(6):e643-53. doi: 10.1200/JOP.2015.009605. Epub 2016 May 3.

INTRODUCTION: The importance of high-quality, timely lung cancer care and the need to have indicators to measure timeliness are increasingly discussed in the United States. This study explored when and why delays occur in lung cancer care and compared timeliness between two states with divergent disease incidence. **METHODS:** Patients with small-cell or non-small-cell lung cancer were recruited through cancer centers, outpatient clinics, and community approaches, and interviewed over the phone. Statistical analysis of patient-reported dates included descriptive statistics and comparing time intervals between states and across the sites with Mann-Whitney U tests. Additionally, data from patients with longer timelines were qualitatively analyzed to identify possible reasons for delays. **RESULTS:** On the basis of the dates reported by 275 patients, the median time from first presentation to a clinician to treatment was 52 days; 29% of patients experienced a wait of 90 days or more. Median times for key intervals were 36.5 days from abnormal radiograph to treatment, 9.5 days from initial presentation to specialist referral, 15 days from patient informed of diagnosis to first therapy, and 16 days from referral to treatment to first therapy. More than one quarter of patients perceived delays in care. No significant differences in length of time intervals were identified between states. Monitoring of small nodules, missed diagnosis, and other reasons for longer timelines were documented. **CONCLUSION:** Results defined typical time to treatment of patients with lung cancer across a variety of health systems and should facilitate establishing metrics for determining timeliness of lung cancer care.

Copyright © 2016 by American Society of Clinical Oncology.

[Nicotine-Mediated Regulation of Nicotinic Acetylcholine Receptors in Non-Small Cell Lung Adenocarcinoma by E2F1 and STAT1 Transcription Factors.](#) Schaal C1,2, Chellappan S1. *PLoS One.* 2016 May 26;11(5):e0156451. doi: 10.1371/journal.pone.0156451. eCollection 2016.

Cigarette smoking is the major risk factor for non-small cell lung cancer (NSCLC), which accounts for 80% of all lung cancers. Nicotine, the addictive component of tobacco smoke, can induce proliferation, migration, invasion, epithelial-mesenchymal transition (EMT), angiogenesis, and survival in NSCLC cell lines, as well as growth and metastasis of NSCLC in mice. This nicotine-mediated tumor progression is facilitated through activation of nicotinic acetylcholine receptors (nAChRs), specifically the $\alpha 7$ subunit; however, how the $\alpha 7$ nAChR gene is regulated in lung adenocarcinoma is not fully clear. Here we demonstrate that the $\alpha 7$ nAChR gene promoter is differentially regulated by E2F and STAT transcription factors through a competitive interplay; E2F1 induces the promoter, while STAT transcription factors repress it by binding to an overlapping site at a region -294 through -463bp upstream of the transcription start site. Treatment of cells with nicotine induced the mRNA and protein levels of $\alpha 7$ nAChR; this could be abrogated by treatment with inhibitors targeting Src, PI3K, MEK, $\alpha 7$ nAChR, CDK4/6 or a disruptor of the Rb-Raf-1 interaction. Further, nicotine-mediated induction of $\alpha 7$ nAChR was reduced when E2F1 was depleted and in contrast elevated when STAT1 was depleted by siRNAs. Interestingly, extracts from e-cigarettes, which have recently emerged as healthier alternatives to traditional cigarette smoking, can also induce $\alpha 7$ nAChR expression in a manner similar to nicotine. These results suggest an autoregulatory feed-forward loop that induces the levels of $\alpha 7$ nAChR upon exposure to nicotine, which enhances the

strength of the signal. It can be imagined that such an induction of $\alpha 7$ nAChR contributes to the tumor-promoting functions of nicotine.

[Former smokers with non-small-cell lung cancers: a comprehensive investigation of clinicopathologic characteristics, oncogenic drivers, and prognosis.](#)

Zheng S1,2, Wang R3, Zhang Y1,2, et al. *Cancer Med.* 2016 May 26. doi: 10.1002/cam4.764. [Epub ahead of print]

The aim of this present investigation was to evaluate the clinicopathologic characteristics, oncogenic drivers, and prognosis of former smokers with non-small-cell lung cancer (NSCLC), and to compare them with those of the current and never smokers. This investigation was a single-institution retrospective study of 2289 NSCLC patients, who were classified as former, current, or never smokers. A collection was made of the clinicopathological characteristics, spectra of well-identified driver genes and survival rates. The survival rates were compared using log-rank test, and independent prognostic factors, identified using Cox regression analysis. Of 2289 NSCLC patients, 257 (11.2%) were former smokers; 868 (37.9%), current smokers; and 1164 (50.9%), never smokers. Compared with the current, the former were characterized by older age at diagnosis (64.3y vs. 59.9y; $P < 0.001$), earlier TNM stage (stage I, 47.9% vs. 39.5%; $P = 0.017$), fewer solid predominance in adenocarcinomas (16.2% vs. 29.5%; $P = 0.005$), and more EGFR mutation (33.2% vs. 20.7%; $P < 0.001$) but less KRAS mutation (6.7% vs. 11.9%, $P = 0.041$). No statistically significant survival differences were observed between the former and current. However, the light former smokers presented favorable overall survival when compared with the light current and heavy former or current (the light former vs. the heavy former, $P = 0.028$; the light former vs. the light current, $P = 0.048$; and the light former vs. the heavy current, $P = 0.048$). Our findings suggest that the former smokers with NSCLCs can have distinctive clinicopathologic characteristics, oncogenic drivers, and prognosis, and they, especially the light former, can benefit from smoking cessation.

[Early impact of Medicare accountable care organizations on cancer surgery outcomes.](#) Herrel LA1, Norton EC2,3,4, Hawken SR1, Ye Z1, Hollenbeck BK1, Miller DC1. *Cancer.* 2016 May 24. doi: 10.1002/cncr.30111. [Epub ahead of print]

BACKGROUND: Accountable care organizations (ACOs) were established to improve care and outcomes for beneficiaries requiring highly coordinated, complex care. The objective of this study was to evaluate the association between hospital ACO participation and the outcomes of major surgical oncology procedures. **METHODS:** This was a retrospective cohort study of Medicare beneficiaries older than 65 years who were undergoing a major surgical resection for colorectal, bladder, esophageal, kidney, liver, ovarian, pancreatic, lung, or prostate cancer from 2011 through 2013. A difference-in-differences analysis was implemented to compare the postimplementation period (January 2013 through December 2013) with the baseline period (January 2011 through December 2012) to assess the impact of hospital ACO participation on 30-day mortality, complications, readmissions, and length of stay (LOS).

RESULTS: Among 384,519 patients undergoing major cancer surgery at 106 ACO hospitals and 2561 control hospitals, this study found a 30-day mortality rate of 3.4%, a readmission rate of 12.5%, a complication rate of 43.8%, and a prolonged LOS rate of 10.0% in control hospitals and similar rates in ACO hospitals. Secular trends were noted, with reductions in perioperative adverse events in control hospitals between the baseline and postimplementation periods: mortality (percentage-point reduction, 0.1%; $P = .19$), readmissions (percentage-point reduction, 0.4%; $P = .001$), complications (percentage-point reduction, 1.0%; $P < .001$), and prolonged LOS (percentage-point reduction, 1.1%; $P < .001$). After accounting for these secular trends, this study identified no significant effect of hospital participation in an ACO on the frequency of perioperative outcomes (difference-in-differences estimator P values, .24-.72).

CONCLUSIONS: Early hospital participation in the Medicare Shared Savings Program ACO program was not associated with greater reductions in adverse perioperative outcomes for patients undergoing

major cancer surgery in comparison with control hospitals. Cancer 2016. © 2016 American Cancer Society.

Pre-existing diabetes and lung cancer prognosis. Luo J1, Hendryx M2, Qi L3, Ho GY4, Margolis KL5. Br J Cancer. 2016 May 19. doi: 10.1038/bjc.2016.141. [Epub ahead of print]

BACKGROUND: The aims of this study are to investigate the impact of pre-existing diabetes and diabetes treatments on lung cancer prognosis. **METHODS:** A total of 2484 women with confirmed incident lung cancer from the Women's Health Initiative were followed for an average of 2.9 years through the date of death or 29 August 2014. **RESULTS:** Compared with women with lung cancer but without diabetes, women with lung cancer and diabetes had significantly increased risk of overall mortality (HR=1.27, 95% CI: 1.07-1.50). Women with diabetes receiving insulin or metformin or women who had long duration of diabetes also had increased risk of overall mortality. **CONCLUSIONS:** Our large prospective study provides evidence that pre-existing diabetes is associated with poor overall survival among women with lung cancer, but do not support the hypothesis that metformin use may have a protective effect in women with lung cancer and diabetes.

Disparities in cancer treatment among patients infected with the human immunodeficiency virus.

Suneja G1, Lin CC2, Simard EP3, Han X2, Engels EA4, Jemal A2. Cancer. 2016 May 17. doi: 10.1002/cncr.30052. [Epub ahead of print]

BACKGROUND: Patients with cancer who are infected with the human immunodeficiency virus (HIV) are less likely to receive cancer treatment compared with HIV-uninfected individuals. However, to the authors' knowledge, the impact of insurance status and comorbidities is unknown. **METHODS:** Data from the National Cancer Data Base were used to study nonelderly adults diagnosed with several common cancers from 2003 to 2011. Cancer treatment was defined as chemotherapy, surgery, radiotherapy, or any combination during the first course of treatment. Multivariate logistic regression was used to examine associations between HIV status and lack of cancer treatment, and identify predictors for lack of treatment among HIV-infected patients. **RESULTS:** A total of 10,265 HIV-infected and 2,219,232 HIV-uninfected cases were included. In multivariate analysis, HIV-infected patients with cancer were found to be more likely to lack cancer treatment for cancers of the head and neck (adjusted odds ratio [aOR], 1.48; 95% confidence interval [95% CI], 1.09-2.01), upper gastrointestinal tract (aOR, 2.62; 95% CI, 2.04-3.37), colorectum (aOR, 1.70; 95% CI, 1.17-2.48), lung (aOR, 2.46; 95% CI, 2.19-2.76), breast (aOR, 2.14; 95% CI, 1.16-3.98), cervix (aOR, 2.81; 95% CI, 1.77-4.45), prostate (aOR, 2.16; 95% CI, 1.69-2.76), Hodgkin lymphoma (aOR, 1.92; 95% CI, 1.66-2.22), and diffuse large B-cell lymphoma (aOR, 1.82; 95% CI, 1.65-2.00). Predictors of a lack of cancer treatment among HIV-infected individuals varied by tumor type (solid tumor vs lymphoma), but black race and a lack of private insurance were found to be predictors for both groups. **CONCLUSIONS:** In the United States, HIV-infected patients with cancer appear to be less likely to receive cancer treatment regardless of insurance and comorbidities. To the authors' knowledge, the current study is the largest study of cancer treatment in HIV-infected patients with cancer in the United States and provides evidence of cancer treatment disparities even after controlling for differences with regard to insurance status and comorbidities. Further work should focus on addressing differential cancer treatment.

The American Cancer Society challenge goal to reduce US cancer mortality by 50% between 1990 and 2015: Results and reflections.

Byers T1, Wender RC2, Jemal A3, Baskies AM4, Ward EE5, Brawley OW6. CA Cancer J Clin. 2016 May 13. doi: 10.3322/caac.21348. [Epub ahead of print]

In 1996, the Board of Directors of the American Cancer Society (ACS) challenged the United States to reduce what looked to be possible peak cancer mortality in 1990 by 50% by the year 2015. This analysis examines the trends in cancer mortality across this 25-year challenge period from 1990 to 2015. In 2015,

cancer death rates were 26% lower than in 1990 (32% lower among men and 22% lower among women). The 50% reduction goal was more fully met for the cancer sites for which there was enactment of effective approaches for prevention, early detection, and/or treatment. Among men, mortality rates dropped for lung cancer by 45%, for colorectal cancer by 47%, and for prostate cancer by 53%. Among women, mortality rates dropped for lung cancer by 8%, for colorectal cancer by 44%, and for breast cancer by 39%. Declines in the death rates of all other cancer sites were substantially smaller (13% among men and 17% among women). The major factors that accounted for these favorable trends were progress in tobacco control and improvements in early detection and treatment. As we embark on new national cancer goals, this recent past experience should teach us that curing the cancer problem will require 2 sets of actions: making new discoveries in cancer therapeutics and more completely applying those discoveries in cancer prevention we have already made. CA Cancer J Clin 2016. © 2016 American Cancer Society.

[Characteristics of Smoking Patients with Lung Cancer with Emphysematous Bullae.](#) Iwama E1, Okamoto I2, Yabuuchi H3, et al. J Thorac Oncol. 2016 May 7. pii: S1556-0864(16)30405-1. doi: 10.1016/j.jtho.2016.04.024. [Epub ahead of print]

INTRODUCTION: Emphysema is thought to be a risk factor for lung cancer in smokers, with emphysematous bullae (EBs), which are believed to have the potential to give rise to lung cancer. The clinical characteristics of patients with lung cancer with EBs have remained incompletely defined, however. **METHODS:** A total of 488 patients with primary lung cancer with or without EBs as detected by computed tomography were studied retrospectively, and the regional relationship between EBs and the primary cancer was evaluated. **RESULTS:** EBs were detected in 45 of the 488 patients with lung cancer (9.2%) (in 45 of 339 smokers [13.3%] versus in 0 of 149 never-smokers [0%]). The frequency of lung cancer in an upper lobe was significantly higher in smokers with EBs than in those without EBs (71.1% versus 47.3%, $p = 0.0107$). The lobar site of primary lung cancer in smokers with EBs was significantly associated with that of the EBs ($p < 0.0001$). Most primary lung cancers (86.7%) in such patients were found in the area adjoining EBs. Smoking patients with lung cancer with EBs were significantly younger (63.6 versus 67.7 years, $p = 0.0179$) and had tumors with a lower frequency of epidermal growth factor gene (EGFR) mutations (3.8% versus 24.2%, $p = 0.0184$) compared with those without EBs. **CONCLUSIONS:** The clinical characteristics of smoking patients with lung cancer differ according to the absence or presence of EBs, with patients with EBs being potentially more susceptible to the carcinogenic effects of cigarette smoke. Further analysis of genetic alterations is warranted to elucidate the mechanism of carcinogenesis for lung cancer associated with EBs.