Caring Ambassadors Lung Cancer Program
Literature Review, October – November 2017

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

MicroRNA-384 represses the growth and invasion of non-small-cell lung cancer by targeting astrocyte elevated gene-1/Wnt signaling. Fan N1, Zhang J2, Cheng C3, Zhang X3, Feng J4, Kong R5. Biomed Pharmacother. 2017 Nov;95:1331-1337. doi: 10.1016/j.biopha.2017.08.143. Epub 2017 Oct 6. Dysregulation of microRNA (miRNA) expression is a critical event in the development and progression of non-small-cell lung cancer (NSCLC). miR-384 has been identified as a novel cancer-related miRNA in numerous cancers, but little is known about its role and functional mechanism in NSCLC. In this study, we found that miR-384 was significantly downregulated in NSCLC tissues and cell lines. The overexpression of miR-384 repressed the growth and invasion of NSCLC cells, whereas its suppression showed the opposite effect. Moreover, astrocyte elevated gene-1 (AEG-1) was identified as a target gene of miR-384. The overexpression of miR-384 significantly decreased AEG-1 expression and Wnt signaling, whereas its suppression promoted this pathway. Furthermore, miR-384 was inversely correlated with AEG-1 expression in NSCLC tissues. Additionally, restoration of AEG-1 expression in miR-384-overexpressing cells significantly reversed the antitumor effects of miR-384. Taken together, these results reveal that miR-384 represses the growth and invasion of NSCLC cells by targeting AEG-1. Our study suggest that miR-384 and AEG-1 may serve as potential targets for the diagnosis and treatment of NSCLC.

Evolution and clinical impact of co-occurring genetic alterations in advanced-stage EGFR-mutant lung cancers.
Blakely CM1,2, Watkins TBK3, Wu W1,2, et al. Nat Genet. 2017 Nov 6. doi: 10.1038/ng.3990. [Epub ahead of print] Nat Genet. 2017 Nov 6. doi: 10.1038/ng.3990. [Epub ahead of print]
A widespread approach to modern cancer therapy is to identify a single oncogenic driver gene and target its mutant-protein product (for example, EGFR-inhibitor treatment in EGFR-mutant lung cancers). However, genetically driven resistance to targeted therapy limits patient survival. Through genomic analysis of 1,122 EGFR-mutant lung cancer cell-free DNA samples and whole-exome analysis of seven longitudinally collected tumor samples from a patient with EGFR-mutant lung cancer, we identified critical co-occurring oncogenic events present in most advanced-stage EGFR-mutant lung cancers. We

defined new pathways limiting EGFR-inhibitor response, including WNT/β-catenin alterations and cell-cycle-gene (CDK4 and CDK6) mutations. Tumor genomic complexity increases with EGFR-inhibitor treatment, and co-occurring alterations in CTNNB1 and PIK3CA exhibit nonredundant functions that cooperatively promote tumor metastasis or limit EGFR-inhibitor response. This study calls for revisiting the prevailing single-gene driver-oncogene view and links clinical outcomes to co-occurring genetic alterations in patients with advanced-stage EGFR-mutant lung cancer.

PPARγ agonist efatutazone and gefitinib synergistically inhibit the proliferation of EGFR-TKI-resistant lung adenocarcinoma cells via the PPARγ/PTEN/Akt pathway. Ni J1, Zhou LL2, Ding L3, et al. Exp Cell Res. 2017 Oct 25. pii: S0014-4827(17)30574-8. doi: 10.1016/j.yexcr.2017.10.024. [Epub ahead of print]
Development of acquired resistance to EGFR-TKI therapy continues to be a serious clinical problem in Lung adenocarcinoma management. Peroxisome proliferator-activated receptor gamma (PPARγ) agonists demonstrate anti-tumor activity likely via transactivating genes that regulate cell proliferation, differentiation and apoptosis. Efatutazone, a novel later generation PPARγ agonist, selectively activates PPARγ target genes and has antiproliferative effects in a range of malignancies. However, the exact function and molecular mechanism of PPARγ agonists efatutazone in EGFR-TKI gefitinib-resistance of Lung adenocarcinoma has not been determined. In this study, we studied the development of acquired resistance to an EGFR-TKI gefitinib in lung adenocarcinoma cells and investigated the antiproliferative effects of efatutazone in the acquired resistant cells. The treatment of gefitinib-resistant cells with efatutazone reduced the growth of gefitinib-resistant cells in a dose- and time-dependent manner, and facilitated the anti-proliferative effects of gefitinib. Mechanistic investigations suggested that efatutazone acted by upregulating protein expression of PPARγ, phosphatase and tensin homolog (PTEN), inactivating the Akt pathway, followed by dephosphorylation of p21Cip1 at Thr145 without affecting the transcriptional levels. Our results suggested that efatutazone, alone or in combination with gefitinib, might offer therapeutic effects in lung adenocarcinoma.

miR-608 regulates apoptosis in human lung adenocarcinoma via regulation of AKT2. Othman N1, Nagoor NH1. Int J Oncol. 2017 Oct 23. doi: 10.3892/ijo.2017.4174. [Epub ahead of print]
Lung cancer remains a major health problem with a low 5-year survival rate of patients. Recent studies have shown that dysregulation of microRNAs (miRNAs) are prevalent in lung cancer and these aberrations play a significant role in the progression of tumour progression. In the present study, bioinformatics analyses was employed to predict potential miR-608 targets, which are associated with signaling pathways involved in cancer. Luciferase reporter assay identified AKT2 as a novel target of miR-608, and suppression of its protein levels was validated through western blot analysis. Zebrafish embryos were microinjected with cells transfected with miR-608 to elucidate the role of miR-608 in vivo, and immunostained with antibodies to detect activated caspase-3. We present the first evidence that miR-608 behaves as a tumour suppressor in A549 and SK-LU-1 cells through the regulation of AKT2, suggesting that selective targeting of AKT2 via miR-608 may be developed as a potential therapeutic strategy for miRNA-based non-small cell lung cancer (NSCLC) therapy.

SCREENING, DIAGNOSIS AND STAGING

Timeliness of Care and Lung Cancer Tumor-Stage Progression: How Long Can We Wait? Maiga AW1, Deppen SA1, Pinkerman R2, et al. Ann Thorac Surg. 2017 Oct 12. pii: S0003-4975(17)30948-7. doi: 10.1016/j.athoracsur.2017.06.051. [Epub ahead of print]
BACKGROUND: Timely care of lung cancer is presumed critical, yet clear evidence of stage progression with delays in care is lacking. We investigated the reasons for delays in treatment and the

impact these delays have on tumor-stage progression. **METHODS:** We queried our retrospective database of 265 veterans who underwent cancer resection from 2005 to 2015. We extracted time intervals between nodule identification, diagnosis, and surgical resection; changes in nodule radiographic size over time; final pathologic staging; and reasons for delays in care. Pearson's correlation and Fisher's exact test were used to compare cancer growth and stage by time to treatment. **RESULTS:** Median time from referral to surgical evaluation was 11 days (interquartile range, 8 to 17). Median time from identification to therapeutic resection was 98 days (interquartile range, 66 to 139), and from diagnosis to resection, 53 days (interquartile range, 35 to 77). Sixty-eight patients (26%) were diagnosed at resection; the remainder had preoperative tissue diagnoses. No significant correlation existed between tumor growth and time between nodule identification and resection, or between tumor growth and time between diagnosis and resection. Among 197 patients with preoperative diagnoses, 42% (83) had intervals longer than 60 days between diagnosis and resection. Most common reasons for delay were cardiac clearance, staging, and smoking cessation. Larger nodules had fewer days between identification and resection (p = 0.03). **CONCLUSIONS:** Evaluation, staging, and smoking cessation drive resection delays. The lack of association between tumor growth and time to treatment suggests other clinical or biological factors, not time alone, underlie growth risk. Until these factors are identified, delays to diagnosis and treatment should be minimized.

Access to Lung Cancer Screening Services: Preliminary Analysis of Geographic Service Distribution Using the ACR Lung Cancer Screening Registry. Charkhchi P1, Kolenic GE2, Carlos RC3. J Am Coll Radiol. 2017 Nov;14(11):1388-1395. doi: 10.1016/j.jacr.2017.06.024.
PURPOSE: Lung cancer has the highest mortality rate among all types of cancer in the United States. The National Lung Screening Trial demonstrated that low-dose CT for lung cancer screening decreases both lung cancer-related mortality and all-cause mortality. Currently, the only CMS-approved lung cancer screening registry is the Lung Cancer Screening Registry (LCSR) administered by the ACR. The aims of this study were to assess access to lung cancer screening services as estimated by the number and distribution of screening facilities participating in the LCSR, by state, and to evaluate state-level covariates that correlate with access. **METHODS:** The ACR LCSR list of participating lung cancer screening facilities was used as a proxy for the availability of lung cancer screening facilities in each state. Additionally, we normalized the number of facilities by state by the number of screening-eligible individuals using Behavioral Risk Factor Surveillance System data. State-level demographics were obtained from the 2015 Behavioral Risk Factor Surveillance System: poverty level, insured population, unemployed, black, and Latino. State-specific lung cancer incidence and death rates, number of active physicians per 100,000, and Medicare expenditure per capita were obtained. Linear regression models were performed to examine the influence of these state-level covariates on state-level screening facility number. QGIS, an open-source geographic information system, was used to map the distribution of lung cancer screening facilities and to estimate the nearest neighbor index, a measure of facility clustering within each state. **RESULTS:** As of November 18, 2016, 2,423 facilities participated in the LCSR. When adjusted by the rate of screening-eligible individuals per 100,000, the median population-normalized facility number was 15.7 (interquartile range, 10.7-19.3). There was a positive independent effect (coefficient = 12.87; 95% confidence interval, 10.93-14.8) between state-level number of screening facilities and rate of screening-eligible individuals per 100,000. There were no significant correlations between number of facilities and lung cancer outcomes, state demographic characteristics, or physician supply and Medicare expenditure. In most states, facilities are clustered rather than dispersed, with a median nearest neighbor index of 0.65 (interquartile range, 0.51-0.81). **CONCLUSIONS:** Facility number correlated with the rate of screening-eligible individuals per 100,000, a measure of the at-risk population. Alignment of screening facility number and distribution with other clinically relevant epidemiologic factors remains a public health opportunity.

Henschke CI1, Salvatore M2, Cham M2, Powell CA3, DiFabrizio L3, Flores R4, Kaufman A4, Eber C2, Yip R2, Yankelevitz DF2; International Early Lung Cancer Action Program Investigators. Eur Radiol. 2017 Oct 5. doi: 10.1007/s00330-017-5029-z. [Epub ahead of print]

OBJECTIVES: Differences in results of baseline and subsequent annual repeat rounds provide important information for optimising the regimen of screening. **METHODS:** A prospective cohort study of 65,374 was reviewed to examine the frequency/percentages of the largest noncalcified nodule (NCN), lung cancer cell types and Kaplan-Meier (K-M) survival rates, separately for baseline and annual rounds. **RESULTS:** Of 65,374 baseline screenings, NCNs were identified in 28,279 (43.3%); lung cancer in 737 (1.1%). Of 74,482 annual repeat screenings, new NCNs were identified in 4959 (7%); lung cancer in 179 (0.24%). Only adenocarcinoma was diagnosed in subsolid NCNs. Percentages of lung cancers by cell type were significantly different ($p < 0.0001$) in the baseline round compared with annual rounds, reflecting length bias, as were the ratios, reflecting lead times. Long-term K-M survival rate was 100% for typical carcinoids and for adenocarcinomas manifesting as subsolid NCNs; 85% (95% CI 81-89%) for adenocarcinoma, 74% (95% CI 63-85%) for squamous cell, 48% (95% CI 34-62%) for small cell. The rank ordering by lead time was the same as the rank ordering by survival rates. **CONCLUSIONS:** The significant differences in the frequency of NCNs and frequency and aggressiveness of diagnosed cancers in baseline and annual repeat need to be recognised for an optimal regimen of screening. **KEY POINTS:** • Lung cancer aggressiveness varies considerably by cell type and nodule consistency. • Kaplan-Meier survival rates varied by cell type between 100% and 48%. • The percentages of lung cancers by cell type in screening rounds reflect screening biases. • Rank ordering by cell type survival is consistent with that by lead times. • Empirical evidence provides critical information for the regimen of screening.

Lim WH1, Park CM2,3,4, Yoon SH1,5, Lim HJ6, Hwang EJ1, Lee JH1, Goo JM1,5,7. Eur Radiol. 2017 Oct 2. doi: 10.1007/s00330-017-5058-7. [Epub ahead of print]

OBJECTIVES: To evaluate the time-dependent incidence, risk factors and clinical significance of percutaneous lung biopsy (PLB)-related pneumothorax. **METHODS:** From January 2012-November 2015, 3,251 patients underwent 3,354 cone-beam CT-guided PLBs for lung lesions. Cox, logistic and linear regression analyses were performed to identify time-dependent risk factors of PLB-related pneumothorax, risk factors of drainage catheter insertion and those of prolonged catheter placement, respectively. **RESULTS:** Pneumothorax occurred in 915/3,354 PLBs (27.3 %), with 230/915 (25.1 %) occurring during follow-ups. Risk factors for earlier occurrence of PLB-related pneumothorax include emphysema (HR=1.624), smaller target (HR=0.922), deeper location (HR=1.175) and longer puncture time (HR=1.036), while haemoptysis (HR=0.503) showed a protective effect against earlier development of pneumothorax. Seventy-five cases (8.2 %) underwent chest catheter placement. Mean duration of catheter placement was 3.2±2.0 days. Emphysema (odds ratio [OR]=2.400) and longer puncture time (OR=1.053) were assessed as significant risk factors for catheter insertion, and older age (parameter estimate=1.014) was a predictive factor for prolonged catheter placement. **CONCLUSION:** PLB-related pneumothorax occurred in 27.3 %, of which 25.1 % developed during follow-ups. Smaller target size, emphysema, deeply-located lesions were significant risk factors of PLB-related pneumothorax. Emphysema and older age were related to drainage catheter insertion and prolonged catheter placement, respectively. **KEY POINTS:** • One-fourth of percutaneous lung biopsy (PLB)-related pneumothorax occurs during follow-up. • Smaller, deeply-located target and emphysema lead to early occurrence of pneumothorax. • Emphysema is related to drainage catheter insertion for PLB-related pneumothorax. •

Older age may lead to prolonged catheter placement for PLB-related pneumothorax. • Tailored management can be possible with time-dependent information of PLB-related pneumothorax.

Programmed Death-Ligand 1 Immunohistochemistry Testing: A Review of Analytical Assays and Clinical Implementation in Non-Small-Cell Lung Cancer.

Büttner R1, Gosney JR1, Skov BG1, et al. J Clin Oncol. 2017 Oct 20:JCO2017747642. doi: 10.1200/JCO.2017.74.7642. [Epub ahead of print]

PURPOSE: Three programmed death-1/programmed death-ligand 1 (PD-L1) inhibitors are currently approved for treatment of non-small-cell lung cancer (NSCLC). Treatment with pembrolizumab in NSCLC requires PD-L1 immunohistochemistry (IHC) testing. Nivolumab and atezolizumab are approved without PD-L1 testing, though US Food and Drug Administration-cleared complementary PD-L1 tests are available for both. PD-L1 IHC assays used to assess PD-L1 expression in patients treated with programmed death-1/PD-L1 inhibitors in clinical trials include PD-L1 IHC 28-8 pharmDx (28-8), PD-L1 IHC 22C3 pharmDx (22C3), Ventana PD-L1 SP142 (SP142), and Ventana PD-L1 SP263 (SP263). Differences in antibodies and IHC platforms have raised questions about comparability among these assays and their diagnostic use. This review provides practical information to help physicians and pathologists understand analytical features and comparability of various PD-L1 IHC assays and their diagnostic use. Methods We reviewed and summarized published or otherwise reported studies (January 2016 to January 2017) on clinical trial and laboratory-developed PD-L1 IHC assays (LDAs). Studies assessing the effect of diagnostic methods on PD-L1 expression levels were analyzed to address practical issues related to tissue samples used for testing. Results High concordance and interobserver reproducibility were observed with the 28-8, 22C3, and SP263 clinical trial assays for PD-L1 expression on tumor cell membranes, whereas lower PD-L1 expression was detected with SP142. Immune-cell PD-L1 expression was variable and interobserver concordance was poor. Inter- and intratumoral heterogeneity had variable effects on PD-L1 expression. Concordance among LDAs was variable. **CONCLUSION:** High concordance among 28-8, 22C3, and SP263 when assessing PD-L1 expression on tumor cell membranes suggests possible interchangeability of their clinical use for NSCLC but not for assessment of PD-L1 expression on immune cells. Development of LDAs requires stringent standardization before their recommendation for routine clinical use.

Quality assurance and quantitative imaging biomarkers in low-dose CT lung cancer screening.

Rydzak CE1, Armato SG2, Avila RS3, Mulshine JL4, Yankelevitz DF5, Gierada DS1. Br J Radiol. 2017 Oct 27:20170401. doi: 10.1259/bjr.20170401. [Epub ahead of print]

After years of assessment through controlled clinical trials, low-dose CT screening for lung cancer is becoming part of clinical practice. As with any cancer screening test, those undergoing lung cancer screening are not being evaluated for concerning signs or symptoms, but are generally in good health and proactively trying to prevent premature death. Given the resultant obligation to achieve the screening aim of early diagnosis while also minimizing the potential for morbidity from workup of indeterminate but ultimately benign screening abnormalities, careful implementation of screening with conformance to currently recognized best practices and a focus on quality assurance is essential. In this review, we address the importance of each component of the screening process to optimize the effectiveness of CT screening, discussing options for quality assurance at each step. We also discuss the potential added advantages, quality assurance requirements and current status of quantitative imaging biomarkers related to lung cancer screening. Finally, we highlight suggestions for improvements and needs for further evidence in evaluating the performance of CT screening as it transitions from the research trial setting into daily clinical practice.

[Liquid Biopsy and Therapeutic Targets: Present and Future Issues in Thoracic Oncology.](#) Hofman P1,2,3. Cancers (Basel). 2017 Nov 10;9(11). pii: E154. doi: 10.3390/cancers9110154.

The practice of liquid biopsy (LB) has revolutionized the care of patients with metastatic lung cancer. Many oncologists now use this approach in daily practice, applying precise procedures for the detection of activating or resistance mutations in EGFR. These tests are performed with plasma DNA and have been approved as companion diagnostic test for patients treated with tyrosine kinase inhibitors. ALK is another important target in lung cancer since it leads to treatment of patients who are positive for a rearrangement in ALK identified with tumor tissue. By analogy with EGFR, LB for detection of genomic alterations in ALK (rearrangements or mutations) has been rapidly adopted in the clinic. However, this promising approach has some limitations and has not yet been disseminated as much as the blood test targeting EGFR. In addition to these two therapeutic targets LB can be used for evaluation of the genomic status of other genes of interest of patients with lung cancer (ROS1, RET, NTRK MET, BRAF, HER2, etc.). LB can be performed to evaluate a specific target or for a more or less complex panel of genes. Considering the number of potential targets for clinical trials, techniques of next-generation sequencing of circulating DNA are on the rise. This review will provide an update on the contribution of LB to care of patients with metastatic lung cancer, including the present limits of this approach, and will consider certain perspectives.

[Liquid biopsy in non-small cell lung cancer: a key role in the future of personalized medicine?](#)
Pi C1,2, Zhang MF1,2, Peng XX1,3, Zhang YC1,2, Xu CR1, Zhou Q1,2. Expert Rev Mol Diagn. 2017 Oct 23. doi: 10.1080/14737159.2017.1395701. [Epub ahead of print]

INTRODUCTION: Liquid biopsies, especially the analysis of circulating tumor DNA (ctDNA), as a novel and non-invasive method for the diagnosis and monitoring of non-small cell lung cancer (NSCLC) have already been implemented in clinical settings. The majority of ctDNA is released from apoptotic or necrotic tumor cells, thus reflecting the genetic profile of a tumor. Numerous studies have reported a high concordance in mutation profiles derived from liquid biopsy and tissue biopsy, especially in driver genes. Liquid biopsy could overcome the clonal heterogeneity of tumour biopsy, as it provides a single snapshot of a tumour tissue. Moreover, non-invasiveness is the biggest advantage for liquid biopsy, and the procedure can be repeatedly performed during the treatment for the purpose of monitoring. Therefore, ctDNA could act as a potential complementary method for tissue biopsies in diagnosis, prognostic, treatment response and resistance. Areas covered: This review summarizes the recent advancements in liquid biopsy with a focus on NSCLC, including its applications and technologies associated with assessing ctDNA. The authors conclude the review by discussing the challenges associated with liquid biopsy. Expert commentary: The analysis of ctDNA represents a promising method for liquid biopsy, which will be a novel and potentially complementary method in diagnosis, treatment and prognostic in NSCLC at all stages.

[Development and Usability Testing of a Computer-Tailored Decision Support Tool for Lung Cancer Screening: Study Protocol.](#) Carter-Harris L#1,2, Comer RS#3, Goyal A#3, Vode EC#1, Hanna N#4,5, Ceppa D#2,4, Rawl SM#1,2. JMIR Res Protoc. 2017 Nov 16;6(11):e225. doi: 10.2196/resprot.8694.

BACKGROUND: Awareness of lung cancer screening remains low in the screening-eligible population, and when patients visit their clinician never having heard of lung cancer screening, engaging in shared decision making to arrive at an informed decision can be a challenge. Therefore, methods to effectively support both patients and clinicians to engage in these important discussions are essential. To facilitate shared decision making about lung cancer screening, effective methods to prepare patients to have these important discussions with their clinician are needed. **OBJECTIVE:** Our objective is to develop a computer-tailored decision support tool that meets the certification criteria of the International Patient

Decision Aid Standards instrument version 4.0 that will support shared decision making in lung cancer screening decisions. **METHODS:** Using a 3-phase process, we will develop and test a prototype of a computer-tailored decision support tool in a sample of lung cancer screening-eligible individuals. In phase I, we assembled a community advisory board comprising 10 screening-eligible individuals to develop the prototype. In phase II, we recruited a sample of 13 screening-eligible individuals to test the prototype for usability, acceptability, and satisfaction. In phase III, we are conducting a pilot randomized controlled trial (RCT) with 60 screening-eligible participants who have never been screened for lung cancer. Outcomes tested include lung cancer and screening knowledge, lung cancer screening health beliefs (perceived risk, perceived benefits, perceived barriers, and self-efficacy), perception of being prepared to engage in a patient-clinician discussion about lung cancer screening, occurrence of a patient-clinician discussion about lung cancer screening, and stage of adoption for lung cancer screening. **RESULTS:** Phases I and II are complete. Phase III is underway. As of July 15, 2017, 60 participants have been enrolled into the study, and have completed the baseline survey, intervention, and first follow-up survey. We expect to have results by December 31, 2017 and to have data analysis completed by March 1, 2018. **CONCLUSIONS:** Results from usability testing indicate that the computer-tailored decision support tool is easy to use, is helpful, and provides a satisfactory experience for the user. At the conclusion of phase III (pilot RCT), we will have preliminary effect sizes to inform a future fully powered RCT on changes in (1) knowledge about lung cancer and screening, (2) perceived risk of lung cancer, (3) perceived benefits of lung cancer screening, (4) perceived barriers to lung cancer screening, (5) self-efficacy for lung cancer screening, and (6) perceptions of being adequately prepared to engage in a discussion with their clinician about lung cancer screening.

[Preliminary Results of Lung Cancer Screening in a Socioeconomically Disadvantaged Population.](#)
Guichet PL1, Liu BY1, Desai B1, Surani Z2, Cen SY1, Lee C1. AJR Am J Roentgenol. 2017 Nov 22:1-8. doi: 10.2214/AJR.17.18853. [Epub ahead of print]
OBJECTIVE: The objective of our study was to describe the preliminary results of our clinical low-dose CT (LDCT) lung cancer screening program targeting a minority, socioeconomically disadvantaged, high-risk population different from that studied in the National Lung Screening Trial (NLST). **MATERIALS AND METHODS:** Community partner clinics in an underserved region of south Los Angeles County referred interested candidates to our program. All patients met National Comprehensive Cancer Network eligibility criteria for lung cancer screening. **RESULTS:** From July 21, 2015, through April 3, 2017, 889 individuals were referred to the program. Of the 329 eligible participants, 275 (mean age, 59 years; 52% men) underwent baseline screening LDCT: 84% of patients were black, and 66% had a high school education or less. The median pack-years was 40, and 81% of patients were current smokers. Thirty-one percent of participants reported occupational exposure to one or more known lung carcinogens. Lung CT Screening Reporting and Data System (Lung-RADS) categories were assigned using baseline LDCT examinations: Lung-RADS category 1 or 2 were assigned in 86% of patients, category 3 in 7%, category 4A in 4%, and category 4B or 4X in 3%. Lung cancer has been diagnosed in two of these patients (0.7%) to date: stage IIIB small cell lung carcinoma in one patient and stage IV lung cancer of unknown type in the other patient. Among the 275 patients, 29% had potentially clinically significant incidental findings. **CONCLUSION:** Lung cancer screening with LDCT in a minority, socioeconomically disadvantaged, high-risk population is feasible but may yield a different lung cancer profile than screening populations in more privileged communities. More follow-up time is required to determine whether the reduction in lung cancer mortality shown in the NLST applies to this underserved population.

NSCLC - SURGERY

[Margin Width of Resected Lepidic Lung Cancer Does Not Affect Recurrence After Sublobar Resection.](#) Moon Y1, Lee KY2, Park JK3. World J Surg. 2017 Oct 17. doi: 10.1007/s00268-017-4291-1. [Epub ahead of print]

BACKGROUND: A sufficient resection margin is required for the sublobar resection of lung cancers. However, the width of the resection margin may not be important in lepidic adenocarcinoma, because such tumors are non- or minimally invasive. The purpose of this study was to determine the effect of resection margin width on the outcome of patients with lepidic-dominant adenocarcinoma after sublobar resection. **METHODS:** This study included 133 patients with small (≤ 2 cm), clinical N0M0 lung cancer who underwent sublobar resection with curative intent. The patients were divided into 4 groups: Group A, lepidic tumor with margin/tumor ratio <1; Group B, lepidic tumor with margin/tumor ratio ≥ 1; Group C, non-lepidic tumor with margin/tumor ratio <1; Group D, non-lepidic tumor with margin/tumor ratio ≥ 1. The clinicopathological features and survival outcomes between Group A and B patients, and between Group C and D patients were compared. **RESULTS:** The 5-year recurrence-free survival (RFS) rates of Group A and B patients were both 100%. The 5-year RFS rates of Group C and D patients were 49.9 and 97.1%, respectively (p = 0.009). By multivariate analysis, the margin/tumor ratio was a significant independent factor for recurrence in patients with non-lepidic tumors (hazard ratio = 0.157, 95% confidence interval 0.027-0.898; p = 0.037). **CONCLUSIONS:** Tumor recurrence after sublobar resection is not associated with short resection margins in patients with lepidic tumors. However, a short resection margin is a significant risk factor for recurrence in patients with non-lepidic tumors.

[Outcomes Following Video Assisted Thoracoscopic Lobectomy versus Open Lobectomy for Early Stage Lung Cancer in Older Adults.](#) Ezer N1,2, Kale M3, Sigel K4, Lakha S5, Mhango G6, Goodman E7, Nicastri D8, Swanson S9, Neugut A10, Wisnivesky JP11. Ann Am Thorac Soc. 2017 Nov 9. doi: 10.1513/AnnalsATS.201612-980OC. [Epub ahead of print]

RATIONALE: Video-assisted thoracoscopic surgery and open lobectomy are both standard of care for treatment of early stage NSCLC because of equivalent long-term survival. **OBJECTIVE:** To evaluated whether the improved peri-operative outcomes associated with VATS are explained by differences in case volume and specialty training. **METHODS:** We analyzed the Surveillance, Epidemiology and End Results-Medicare linked registry to identify stage I-II NSCLC in patients above 65 years of age. We used a propensity score model to adjust for differences in patient characteristics undergoing VATS-vs. open lobectomy. Perioperative complications, extended length of stay, and perioperative mortality among patients were compared after adjustment for surgeon's volume and specialty using linear mixed models. We compared survival using a Cox model with robust standard errors. **RESULTS:** We identified 9,508 patients in the registry who underwent lobectomy for early stage NSCLC. VATS lobectomies were more commonly performed by high volume surgeons (p<0.001) and thoracic surgeons (p=0.01). VATS lobectomy was associated with decreased adjusted odds of cardiovascular complications (OR: 0.65; 95% CI: 0.47-0.90), thromboembolic complications (OR: 0.47; 95% CI: 0.38-0.58), extrapulmonary infections (OR: 0.75; 95% CI: 0.61-0.94), extended length of stay (OR: 0.47; 95% CI: 0.40-0.56), and perioperative mortality (OR: 0.33; 95% CI: 0.23-0.48) even after controlling for differences in surgeon volume and specialty. Long-term survival was equivalent for VATS and open lobectomy (HR: 0.95; 95% CI: 0.85-1.08) after controlling for patient and tumor characteristics, surgeon volume and specialization. **CONCLUSIONS:** In patients above 65 years of age VATS is associated with better postoperative outcomes than open lobectomy even after controlling for surgeon's experience. Increased adoption of VATS may improve perioperative outcomes.

[Oncologic considerations in the elderly.](#) Kamel MK1, Port JL. Curr Opin Anaesthesiol. 2017 Nov 8. doi: 10.1097/ACO.0000000000000545. [Epub ahead of print]

PURPOSE OF REVIEW: Elderly patients presenting with thoracic malignancies tend to be largely undertreated because of a presumption that this group will incur a high treatment-associated morbidity and mortality. The current review highlights the current practice and recent updates in the surgical management of thoracic malignancies, mainly lung cancer, in the elderly population. **RECENT FINDINGS:** Lung resections appears to be relatively safe in the elderly patients presenting with lung cancer. Whenever possible, a lobectomy should be offered to patients with a good performance status who present with early stage disease. However, a limited resection may offer a valuable comparable alternative in patients with advanced comorbidities and borderline pulmonary functions. The use of minimally invasive approaches, namely video-assisted thoracoscopic surgery and robotic surgery are associated with lower morbidity and improved perioperative outcomes compared with the traditional thoracotomy approach and are ideal for the aged. In elderly patients presenting with advanced staged lung cancer, major lung resections following induction therapy, although feasible, should be discussed in a multispecialty tumor board committee. **SUMMARY:** There is growing evidence from the literature that surgical resection is relatively safe in the elderly population. Age by itself should not preclude patients from having curative resection. Resections can be tailored to performance status of the patient.

[Fate of Pneumonectomy Patients Variably Captured by Non-Small Cell Lung Cancer Staging System.](#) Dhanasopon AP1, Salazar MC1, Hoag JR2, Rosen JE1, Kim AW1, Detterbeck FC1, Blasberg JD1, Boffa DJ3. Ann Thorac Surg. 2017 Dec;104(6):1829-1836. doi: 10.1016/j.athoracsur.2017.06.073. Epub 2017 Nov 1.

BACKGROUND: Lung cancer patients rely on survival estimates to weigh risks and benefits of treatment. However, pneumonectomy-requiring lung cancer may have inherent oncologic or physiologic survival implications not captured by the current stage classification. Stage-specific survival was evaluated to refine survival expectations for patients with pneumonectomy-requiring disease. **METHODS:** The National Cancer Database was queried for treatment-naive patients who underwent lobectomy or pneumonectomy for stage I to III non-small cell lung cancer between 2004 and 2013. Patients who died within 90 days after resection were excluded. Three-way propensity score weighted multivariable Cox models were built and incorporated into adjusted 5-year overall survival (OS) curves. **RESULTS:** A total of 79,953 patients met inclusion criteria: 75,708 lobectomies (95%) and 4,245 pneumonectomies (5%). Stage I and II patients undergoing right pneumonectomy had worse adjusted 5-year OS than patients undergoing left pneumonectomy, which was worse than lobectomy (stage I: 55%, 58%, 67%; stage II: 37%, 44%, 48%; indicating right pneumonectomy, left pneumonectomy, lobectomy). Stage III right pneumonectomy patients had worse adjusted 5-year OS; however, left pneumonectomy and lobectomy patients were similar (33%, 39%, 40%). A doubly robust Cox model identified a similar pattern for mortality risk for stage I and II (right pneumonectomy > left > lobectomy); however, stage III right pneumonectomy patients had higher mortality risk than lobectomy patients (hazard ratio [HR] 1.23, 95% confidence interval [CI]: 1.17 to 1.28, p < 0.001), whereas left pneumonectomy was similar to lobectomy (HR 1.02, 95% CI: 0.97 to 1.06, p = 0.47). **CONCLUSIONS:** Pneumonectomy-requiring lung cancer embodies a 5-year mortality risk not completely captured by the lung cancer staging system. Refined survival estimates for pneumonectomy patients may enhance shared decision making in this population.

[CA 19-9 and CA 125 as potential predictors of disease recurrence in resectable lung adenocarcinoma.](#) Isaksson S1, Jönsson P2, Monsef N3, Brunnström H1, Bendahl PO1, Jönsson M1,

Staaf J1, Planck M1. PLoS One. 2017 Oct 19;12(10):e0186284. doi: 10.1371/journal.pone.0186284. eCollection 2017.

OBJECTIVES: Among patients who underwent primary surgery for non-small cell lung cancer (NSCLC), recurrent disease is frequent and cannot be accurately predicted solely from TNM stage and histopathological features. The aim of this study was to examine the association of tumor markers in pre-operative serum with recurrent disease. **MATERIAL AND METHODS:** Blood samples were collected prior to lung cancer surgery from 107 patients with stage I-III lung adenocarcinoma surgically treated at Lund University hospital, Lund, Sweden, between 2005 and 2011. The serum tumor markers Carcinoembryonic antigen (CEA), Neuron-specific enolase (NSE), Cancer antigen 125 (CA 125), Human epididymis protein 4 (HE4) and Carbohydrate antigen (CA 19-9) were analyzed retrospectively and clinical follow-up data were collected from patient charts. Forty (37%) patients were diagnosed with recurrent disease. **RESULTS:** Sixty-eight (64%) patients had at least one elevated tumor marker prior to surgery. In analysis of disease-free survival (DFS), CA 125 and/or CA 19-9 were significantly associated with recurrent disease adjusted to stage and adjuvant treatment (hazard ratio 2.8, 95% confidence interval 1.4-5.7, p = 0.006). **CONCLUSION:** High pre-operative serum CA 19-9 and/or CA 125 might indicate an increased incidence of recurrent disease in resectable lung adenocarcinomas.

Coagulation profile in open and video-assisted thoracoscopic lobectomies: a cohort study.
Christensen TD1,2, Vad H1,2, Pedersen S3, Licht PB4, Nybo M5, Hornbech K6, Zois NE7, Hvas AM2,8. Interact Cardiovasc Thorac Surg. 2017 Oct 16. doi: 10.1093/icvts/ivx328. [Epub ahead of print]
OBJECTIVES: Lung cancer patients are perceived to have a relatively high risk of venous thromboembolic events due to an activation of the coagulation system. In terms of activation of the coagulation system, the difference between video-assisted thoracoscopic surgery (VATS) and open lobectomies for primary lung cancer has not been investigated. The aim of this study was to compare the impact on the coagulation system in patients undergoing curative surgery for primary lung cancer by either VATS or open lobectomies. **METHODS:** In total, 62 patients diagnosed with primary lung cancer were allocated to either VATS (n = 32) or open lobectomies (n = 30). All patients received subcutaneous injections with dalteparin (Fragmin®) 5000 IE once daily. The coagulation was assessed pre- and intraoperatively, and the first 2 days postoperatively by standard coagulation blood tests, thromboelastometry (ROTEM®) and thrombin generation. **RESULTS:** The open lobectomies bled more than the VATS group and had a significantly lower platelet count (109/l) on postoperative Days 1 and 2 (198 vs 231 and 194 vs 243, respectively). The open group also had a higher international normalized ratio on postoperative Days 1 and 2 compared with the VATS group (1.21 vs 1.14 and 1.17 vs 1.09, respectively). There were no differences in thromboelastometry (ROTEM®) and thrombin generation parameters. None of the included patients developed venous thromboembolic events. **CONCLUSIONS:** In patients undergoing curative surgery for early-stage primary lung cancer, we observed a statistical non-significant difference and a similar-sized minor impact on the coagulation system.

National Analysis of Unplanned Readmissions After Thoracoscopic Versus Open Lung Cancer Resection. Bhagat R1, Bronsert MR2, Ward AN3, et al. Ann Thorac Surg. 2017 Dec;104(6):1782-1790. doi: 10.1016/j.athoracsur.2017.08.047. Epub 2017 Nov 1.
BACKGROUND: Hospital readmissions are viewed as a mark of inferior health care quality and are penalized. Unplanned postoperative readmission reason and timing after lung resection are not well understood. We examine related, unplanned readmissions after thoracoscopic versus open anatomic lung resections to identify opportunities to improve patient care. **METHODS:** We analyzed the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) data set, 2012 to 2015, characterizing 30-day related, unplanned postoperative readmissions after anatomic lung resections for primary lung cancer. Risk-adjusted comparison of readmission after thoracoscopic and open resection

was performed using propensity matching. **RESULTS:** Patients (n = 9,510) underwent anatomic lung resections; 4,935 (51.9%) were thoracoscopic resections and 4,575 (48.1%) were open resections. Of the thoracoscopic patients, 10.9% experienced one or more complications, versus 19.4% of patients with open resection (p < 0.0001). Of the thoracoscopic patients 5.5% experienced related, unplanned readmissions versus 7.2% of the patients with open resection (p < 0.001). 24.8% of complications after thoracoscopic approach occurred after discharge, versus 15.5% after open approach (p < 0.0001). Timing of unplanned readmission was similar for both groups. The propensity-matched odds ratio of risk of readmission after thoracoscopic versus open resection was 1.16 (95% confidence interval, 0.949 to 1.411, p = 0.15). **CONCLUSIONS:** Open anatomic lung resections for primary lung cancer had nearly twice the complication rate but only a slightly higher readmission rate than thoracoscopic resection. More complications occurred after discharge after thoracoscopic than open resections. Most readmissions occurred within 2 weeks after both thoracoscopic and open resections. Risk-adjusted comparison identified no statistically significant difference in risk of related, unplanned readmission after thoracoscopic versus open resections. Future studies should focus on identification of processes of care to decrease complications and unplanned readmissions after lung cancer resection.

[**Fate of Pneumonectomy Patients Variably Captured by Non-Small Cell Lung Cancer Staging System.**](#) Dhanasopon AP1, Salazar MC1, Hoag JR2, Rosen JE1, Kim AW1, Detterbeck FC1, Blasberg JD1, Boffa DJ3. Ann Thorac Surg. 2017 Dec;104(6):1829-1836. doi: 10.1016/j.athoracsur.2017.06.073. Epub 2017 Nov 1.
BACKGROUND: Lung cancer patients rely on survival estimates to weigh risks and benefits of treatment. However, pneumonectomy-requiring lung cancer may have inherent oncologic or physiologic survival implications not captured by the current stage classification. Stage-specific survival was evaluated to refine survival expectations for patients with pneumonectomy-requiring disease.
METHODS: The National Cancer Database was queried for treatment-naive patients who underwent lobectomy or pneumonectomy for stage I to III non-small cell lung cancer between 2004 and 2013. Patients who died within 90 days after resection were excluded. Three-way propensity score weighted multivariable Cox models were built and incorporated into adjusted 5-year overall survival (OS) curves.
RESULTS: A total of 79,953 patients met inclusion criteria: 75,708 lobectomies (95%) and 4,245 pneumonectomies (5%). Stage I and II patients undergoing right pneumonectomy had worse adjusted 5-year OS than patients undergoing left pneumonectomy, which was worse than lobectomy (stage I: 55%, 58%, 67%; stage II: 37%, 44%, 48%; indicating right pneumonectomy, left pneumonectomy, lobectomy). Stage III right pneumonectomy patients had worse adjusted 5-year OS; however, left pneumonectomy and lobectomy patients were similar (33%, 39%, 40%). A doubly robust Cox model identified a similar pattern for mortality risk for stage I and II (right pneumonectomy > left > lobectomy); however, stage III right pneumonectomy patients had higher mortality risk than lobectomy patients (hazard ratio [HR] 1.23, 95% confidence interval [CI]: 1.17 to 1.28, p < 0.001), whereas left pneumonectomy was similar to lobectomy (HR 1.02, 95% CI: 0.97 to 1.06, p = 0.47). **CONCLUSIONS:** Pneumonectomy-requiring lung cancer embodies a 5-year mortality risk not completely captured by the lung cancer staging system. Refined survival estimates for pneumonectomy patients may enhance shared decision making in this population.

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

[**Cetuximab plus carboplatin and paclitaxel with or without bevacizumab versus carboplatin and paclitaxel with or without bevacizumab in advanced NSCLC (SWOG S0819): a randomised, phase 3 study.**](#) Herbst RS1, Redman MW2, Kim ES3, et al. Lancet Oncol. 2017 Nov 20. pii: S1470-2045(17)30694-0. doi: 10.1016/S1470-2045(17)30694-0. [Epub ahead of print]

BACKGROUND: EGFR antibodies have shown promise in patients with advanced non-small-cell lung cancer (NSCLC), particularly with squamous cell histology. We hypothesised that EGFR copy number by fluorescence in-situ hybridisation (FISH) can identify patients most likely to benefit from these drugs combined with chemotherapy and we aimed to explore the activity of cetuximab with chemotherapy in patients with advanced NSCLC who are EGFR FISH-positive. **METHODS:** We did this open-label, phase 3 study (SWOG S0819) at 277 sites in the USA and Mexico. e randomly assigned (1:1) eligible patients with treatment-naive stage IV NSCLC to receive paclitaxel (200 mg/m2; every 21 days) plus carboplatin (area under the curve of 6 by modified Calvert formula; every 21 days) or carboplatin plus paclitaxel and bevacizumab (15 mg/kg; every 21 days), either with cetuximab (250 mg/m2 weekly after loading dose; cetuximab group) or without (control group), stratified by bevacizumab treatment, smoking status, and M-substage using a dynamic-balancing algorithm. Co-primary endpoints were progression-free survival in patients with EGFR FISH-positive cancer and overall survival in the entire study population. We analysed clinical outcomes with the intention-to-treat principle and analysis of safety outcomes included patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov (number NCT00946712). **FINDINGS:** Between Aug 13, 2009, and May 30, 2014, we randomly assigned 1313 patients to the control group (n=657; 277 with bevacizumab and 380 without bevacizumab in the intention-to-treat population) or the cetuximab group (n=656; 283 with bevacizumab and 373 without bevacizumab in the intention-to-treat population). EGFR FISH was assessable in 976 patients and 400 patients (41%) were EGFR FISH-positive. The median follow-up for patients last known to be alive was 35·2 months (IQR 22·9-39·9). After 194 progression-free survival events in the cetuximab group and 198 in the control group in the EGFR FISH-positive subpopulation, progression-free survival did not differ between treatment groups (hazard ratio [HR] 0·92, 95% CI 0·75-1·12; p=0·40; median 5·4 months [95% CI 4·5-5·7] vs 4·8 months [3·9-5·5]). After 570 deaths in the cetuximab group and 593 in the control group, overall survival did not differ between the treatment groups in the entire study population (HR 0·93, 95% CI 0·83-1·04; p=0·22; median 10·9 months [95% CI 9·5-12·0] vs 9·2 months [8·7-10·3]). In the prespecified analysis of EGFR FISH-positive subpopulation with squamous cell histology, overall survival was significantly longer in the cetuximab group than in the control group (HR 0·58, 95% CI 0·36-0·86; p=0·0071), although progression-free survival did not differ between treatment groups in this subgroup (0·68, 0·46-1·01; p=0·055). Overall survival and progression-free survival did not differ among patients who were EGFR FISH non-positive with squamous cell histology (HR 1·04, 95% CI 0·78-1·40; p=0·77; and 1·02, 0·77-1·36; p=0·88 respectively) or patients with non-squamous histology regardless of EGFR FISH status (for EGFR FISH-positive 0·88, 0·68-1·14; p=0·34; and 0·99, 0·78-1·27; p=0·96; respectively; and for EGFR FISH non-positive 1·00, 0·85-1·17; p=0·97; and 1·03, 0·88-1·20; p=0·69; respectively). The most common grade 3-4 adverse events were decreased neutrophil count (210 [37%] in the cetuximab group vs 158 [25%] in the control group), decreased leucocyte count (103 [16%] vs 74 [20%]), fatigue (81 [13%] vs 74 [20%]), and acne or rash (52 [8%] vs one [<1%]). 59 (9%) patients in the cetuximab group and 31 (5%) patients in the control group had severe adverse events. Deaths related to treatment occurred in 32 (6%) patients in the cetuximab group and 13 (2%) patients in the control group. **INTERPRETATION:** Although this study did not meet its primary endpoints, prespecified subgroup analyses of patients with EGFR FISH-positive squamous-cell carcinoma cancers are encouraging and support continued evaluation of anti-EGFR antibodies in this subpopulation. **FUNDING:** National Cancer Institute and Eli Lilly and Company.

Bevacizumab in Combination with Platinum-Based Chemotherapy in Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer with or without Brain Metastases: A French Cohort Study (EOLE). Bennouna J1, Falchero L, Schott R, Bonnetain F, Coudert M, Ben Hadj Yahia B, Chouaid C. Oncology. 2017 Oct 25. doi: 10.1159/000480702. [Epub ahead of print]

OBJECTIVES: The aim of this study was to describe the characteristics of patients receiving bevacizumab plus first-line metastatic chemotherapy for non-squamous advanced non-small cell lung cancer (aNSCLC), with or without brain metastases, in routine clinical practice. Other objectives were to describe treatment efficacy, modalities of use, and safety. **METHODS:** For this non-interventional, prospective, national, multicentre study, data were collected every 3 months over 18 months. **RESULTS:** Of the 407 patients analysed, 84 (21%) with brain metastases at bevacizumab initiation had poorer general health than patients with no brain metastases (Eastern Cooperative Oncology Group [ECOG] performance status score = 2: 16 vs. 11%). All but 2 patients received bevacizumab (7.5 or 15 mg/kg/3 weeks in 99% of patients) in combination with doublet chemotherapy. Median progression-free survival and overall survival did not differ significantly between patients with or without brain metastases (6.5 months, 95% CI 5.7-8.1 vs. 6.9 months, 95% CI 5.9-7.6, $p = 0.57$; 14.5 months, 95% CI 10.0 vs. 12.5 months, 95% CI 10.1-14.7, $p = 0.33$). In 30 and 32% of the patients, respectively, at least one serious adverse event was reported, with a causal relationship to bevacizumab in 20 and 21% of the patients. **CONCLUSION:** This study confirmed in a real-life setting the safety profile and survival benefits of first-line chemotherapy with bevacizumab in aNSCLC patients with brain metastases.

SELECT-2: a Phase II, double-blind, randomised, placebo-controlled study to assess the efficacy of selumetinib plus docetaxel as a second-line treatment for patients with advanced or metastatic non-small cell lung cancer.

Soria JC1, Fülöp A2, Maciel C3, et al. Ann Oncol. 2017 Oct 3. doi: 10.1093/annonc/mdx628. [Epub ahead of print]

BACKGROUND: Combination of selumetinib plus docetaxel provided clinical benefit in a previous Phase II trial for patients with KRAS-mutant advanced non-small cell lung cancer (NSCLC). The Phase II SELECT-2 trial investigated safety and efficacy of selumetinib plus docetaxel for patients with advanced or metastatic NSCLC. **PATIENTS AND METHODS:** Patients who had disease progression after first-line anti-cancer therapy were randomised (2:2:1) to selumetinib 75 mg BID plus docetaxel 60 mg/m2 or 75 mg/m2 (SEL+DOC 60; SEL+DOC 75), or placebo plus docetaxel 75 mg/m2 (PBO+DOC 75). Patients were initially enrolled independently of KRAS mutation status, but the protocol was amended to include only patients with centrally confirmed KRAS wild-type NSCLC. Primary endpoint was progression-free survival (PFS; RECIST 1.1); statistical analyses compared each selumetinib group with PBO+DOC 75 for KRAS wild-type and overall (KRAS mutant or wild-type) populations. **RESULTS:** 212 patients were randomised; 69% were KRAS wild-type. There were no statistically significant improvements in PFS or overall survival (OS) for overall or KRAS wild-type populations in either selumetinib group compared with PBO+DOC 75. Overall population median PFS for SEL+DOC 60, SEL+DOC 75 compared with PBO+DOC 75 was 3.0, 4.2 and 4.3 months, HRs: 1.12 (90% CI: 0.8, 1.61) and 0.92 (90% CI: 0.65, 1.31), respectively. In the overall population, a higher objective response rate (ORR; investigator assessed) was observed for SEL+DOC 75 (33%) compared with PBO+DOC 75 (14%); odds ratio: 3.26 (90% CI: 1.47, 7.95). Overall the tolerability profile of SEL+DOC was consistent with historical data, without new or unexpected safety concerns identified. **CONCLUSION:** The primary endpoint (PFS) was not met. The higher ORR with SEL+DOC 75 did not translating into prolonged PFS for the overall or KRAS wild-type patient populations. No clinical benefit was observed with SEL+DOC in KRAS wild-type patients compared with docetaxel alone. No unexpected safety concerns were reported. Trial identifier: clinicaltrials.gov NCT01750281.

Spotlight on brigatinib and its potential in the treatment of patients with metastatic ALK-positive non-small cell lung cancer who are resistant or intolerant to crizotinib.

Jain RK1, Chen H1. Lung Cancer (Auckl). 2017 Oct 13;8:169-177. doi: 10.2147/LCTT.S126507. eCollection 2017.

In the last decade, there have been major therapeutic advances in the management of patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer. Crizotinib was the first approved

ALK inhibitor with significant benefits over chemotherapy. However, patients inevitably develop disease progression especially in central nervous system and acquire resistance to crizotinib. Several next-generation ALK inhibitors have been developed to overcome these resistance mechanisms and have demonstrated clinical benefits in crizotinib-refractory non-small cell lung cancer including in central nervous system. Brigatinib is a second-generation ALK inhibitor with high level of activity against ALK and several other targets. It is active in vitro against many ALK kinase domain mutations including L1196M, E1210K, and G1202R which may mediate acquired resistance to other ALK inhibitors. In Phase I/II and ALTA clinical studies, brigatinib has demonstrated substantial and durable responses and intracranial responses after progression on crizotinib. It has acceptable safety profile, but early pulmonary toxicity has been observed prompting to pursue daily dosing of 180 mg (with lead-in). Overall, 180 mg (with lead-in) has showed consistently better efficacy than 90 mg. In this review, we will discuss in detail these two pivotal trials that led to the accelerated approval for brigatinib and its future directions.

[First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced EGFR mutation-positive lung adenocarcinoma (CONVINCE): a phase 3, open-label, randomized study.](#) Shi YK1, Wang L1, Han BH2, et al. Ann Oncol. 2017 Oct 1;28(10):2443-2450. doi: 10.1093/annonc/mdx359.
BACKGROUND: Icotinib has been previously shown to be non-inferior to gefitinib in non-selected advanced non-small-cell lung cancer patients when given as second- or further-line treatment. In this open-label, randomized, phase 3 CONVINCE trial, we assessed the efficacy and safety of first-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance in lung adenocarcinoma patients with epidermal growth factor receptor (EGFR) mutation. **PATIENTS AND METHODS:** Eligible participants were adults with stage IIIB/IV lung adenocarcinoma and exon 19/21 EGFR mutations. Participants were randomly allocated (1 : 1) to receive oral icotinib or 3-week cycle of cisplatin plus pemetrexed for up to four cycles; non-progressive patients after four cycles were maintained with pemetrexed until disease progression or intolerable toxicity. The primary end point was progression-free survival (PFS) assessed by independent response evaluation committee. Other end points included overall survival (OS) and safety. **RESULTS:** Between January 2013 and August 2014, 296 patients were randomized, and 285 patients were treated (148 to icotinib, 137 to chemotherapy). Independent response evaluation committee-assessed PFS was significantly longer in the icotinib group (11.2 versus 7.9 months; hazard ratio, 0.61, 95% confidence interval 0.43-0.87; P = 0.006). No significant difference for OS was observed between treatments in the overall population or in EGFR-mutated subgroups (exon 19 Del/21 L858R). The most common grade 3 or 4 adverse events (AEs) in the icotinib group were rash (14.8%) and diarrhea (7.4%), compared with nausea (45.9%), vomiting (29.2%), and neutropenia (10.9%) in the chemotherapy group. AEs (79.1% versus 94.2%; P < 0.001) and treatment-related AEs (54.1% versus 90.5%; P < 0.001) were significantly fewer in the icotinib group than in the chemotherapy group. **CONCLUSIONS:** First-line icotinib significantly improves PFS of advanced lung adenocarcinoma patients with EGFR mutation with a tolerable and manageable safety profile. Icotinib should be considered as a first-line treatment for this patient population.

[Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial.](#) Shaw AT1, Felip E2, Bauer TM3, et al. Lancet Oncol. 2017 Oct 23. pii: S1470-2045(17)30680-0. doi: 10.1016/S1470-2045(17)30680-0. [Epub ahead of print]
BACKGROUND: Most patients with anaplastic lymphoma kinase (ALK)-rearranged or ROS proto-oncogene 1 (ROS1)-rearranged non-small-cell lung cancer (NSCLC) are sensitive to tyrosine kinase inhibitor (TKI) therapy, but resistance invariably develops, commonly within the CNS. This study aimed to analyse the safety, efficacy, and pharmacokinetic properties of lorlatinib, a novel, highly potent,

selective, and brain-penetrant ALK and ROS1 TKI with preclinical activity against most known resistance mutations, in patients with advanced ALK-positive or ROS1-positive NSCLC. **METHODS:** In this international multicentre, open-label, single-arm, first-in-man phase 1 dose-escalation study, eligible patients had advanced ALK-positive or ROS1-positive NSCLC and were older than 18 years, with an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate end-organ function. Lorlatinib was administered orally to patients at doses ranging from 10 mg to 200 mg once daily or 35 mg to 100 mg twice daily, with a minimum of three patients receiving each dose. For some patients, tumour biopsy was done before lorlatinib treatment to identify ALK resistance mutations. Safety was assessed in patients who received at least one dose of lorlatinib; efficacy was assessed in the intention-to-treat population (patients who received at least one dose of study treatment and had either ALK or ROS1 rearrangement). The primary endpoint was dose-limiting toxicities during cycle 1 according to investigator assessment; secondary endpoints included safety, pharmacokinetics, and overall response. This study is ongoing and is registered with ClinicalTrials.gov, number NCT01970865. **FINDINGS:** Between Jan 22, 2014, and July 10, 2015, 54 patients received at least one dose of lorlatinib, including 41 (77%) with ALK-positive and 12 (23%) with ROS1-positive NSCLC; one patient had unconfirmed ALK and ROS1 status. 28 (52%) patients had received two or more TKIs, and 39 (72%) patients had CNS metastases. The most common treatment-related adverse events among the 54 patients were hypercholesterolaemia (39 [72%] of 54 patients), hypertriglyceridaemia (21 [39%] of 54 patients), peripheral neuropathy (21 [39%] of 54 patients), and peripheral oedema (21 [39%] of 54 patients). One dose-limiting toxicity occurred at 200 mg (the patient did not take at least 16 of 21 prescribed total daily doses in cycle 1 because of toxicities attributable to study drug, which were grade 2 neurocognitive adverse events comprising slowed speech and mentation and word-finding difficulty). No maximum tolerated dose was identified. The recommended phase 2 dose was selected as 100 mg once daily. For ALK-positive patients, the proportion of patients who achieved an objective response was 19 (46%) of 41 patients (95% CI 31-63); for those who had received two or more TKIs, the proportion of patients with an objective response was 11 (42%) of 26 patients (23-63). In ROS1-positive patients, including seven crizotinib-pretreated patients, an objective response was achieved by six (50%) of 12 patients (95% CI 21-79). **INTERPRETATION:** In this phase 1, dose-escalation study, lorlatinib showed both systemic and intracranial activity in patients with advanced ALK-positive or ROS1-positive NSCLC, most of whom had CNS metastases and had previously had two or more TKI treatments fail. Therefore, lorlatinib might be an effective therapeutic strategy for patients with ALK-positive NSCLC who have become resistant to currently available TKIs, including second-generation ALK TKIs, and is being investigated in a phase 3 randomised controlled trial comparing lorlatinib to crizotinib (ClinicalTrials.gov, NCT03052608). **FUNDING:** Pfizer.

[Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057).](#) Horn L1, Spigel DR1, Vokes EE1, et al. Clin Oncol. 2017 Oct 12:JCO2017743062. doi: 10.1200/JCO.2017.74.3062. [Epub ahead of print]
PURPOSE: Nivolumab, a programmed death-1 inhibitor, prolonged overall survival compared with docetaxel in two independent phase III studies in previously treated patients with advanced squamous (CheckMate 017; ClinicalTrials.gov identifier: NCT01642004) or nonsquamous (CheckMate 057; ClinicalTrials.gov identifier: NCT01673867) non-small-cell lung cancer (NSCLC). We report updated results, including a pooled analysis of the two studies. **METHODS:** Patients with stage IIIB/IV squamous (N = 272) or nonsquamous (N = 582) NSCLC and disease progression during or after prior platinum-based chemotherapy were randomly assigned 1:1 to nivolumab (3 mg/kg every 2 weeks) or docetaxel (75 mg/m2 every 3 weeks). Minimum follow-up for survival was 24.2 months. **RESULTS:** Two-year overall survival rates with nivolumab versus docetaxel were 23% (95% CI, 16% to 30%) versus 8% (95% CI, 4%

to 13%) in squamous NSCLC and 29% (95% CI, 24% to 34%) versus 16% (95% CI, 12% to 20%) in nonsquamous NSCLC; relative reductions in the risk of death with nivolumab versus docetaxel remained similar to those reported in the primary analyses. Durable responses were observed with nivolumab; 10 (37%) of 27 confirmed responders with squamous NSCLC and 19 (34%) of 56 with nonsquamous NSCLC had ongoing responses after 2 years' minimum follow-up. No patient in either docetaxel group had an ongoing response. In the pooled analysis, the relative reduction in the risk of death with nivolumab versus docetaxel was 28% (hazard ratio, 0.72; 95% CI, 0.62 to 0.84), and rates of treatment-related adverse events were lower with nivolumab than with docetaxel (any grade, 68% v 88%; grade 3 to 4, 10% v 55%). **CONCLUSION:** Nivolumab provides long-term clinical benefit and a favorable tolerability profile compared with docetaxel in previously treated patients with advanced NSCLC.

Impact of Nivolumab Versus Docetaxel on Health-Related Quality of Life and Symptoms in Patients With Advanced Squamous Non-Small Cell Lung Cancer: Results From the CheckMate 017 Study. Reck M1, Taylor F2, Penrod JR3, DeRosa M2, Morrissey L2, Dastani H3, Orsini L3, Gralla RJ4. J Thorac Oncol. 2017 Nov 9. pii: S1556-0864(17)32878-2. doi: 10.1016/j.jtho.2017.10.029. [Epub ahead of print]
INTRODUCTION: In the phase III CheckMate 017 study, nivolumab prolonged overall survival versus docetaxel in previously treated patients with advanced squamous non-small cell lung cancer (NSCLC). Study objectives included health-related quality of life (HRQoL) and symptom assessments.
METHODS: Patients serially completed Lung Cancer Symptom Scale (LCSS) and European Quality of Life Five Dimensions (EQ-5D) questionnaires. The LCSS average symptom burden index (ASBI; mean score for six lung cancer-specific symptoms; range, 0-100), LCSS 3-item global index, EQ-5D utility index, and EQ-5D visual analog scale scores were analyzed. The proportion of patients exhibiting clinically meaningful improvement (≥10-point decrease) in ASBI scores by week 12 was a secondary end point. Mixed-effect model repeated measures analysis of HRQoL changes from baseline and analyses of time to HRQoL deterioration were conducted. **RESULTS:** Baseline mean (SD) LCSS ASBI scores were similar in nivolumab (29.6 [16.4]) and docetaxel (29.6 [14.7]) groups. By week 12, the proportion of patients (95% CI) with clinically meaningful improvement in ASBI scores was 20.0% (13.6-27.7) with nivolumab and 21.9% (15.3-29.8) with docetaxel. At weeks 16-54, significant improvements in ASBI scores from baseline were seen with nivolumab; clinically meaningful improvements were observed at weeks 42-84. No significant changes in ASBI scores from baseline were observed with docetaxel; at week 36, a clinically meaningful deterioration was seen. Improvements in HRQoL with nivolumab versus docetaxel were supported by other measures, and time to first HRQoL deterioration was longer.
CONCLUSION: Nivolumab alleviates symptom burden and improves health status versus docetaxel as second-line squamous NSCLC treatment.

Predictive Factors for Poor Progression-free Survival in Patients with Non-small Cell Lung Cancer Treated with Nivolumab. Taniguchi Y1, Tamiya A2, Isa SI3, et al. Anticancer Res. 2017 Oct;37(10):5857-5862.
BACKGROUND: Nivolumab has shown promising effects in patients with non-small-cell lung cancer (NSCLC) as a second- or later-line treatment. This study aimed to identify patients who would not experience any benefit from nivolumab treatment. **MATERIALS AND METHODS:** In this study, data for 201 patients treated with nivolumab during 17 December 2015 to 31 July 2016 at three respiratory medical centers in Japan were retrospectively reviewed. We collected clinical data at the time of nivolumab treatment commencement. We investigated the relationship between progression-free survival (PFS) and patient characteristics. **RESULTS:** In both univariate and multivariate analysis, performance status (PS) score ≥2, steroid use at baseline and lactate dehydrogenase (LDH) level >240 IU/l were significantly associated with poor PFS (all p<0.05). **CONCLUSION:** PS score ≥2, steroid use at baseline

and a high LDH level were predictive of poor PFS in patients with NSCLC treated with nivolumab. Careful monitoring is recommended for treating such patients with nivolumab (UMIN-ID: UMIN000025908).

Very early response of circulating tumour-derived DNA in plasma predicts efficacy of nivolumab treatment in patients with non-small cell lung cancer.

Iijima Y1, Hirotsu Y2, Amemiya K2, et al. Eur J Cancer. 2017 Nov;86:349-357. doi: 10.1016/j.ejca.2017.09.004. Epub 2017 Nov 5.

INTRODUCTION: Immunotherapy has become a treatment option for lung cancer. The utility of nivolumab as second-line treatment for non-small cell lung cancer has been proven, but predictive biomarkers influencing its efficacy remain unknown. **METHODS:** This study involved 14 patients who were treated with nivolumab from February 1 to September 30, 2016. The early response of the level of circulating tumour DNA (ctDNA) after starting nivolumab was evaluated to ascertain whether it could predict treatment outcome. **RESULTS:** Of the 14 patients, six were responders and eight were non-responders. DNA was analysed in both tumour tissue and plasma samples. Only somatic mutations confirmed by analysis of tumour tissue were defined as ctDNA. ctDNA was detected more often in the serial plasma samples of patients with high tumour volume (TV) (p = 0.02). ctDNA was detected in seven cases; basal and serial ctDNA analysis revealed that a decrease in allelic frequency (AF) of ctDNA showed high-level correspondence with a good durable response. When "2 weeks" was set as a clinically significant time point, changes in representative mutations of each case, defined as one of the highest baseline AF, showed 100% concordance with the response. **CONCLUSIONS:** In patients with high TV, plasma analysis of ctDNA, as validated by tumour tissue, suggested that a durable good response to nivolumab could be predicted within 2 weeks.

The Association Between Chemotherapy Immediately Before Nivolumab and Outcomes Thereafter.

Nakahama K1, Isa SI2, Tamiya A3, et al. Anticancer Res. 2017 Oct;37(10):5885-5891.

BACKGROUND/AIM: We investigated whether the efficacy and type of pre-nivolumab chemotherapy influence outcomes in non-small cell lung cancer patients following nivolumab treatment. **PATIENTS AND METHODS:** In this multicenter study, 199 patients treated with nivolumab were retrospectively reviewed. We analyzed the relationships between the clinical response to nivolumab and to chemotherapy administered immediately beforehand. **RESULTS:** Patients who achieved objective responses to pretreatments showed higher disease control rates with nivolumab than patients who did not (64% vs. 47%, p=0.03), as did those who achieved disease control with pretreatments (62% vs. 35%, p<0.001). Bevacizumab-pretreated patients tended to show better objective response rates with nivolumab (27% vs. 13%, p=0.06); the objective response rate to nivolumab was significantly higher in bevacizumab-pretreated patients who showed clinical responses (42% vs. 9.1%, p=0.02). **CONCLUSION:** Achievement of a clinical response to chemotherapy immediately before nivolumab, particularly when combined with bevacizumab, increases the likelihood of disease control post-nivolumab.

Phase I study of the combination of quinacrine and erlotinib in patients with locally advanced or metastatic non small cell lung cancer.

Bhateja P1,2, Dowlati A3,4, Sharma N5. Invest New Drugs. 2017 Oct 2. doi: 10.1007/s10637-017-0515-3. [Epub ahead of print]

INTRODUCTION: Preclinical data suggest quinacrine acts as an inhibitor of FACT (facilitates chromatin transcription) complex, which may play a role in TKI (tyrosine kinase inhibitor) resistance. The aim of this Phase I study was to study the safety and assess the maximum tolerated dose of quinacrine in combination with erlotinib in non small cell lung cancer (NSCLC). **METHODS:** This was a phase I study with standard 3 + 3 dose escalation design with the primary aim of determining the maximum tolerated dose. Two of 3 patients enrolled at dose level 1 experienced dose limiting toxicity (DLT). The next 6

patients were enrolled at dose level - 1 and none of these 6 patients experienced DLT. The dose of 50 mg of quinacrine every other day with 150 mg of erlotinib was established as the maximum tolerated and the recommended phase II dose. One of 3 patients treated at dose level 1 had stable disease. One of 6 patients treated at dose level - 1 had partial response for 6 months, the rest had progressive disease at the time of first assessment. **CONCLUSION:** Combination of quinacrine and erlotinib was well tolerated but showed limited efficacy in advanced NSCLC.

Gefitinib Plus Chemotherapy Versus Chemotherapy in Epidermal Growth Factor Receptor Mutation-Positive Non-Small-Cell Lung Cancer Resistant to First-Line Gefitinib (IMPRESS): Overall Survival and Biomarker Analyses. Mok TSK1, Kim SW1, Wu YL1, et al. J Clin Oncol. 2017 Oct 2:JCO2017739250. doi: 10.1200/JCO.2017.73.9250. [Epub ahead of print]
PURPOSE: The Iressa Mutation-Positive Multicentre Treatment Beyond ProgRESsion Study (IMPRESS) compared the continuation of gefitinib plus chemotherapy with placebo plus chemotherapy in patients with epidermal growth factor receptor (EGFR) mutation-positive advanced non-small-cell lung cancer with progression (Response Evaluation Criteria in Solid Tumors 1.1) after first-line gefitinib. Primary results indicated no difference between treatments in terms of progression-free survival (PFS). The current analysis presents final, mature, overall survival (OS) data, together with exploratory analyses that examined whether specific biomarkers, including T790M mutation status, were able to differentiate a relative treatment effect. Patients and **METHODS:** Patients were randomly assigned to gefitinib 250 mg or placebo, in addition to cisplatin 75 mg/m2 plus pemetrexed 500 mg/m2 (maximum of six cycles of chemotherapy). EGFR mutation status was determined from plasma-derived circulating free tumor-derived DNA samples (beads, emulsification, amplification, and magnetics digital polymerase chain reaction assay, allelic fraction analysis). **RESULTS:** A total of 265 patients with non-small-cell lung cancer were randomly assigned, and overall data maturity was 66%. Continuation of gefitinib plus cisplatin and pemetrexed was detrimental to OS when compared with placebo plus cisplatin and pemetrexed (hazard ratio [HR], 1.44; 95% CI, 1.07 to 1.94; P = .016; median OS, 13.4 v 19.5 months). The detriment was statistically significant in patients with T790M mutation-positive plasma samples (HR, 1.49; 95% CI, 1.02 to 2.21), whereas statistical significance was not reached in T790M mutation-negative patients (HR, 1.15; 95% CI, 0.68 to 1.94). PFS in T790M mutation-positive patients was similar between treatments, and the difference observed in T790M mutation-negative patients did not reach statistical significance (HR, 0.67; 95% CI, 0.43 to 1.03; P = .0745). **CONCLUSION:** Final OS data from IMPRESS are supportive of earlier PFS results and are sufficient to warn physicians against the continuation of treatment with first-generation EGFR tyrosine kinase inhibitors beyond radiologic disease progression when chemotherapy is initiated. Plasma biomarker analyses suggest that this effect may be driven by T790M-positive status.

Role of chemotherapy and targeted therapy in early-stage non-small cell lung cancer. Nagasaka M1,2, Gadgeel SM3. Expert Rev Anticancer Ther. 2017 Nov 26:1-8. doi: 10.1080/14737140.2018.1409624. [Epub ahead of print]
Adjuvant platinum based chemotherapy is accepted as standard of care in stage II and III non-small cell lung cancer (NSCLC) patients and is often considered in patients with stage IB disease who have tumors ≥ 4 cm. The survival advantage is modest with approximately 5% at 5 years. Areas covered: This review article presents relevant data regarding chemotherapy use in the perioperative setting for early stage NSCLC. A literature search was performed utilizing PubMed as well as clinical trial.gov. Randomized phase III studies in this setting including adjuvant and neoadjuvant use of chemotherapy as well as ongoing trials on targeted therapy and immunotherapy are also discussed. Expert commentary: With increasing utilization of screening computed tomography scans, it is possible that the percentage of early stage NSCLC patients will increase in the coming years. Benefits of adjuvant chemotherapy in early stage

NSCLC patients remain modest. There is a need to better define patients most likely to derive survival benefit from adjuvant therapy and spare patients who do not need adjuvant chemotherapy due to the toxicity of such therapy. Trials for adjuvant targeted therapy, including adjuvant EGFR-TKI trials and trials of immunotherapy drugs are ongoing and will define the role of these agents as adjuvant therapy.

[Exploratory analysis of the association of depth of response and survival in patients with metastatic non-small-cell lung cancer treated with a targeted therapy or immunotherapy.](#) McCoach CE1, Blumenthal GM2, Zhang L3, et al. Ann Oncol. 2017 Nov 1;28(11):2707-2714. doi: 10.1093/annonc/mdx414.

BACKGROUND: Response Evaluation Criteria in Solid Tumors (RECIST) permits rapid evaluation of new therapeutic strategies in cancer. However, RECIST does not capture the heterogeneity of response in highly active therapies. Depth of tumor response may provide a more granular view of response. We explored the association between, depth of response (DepOR), with overall survival (OS) and progression-free survival (PFS) for patients with NSCLC being treated with an ALK inhibitor (ALKi) or an anti-PD-1 antibody (Ab). **METHODS:** Experimental arms from two randomized controlled trials (RCTs) of an ALKi and two RCTs of an anti-PD-1 Ab were separately pooled. Patient responses were grouped into DepOR 'quartiles' by percentage of maximal tumor shrinkage (Q1 = 1%-25%, Q2 = 26%-50%, Q3 = 51%-75%, and Q4 = 76%-100%), Q0 had no shrinkage. We carried out a retrospective exploratory responder analysis to evaluate the association between DepOR and OS or PFS using hazard ratios (HR) generated by the Cox proportional hazards model. **RESULTS:** In the pooled ALK analysis there were 12, 39, 70, 144, and 40 patients in quartiles 0-4, respectively. The DepOR versus PFS/OS analyses HR were: 0.19/0.94 for Q1 0.11/0.56 for Q2, 0.05/0.28 for Q3, and 0.03/0.05 for Q4. In the PD-1 trials within quartiles 0-4 there were 168, 70, 44, 45, and 28 patients, respectively. The DepOR versus PFS/OS analyses HR were 0.3/0.52 for Q1, 0.22/0.47 for Q2, 0.09/0.07 for Q3, and 0.07/0.14 for Q4. **CONCLUSIONS:** Our analysis suggests a greater DepOR is associated with longer PFS and OS for patients receiving ALKi or anti-PD1 Ab. Overall, this suggests that DepOR may provide an additional outcome measure for clinical trials, and may allow better comparisons of treatment activity.

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NSCLC – RADIOTHERAPY

[Patterns and correlates of treatment failure in relation to isodose distribution in non-small cell lung cancer: An analysis of 1522 patients in the modern era.](#)
[Pezzi](#) TA1, Tang C1, Swanick CW1, Fang P1, Hess K2, Xu T1, Hahn SM1, Chang JY1, Liao Z1, Gomez D3. Radiother Oncol. 2017 Oct 17. pii: S0167-8140(17)32585-9. doi: 10.1016/j.radonc.2017.09.018. [Epub ahead of print]

BACKGROUND AND PURPOSE: To examine the relationship between radiation dose and tumor control in limited stage non-small cell lung cancer (NSCLC). **MATERIALS AND METHODS:** We searched a database of 1552 patients who received radiation therapy for non-metastatic NSCLC between 2000 and 2016. The primary endpoint was freedom from in-field failure.

RESULTS: Increasing BED correlated with decreasing estimated gross tumor volume-planning target volume expansion, and on multivariable analysis increasing BED was associated with an increased chance of field-edge failures (hazard ratio [HR] 1.032, 95% confidence interval [CI] 1.004-1.062, P = 0.027). Increasing BED also correlated with improved freedom from in-field failure on multivariable analysis (HR 0.978, 95% CI 0.964-0.993, P = 0.003), with the dose-response curve showing a sigmoidal relationship between increasing BED and freedom from in-field failure. **CONCLUSION:** In this large study of patients treated in the modern era with varying dose fractionation regimens, higher BED was associated with improved freedom from in-field failure, and that this relationship appeared to be consistent with the classically described sigmoid shape. We also found that increased BED was associated

with higher field-edge failures, implying that margin size may need to be further studied in patients receiving ablative regimens of radiation.

[A prospective evaluation of hippocampal radiation dose volume effects and memory deficits following cranial irradiation.](#) Ma TM1, Grimm J1, McIntyre R1, Anderson-Keightly H1, Kleinberg LR1, Hales RK1, Moore J1, Vannorsdall T2, Redmond KJ3. Radiother Oncol. 2017 Nov;125(2):234-240. doi: 10.1016/j.radonc.2017.09.035. Epub 2017 Nov 8.
BACKGROUND AND PURPOSE: To prospectively evaluate hippocampal radiation dose volume effects and memory decline following cranial irradiation. **MATERIAL AND METHODS:** Effects of hippocampal radiation over a wide range of doses were investigated by combining data from three prospective studies. In one, adults with small cell lung cancer received hippocampal-avoidance prophylactic cranial irradiation. In the other two, adults with glioblastoma multiforme received neural progenitor cell sparing radiation or no sparing with extra dose delivered to subventricular zone. Memory was measured by the Hopkins Verbal Learning Test-Revised Delayed Recall (HVLT-R DR) at 6 months after radiation. Dose-volume histograms were generated and dose-response data were fitted to a nonlinear model. **RESULTS:** Of 60 patients enrolled, 30 were analyzable based on HVLT-R DR testing completion status, baseline HVLT-R DR and intracranial metastasis/recurrence or prior hippocampal resection status. We observed a dose-response of radiation to the hippocampus with regard to decline in HVLT-R DR. D50% of the bilateral hippocampi of 22.1 Gy is associated with 20% risk of decline. **CONCLUSIONS:** This prospective study demonstrates an association between hippocampal dose volume effects and memory decline measured by HVLT-R DR over a wide dose range. These data support a potential benefit of hippocampal sparing and encourage continued trial enrollment.

[An investigation into the range dependence of target delineation strategies for stereotactic lung radiotherapy.](#) Mohatt DJ1, Keim JM2, Greene MC2, Patel-Yadav A2, Gomez JA2, Malhotra HK3,2. Radiat Oncol. 2017 Nov 3;12(1):166. doi: 10.1186/s13014-017-0907-8.
BACKGROUND: The "gold standard" approach for defining an internal target volume (ITV) is using 10 gross tumor volume (GTV) phases delineated over the course of one respiratory cycle. However, different sites have adopted several alternative techniques which compress all temporal information into one CT image set to optimize work flow efficiency. The purpose of this study is to evaluate alternative target segmentation strategies with respect to the 10 phase gold standard. **METHODS:** A Quasar respiratory motion phantom was employed to simulate lung tumor movement. Utilizing 4DCT imaging, a gold standard ITV was created by merging 10 GTV time resolved image sets. Four alternative planed ITV's were compared using free breathing (FB), average intensity projection (AIP), maximum image projection (MIP), and an augmented FB (FB-Aug) set where the ITV included structures from FB plus max-inhale/exhale image sets. Statistical analysis was performed using the Dice similarity coefficient (DSC). Seventeen patients previously treated for lung SBRT were also included in this retroactive study. **RESULTS:** PTV's derived from the FB image set are the least comparable with the 10 phase benchmark (DSC = 0.740-0.408). For phantom target motion greater than 1 cm, FB and AIP ITV delineation exceeded the 10 phase benchmark by 2% or greater, whereas MIP target segmentation was found to be consistently within 2% agreement with the gold standard (DSC > 0.878). Clinically, however, the FB-Aug method proved to be most favorable for tumor movement up to 2 cm (DSC = 0.881 ± 0.056). **CONCLUSION:** Our results indicate the range of tumor motion dictates the accuracy of the defined PTV with respect to the gold standard. When considering delineation efficiency relative to the 10 phase benchmark, the FB-Aug technique presents a potentially proficient and viable clinical alternative. Among various techniques used for image segmentation, a judicious balance between accuracy and efficiency is inherently required to account for tumor trajectory, range and rate of mobility.

Clinical decision support of radiotherapy treatment planning: A data-driven machine learning strategy for patient-specific dosimetric decision making. Valdes G1, Simone CB 2nd2, Chen J3, Lin A4, Yom SS5, Pattison AJ6, Carpenter CM6, Solberg TD3. Radiother Oncol. 2017 Nov 18. pii: S0167-8140(17)32654-3. doi: 10.1016/j.radonc.2017.10.014. [Epub ahead of print]

BACKGROUND AND PURPOSE: Clinical decision support systems are a growing class of tools with the potential to impact healthcare. This study investigates the construction of a decision support system through which clinicians can efficiently identify which previously approved historical treatment plans are achievable for a new patient to aid in selection of therapy. **MATERIAL AND METHODS:** Treatment data were collected for early-stage lung and postoperative oropharyngeal cancers treated using photon (lung and head and neck) and proton (head and neck) radiotherapy. Machine-learning classifiers were constructed using patient-specific feature-sets and a library of historical plans. Model accuracy was analyzed using learning curves, and historical treatment plan matching was investigated. **RESULTS:** Learning curves demonstrate that for these datasets, approximately 45, 60, and 30 patients are needed for a sufficiently accurate classification model for radiotherapy for early-stage lung, postoperative oropharyngeal photon, and postoperative oropharyngeal proton, respectively. The resulting classification model provides a database of previously approved treatment plans that are achievable for a new patient. An exemplary case, highlighting tradeoffs between the heart and chest wall dose while holding target dose constant in two historical plans is provided. **CONCLUSIONS:** We report on the first artificial-intelligence based clinical decision support system that connects patients to past discrete treatment plans in radiation oncology and demonstrate for the first time how this tool can enable clinicians to use past decisions to help inform current assessments. Clinicians can be informed of dose tradeoffs between critical structures early in the treatment process, enabling more time spent on finding the optimal course of treatment for individual patients.

Intra- and inter-fractional liver and lung tumor motions treated with SBRT under active breathing control. Lu L1, Diaconu C1, Djemil T1, Videtic GM1, Abdel-Wahab M1, Yu N1, Greskovich J Jr1, Stephans KL1, Xia P1. J Appl Clin Med Phys. 2017 Nov 20. doi: 10.1002/acm2.12220. [Epub ahead of print]

PURPOSE: To assess intra- and inter-fractional motions of liver and lung tumors using active breathing control (ABC). **METHODS AND MATERIALS:** Nineteen patients with liver cancer and 15 patients with lung cancer treated with stereotactic body radiotherapy (SBRT) were included in this retrospective study. All patients received a series of three CTs at simulation to test breath-hold reproducibility. The centroids of the whole livers and of the lung tumors from the three CTs were compared to assess intra-fraction variability. For 15 patients (8 liver, 7 lung), ABC-gated kilovoltage cone-beam CTs (kV-CBCTs) were acquired prior to each treatment, and the centroids of the whole livers and of the lung tumors were also compared to those in the planning CTs to assess inter-fraction variability. **RESULTS:** Liver intra-fractional systematic/random errors were 0.75/0.39 mm, 1.36/0.97 mm, and 1.55/1.41 mm at medial-lateral (ML), anterior-posterior (AP), and superior-inferior (SI) directions, respectively. Lung intra-fractional systematic/random errors were 0.71/0.54 mm (ML), 1.45/1.10 mm (AP), and 3.95/1.93 mm (SI), respectively. Substantial intra-fraction motions (>3 mm) were observed in 26.3% of liver cancer patients and in 46.7% of lung cancer patients. For both liver and lung tumors, most inter-fractional systematic and random errors were larger than the corresponding intra-fractional errors. However, these inter-fractional errors were mostly corrected by the treatment team prior to each treatment based on kV CBCT-guided soft tissue alignment, thereby eliminating their effects on the treatment planning margins. **CONCLUSIONS:** Intra-fractional motion is the key to determine the planning margins since inter-fractional motion can be compensated based on daily gated soft tissue imaging guidance of CBCT. Patient-specific treatment planning margins instead of recipe-based margins were suggested, which can benefit mostly for the patients with small intra-fractional motions.

[Dose to mass for evaluation and optimization of lung cancer radiation therapy.](#) Tyler Watkins W1, Moore JA2, Hugo GD3, Siebers JV4. Radiother Oncol. 2017 Oct 11. pii: S0167-8140(17)32563-X. doi: 10.1016/j.radonc.2017.09.002. [Epub ahead of print]

PURPOSE: To evaluate potential organ at risk dose-sparing by using dose-mass-histogram (DMH) objective functions compared with dose-volume-histogram (DVH) objective functions. **METHODS:** Treatment plans were retrospectively optimized for 10 locally advanced non-small cell lung cancer patients based on DVH and DMH objectives. DMH-objectives were the same as DVH objectives, but with mass replacing volume. Plans were normalized to dose to 95% of the PTV volume (PTV-D95v) or mass (PTV-D95m). For a given optimized dose, DVH and DMH were intercompared to ascertain dose-to-volume vs. dose-to-mass differences. Additionally, the optimized doses were intercompared using DVH and DMH metrics to ascertain differences in optimized plans. Mean dose to volume, $D\bar{v}$, mean dose to mass, $D\bar{M}$, and fluence maps were intercompared. **RESULTS:** For a given dose distribution, DVH and DMH differ by >5% in heterogeneous structures. In homogeneous structures including heart and spinal cord, DVH and DMH are nearly equivalent. At fixed PTV-D95v, DMH-optimization did not significantly reduce dose to OARs but reduced PTV-$D\bar{v}$ by 0.20±0.2Gy (p=0.02) and PTV-$D\bar{M}$ by 0.23±0.3Gy (p=0.02). Plans normalized to PTV-D95m also result in minor PTV dose reductions and esophageal dose sparing ($D\bar{v}$ reduced 0.45±0.5Gy, p=0.02 and $D\bar{M}$ reduced 0.44±0.5Gy, p=0.02) compared to DVH-optimized plans. Optimized fluence map comparisons indicate that DMH optimization reduces dose in the periphery of lung PTVs. **CONCLUSIONS:** DVH- and DMH-dose indices differ by >5% in lung and lung target volumes for fixed dose distributions, but optimizing DMH did not reduce dose to OARs. The primary difference observed in DVH- and DMH-optimized plans were variations in fluence to the periphery of lung target PTVs, where low density lung surrounds tumor.

[Whole brain radiotherapy after stereotactic radiosurgery or surgical resection among patients with one to three brain metastases and favorable prognoses: a secondary analysis of EORTC 22952-26001.](#) Churilla TM1, Handorf E1, Collette S2, et al. Ann Oncol. 2017 Oct 1;28(10):2588-2594. doi: 10.1093/annonc/mdx332.

BACKGROUND: The absence of a survival benefit for whole brain radiotherapy (WBRT) among randomized trials has been attributed to a competing risk of death from extracranial disease. We re-analyzed EORTC 22952 to assess the impact of WBRT on survival for patients with controlled extracranial disease or favorable prognoses. **PATIENTS AND METHODS:** We utilized Cox regression, landmark analysis, and the Kaplan-Meier method to evaluate the impact of WBRT on survival accounting for (i) extracranial progression as a time-dependent covariate in all patients and (ii) diagnosis-specific graded prognostic assessment (GPA) score in patients with primary non-small-cell lung cancer (NSCLC). **RESULTS:** A total of 329 patients treated per-protocol were included for analysis with a median follow up of 26 months. One hundred and fifteen (35%) patients had no extracranial progression; 70 (21%) patients had progression <90 days, 65 (20%) between 90 and 180 days, and 79 (24%) patients >180 days from randomization. There was no difference in the model-based risk of death in the WBRT group before [hazard ratio (HR) (95% CI)=0.70 (0.45-1.11), P = 0.133), or after [HR (95% CI)=1.20 (0.89-1.61), P = 0.214] extracranial progression. Among 177 patients with NSCLC, 175 had data available for GPA calculation. There was no significant survival benefit to WBRT among NSCLC patients with favorable GPA scores [HR (95% CI)=1.10 (0.68-1.79)] or unfavorable GPA scores [HR (95% CI)=1.11 (0.71-1.76)]. **CONCLUSIONS:** Among patients with limited extracranial disease and one to three brain metastases at enrollment, we found no significant survival benefit to WBRT among NSCLC patients with favorable GPA scores or patients with any histology and controlled extracranial disease status. This exploratory analysis of phase III data supports the practice of omitting WBRT for patients with limited brain metastases undergoing SRS and close surveillance.

Biopsy of enlarging lesions after stereotactic radiosurgery for brain metastases frequently reveals radiation necrosis. Narloch JL1, Farber SH1, Sammons S1, et al. Neuro Oncol. 2017 Oct 1;19(10):1391-1397. doi: 10.1093/neuonc/nox090.

BACKGROUND: Stereotactic radiosurgery (SRS) offers excellent local control for brain metastases (BM) with low rates of toxicity. Radiation necrosis (RN) may occur after treatment and is challenging to distinguish from local recurrence (LR). We evaluated enlarging brain lesions following SRS that were subsequently biopsied to differentiate RN versus LR. **METHODS:** This study reviewed patients receiving SRS for BM between 2008 and 2012 who underwent a biopsy for suspicion of RN versus LR on MRI. Data collection included demographics, radiation parameters, imaging findings, and post-biopsy pathology. Kaplan-Meier methods determined overall survival. Fisher's exact test assessed for association between lesion biopsy result and variables of interest. **RESULTS:** Thirty-four patients with 35 biopsied BM were included. Lesions were biopsied a median of 8.8 months after SRS. Most patients had primary lung cancer (11; 31.4%). Eleven (31.4%) biopsies were positive for LR and 24 (68.6%) showed RN only. Median overall survival was longer for patients with RN (31.0 mo) than for patients with LR (14.5 mo; P = 0.135). Time from SRS to biopsy was significantly different between RN and LR groups; 10 lesions (52.5%) biopsied ≤9 months after SRS showed LR, whereas 1 lesion (6.3%) biopsied >9 months after SRS showed LR (P = 0.004). For 16 (65.7%) lesions, management was changed or directed by the biopsy results. **CONCLUSIONS:** Stereotactic biopsy for accessible enlarging lesions after SRS appears diagnostically valuable in patients with few lesions and changes clinical management. RN should be suspected in patients with an enlarging lesion more than 9 months post-SRS.

T2-Weighted 4D Magnetic Resonance Imaging for Application in Magnetic Resonance-Guided Radiotherapy Treatment Planning. Freedman JN1, Collins DJ, Bainbridge H, et al. Invest Radiol. 2017 Oct;52(10):563-573. doi: 10.1097/RLI.0000000000000381.

OBJECTIVES: The aim of this study was to develop and verify a method to obtain good temporal resolution T2-weighted 4-dimensional (4D-T2w) magnetic resonance imaging (MRI) by using motion information from T1-weighted 4D (4D-T1w) MRI, to support treatment planning in MR-guided radiotherapy. **MATERIALS AND METHODS:** Ten patients with primary non-small cell lung cancer were scanned at 1.5 T axially with a volumetric T2-weighted turbo spin echo sequence gated to exhalation and a volumetric T1-weighted stack-of-stars spoiled gradient echo sequence with golden angle spacing acquired in free breathing. From the latter, 20 respiratory phases were reconstructed using the recently developed 4D joint MoCo-HDTV algorithm based on the self-gating signal obtained from the k-space center. Motion vector fields describing the respiratory cycle were obtained by deformable image registration between the respiratory phases and projected onto the T2-weighted image volume. The resulting 4D-T2w volumes were verified against the 4D-T1w volumes: an edge-detection method was used to measure the diaphragm positions; the locations of anatomical landmarks delineated by a radiation oncologist were compared and normalized mutual information was calculated to evaluate volumetric image similarity. **RESULTS:** High-resolution 4D-T2w MRI was obtained. Respiratory motion was preserved on calculated 4D-T2w MRI, with median diaphragm positions being consistent with less than 6.6 mm (2 voxels) for all patients and less than 3.3 mm (1 voxel) for 9 of 10 patients. Geometrical positions were coherent between 4D-T1w and 4D-T2w MRI as Euclidean distances between all corresponding anatomical landmarks agreed to within 7.6 mm (Euclidean distance of 2 voxels) and were below 3.8 mm (Euclidean distance of 1 voxel) for 355 of 470 pairs of anatomical landmarks. Volumetric image similarity was commensurate between 4D-T1w and 4D-T2w MRI, as mean percentage differences in normalized mutual information (calculated over all respiratory phases and patients), between corresponding respiratory phases of 4D-T1w and 4D-T2w MRI and the tie-phase of 4D-T1w and 3-dimensional T2w MRI, were consistent to 0.41% ± 0.37%. Four-dimensional T2w MRI displayed tumor

extent, structure, and position more clearly than corresponding 4D-T1w MRI, especially when mobile tumor sites were adjacent to organs at risk. **CONCLUSIONS:** A methodology to obtain 4D-T2w MRI that retrospectively applies the motion information from 4D-T1w MRI to 3-dimensional T2w MRI was developed and verified. Four-dimensional T2w MRI can assist clinicians in delineating mobile lesions that are difficult to define on 4D-T1w MRI, because of poor tumor-tissue contrast.

[Dose-Volume Predictors of Esophagitis After Thoracic Stereotactic Body Radiation Therapy.](#)
Harder EM1, Chen ZJ, Park HS, Mancini BR, Decker RH. Am J Clin Oncol. 2017 Oct;40(5):477-482. doi: 10.1097/COC.0000000000000195.
OBJECTIVES: Esophageal toxicity has become a major concern as stereotactic hypofractionated radiation therapy is increasingly utilized for central pulmonary tumors. Our purpose was to define esophageal dosimetric parameters that predict potentially dose-limiting toxicities. **MATERIALS AND METHODS:** In total, 157 patients with a planning target volume ≤5 cm from the esophagus were selected from an institutional database. Toxicity was scored with the CTCAE v4.0. Esophageal Dmax and Dv (dose D in Gy covering volume v in mL) in 0.5 mL increments were collected. Corresponding biologically effective dose (BED) was calculated for α/β=10,3 (BED10, BED3). Normal tissue complication probability was computed with conventionally fractionated radiotherapy parameters and equivalent dose in 2 Gy per fraction (EQD2). Dosimetric predictors were identified with multivariate logistic regression with a manual forward stepwise selection technique. **RESULTS:** The grade≥2 esophagitis rate was 5.7%. BED10 to 1.5 mL was the best predictor of esophagitis. BED10 to 0.5, 1.0, 2.0, 3.0, and 3.5 mL were also predictive but less strong. Results were similar when BED3 and physical dose were examined. Tumor-esophageal distance correlated with esophagitis (10.5% risk of≥grade 2 events with distance≤3.9 cm vs. 1.3% when>3.9 cm, P=0.016). BED10 to 1.5 mL correlated well with EQD2 normal tissue complication probability estimates. **CONCLUSIONS:** BED to 1.5 mL was the strongest predictor of grade≥2 esophagitis (independent of α/β ratio) with a 10.6% toxicity risk when BED10>21.1 Gy (14.3 Gy in 3 fractions, 16.0 Gy in 5). The overall rate of severe toxicity is low, suggesting that higher doses may be tolerable.

[Prognostic factors affecting survival after whole brain radiotherapy in patients with brain metastasized lung cancer.](#)
Tsakonas G1,2, Hellman F1, Gubanski M1, Friesland S1, Tendler S1,2, Lewensohn R1,2, Ekman S1,2, de Petris L1,2. Acta Oncol. 2017 Oct 6:1-8. doi: 10.1080/0284186X.2017.1386799. [Epub ahead of print]
BACKGROUND: Whole-brain radiotherapy (WBRT) has been the standard of care for multiple NSCLC brain metastases but due to its toxicity and lack of survival benefit, its use in the palliative setting is being questioned. **PATIENT AND METHODS:** This was a single institution cohort study including brain metastasized lung cancer patients who received WBRT at Karolinska University Hospital. Information about Recursive Partitioning Analysis (RPA) and Graded Prognostic Assessment (GPA) scores, demographics, histopathological results and received oncological therapy were collected. Predictors of overall survival (OS) from the time of received WBRT were identified by Cox regression analyses. OS between GPA and RPA classes were compared by pairwise log rank test. A subgroup OS analysis was performed stratified by RPA class. **RESULTS:** The cohort consisted of 280 patients. RPA 1 and 2 classes had better OS compared to class 3, patients with GPA <1.5 points had better OS compared to GPA≥ 1.5 points and age >70 years was associated with worse OS (p< .0001 for all comparisons). In RPA class 2 subgroup analysis GPA ≥1.5 points, age ≤70 years and CNS surgery before salvage WBRT were independent positive prognostic factors. **CONCLUSIONS:** RPA class 3 patients should not receive WBRT, whereas RPA class 1 patients should receive WBRT if clinically indicated. RPA class 2 patients with age ≤70 years and GPA ≥1.5 points should be treated as RPA 1. WBRT should be omitted in RPA 2

patients with age >70. In RPA 2 patients with age ≤70 years and GPA <1.5 points WBRT could be a reasonable option.

[Role of Patient Coping Strategies in Understanding the Effects of Early Palliative Care on Quality of Life and Mood.](#) Greer JA1, Jacobs JM1, El-Jawahri A1, et al. J Clin Oncol. 2017 Nov 15:JCO2017737221. doi: 10.1200/JCO.2017.73.7221. [Epub ahead of print]
PURPOSE: The early integration of oncology and palliative care (EIPC) improves quality of life (QOL) and mood for patients with advanced cancer. However, the mechanisms by which EIPC benefits these outcomes remain unclear. We therefore examined whether EIPC improved patients' coping strategies and if changes in coping accounted for intervention effects on QOL and depressive symptoms. Patients and **METHODS:** For this secondary analysis of an EIPC trial, we examined data from 350 patients with newly diagnosed incurable lung or GI cancer. Participants completed assessments of QOL (Functional Assessment of Cancer Therapy-General), depressive symptoms (Patient Health Questionnaire-9), and coping (Brief COPE) at baseline and 24 weeks. We used linear regression to test intervention effects on use of coping strategies and mediation regression models with bias-corrected bootstrapping to examine whether improvements in coping mediated the effects of early palliative care on patient-reported outcomes. **RESULTS:** Compared with usual oncology care, EIPC significantly increased patient use of approach-oriented coping strategies (B = 1.09; SE = 0.44; P = .01) and slightly reduced use of avoidant strategies (B = -0.44; SE = 0.23; P = .06) from baseline to 24 weeks. Also, the increased use of approach-oriented coping and reduction in avoidant coping were associated with higher QOL and lower depressive symptoms at 24 weeks. The positive changes in approach-oriented coping, but not avoidant coping, significantly mediated the effects of EIPC on QOL (indirect effect, 1.27; 95% CI, 0.33 to 2.86) and depressive symptoms (indirect effect, -0.39; 95% CI, -0.87 to -0.08). **CONCLUSION:** Patients with incurable cancer who received EIPC showed increased use of approach-oriented coping, which was associated with higher QOL and reduced depressive symptoms. Palliative care may improve these outcomes by providing patients with the skills to cope effectively with life-threatening illness.

SMALL CELL LUNG CANCER - SCLC

[The role of prophylactic cranial irradiation for patients with small-cell lung cancer.](#) Nakahara Y1, Sasaki J2, Fukui T1, Otani S1, Igawa S1, Hayakawa K3, Masuda N1. Jpn J Clin Oncol. 2017 Oct 25:1-5. doi: 10.1093/jjco/hyx146. [Epub ahead of print]
Small-cell lung cancer (SCLC) has a particular propensity to metastasize to the brain, affecting ~10% of SCLC patients at diagnosis, but may occur in more than 50% of 2-year survivors. Most cytotoxic drugs have limited ability to cross the blood-brain barrier, and the effectiveness of chemotherapy for brain metastasis is limited. Therefore, prophylactic cranial irradiation (PCI) has been proposed to treat SCLC. A meta-analysis revealed that PCI significantly decreased the risk of brain metastasis and increased the 3-year survival rate; it has been established as a standard therapy for limited-disease SCLC. However, certain aspects of PCI remain unclarified, including the roles in resected SCLC and extensive-disease SCLC, and its neurotoxicities. In addition, information on PCI has been obtained from old clinical trials without the use of new imaging devices, such as magnetic resonance imaging. Evidence from advanced imaging techniques is needed in this era.

[Prophylactic Cranial Irradiation for Extensive Small-Cell Lung Cancer.](#) Schild SE1, Sio TT1, Daniels TB1, Chun SG1, Rades D1. Oncol Pract. 2017 Nov;13(11):732-738. doi: 10.1200/JOP.2017.026765.
Small-cell lung cancer (SCLC) has a high predilection for metastasizing to the brain after chemotherapy. This has been blamed on the blood-brain barrier, which prevents chemotherapy from penetrating into the

brain, thus creating a sanctuary site. It has been estimated that up to three quarters of patients with SCLC will eventually develop brain metastases. This led investigators to administer prophylactic cranial irradiation (PCI) to decrease this risk. Several trials were performed in patients with SCLC after initial therapy (chemotherapy with or without thoracic radiotherapy) that compared the outcomes of PCI versus no PCI. Early trials generally found that PCI significantly decreased the risk of brain metastases but did not significantly improve survival. These trials were re-evaluated in two larger meta-analyses that included patients with either limited-stage SCLC or extensive-stage SCLC (ESCLC). Both meta-analyses reported that PCI significantly decreased brain metastases and improved survival in patients who had a complete response following initial therapy. These studies were performed before the advent of modern imaging with computed tomography or magnetic resonance imaging (MRI). There have been two modern trials of PCI versus no PCI in patients with ESCLC and both found that PCI decreases brain metastases. The first did not include brain MRI before registration and found that PCI improved survival, whereas the second study did include MRI before registration and at frequent intervals thereafter. That trial found that PCI did not confer a survival advantage. This review will examine the evidence and provide recommendations regarding the role of PCI for patients with ESCLC.

Randomized Phase III Trial of Low Molecular Weight Heparin Enoxaparin in Addition to Standard Treatment in Small Cell Lung Cancer: the RASTEN Trial. Ek L1, Gezelius E2,3, Bergman B4, et al. Ann Oncol. 2017 Nov 2. doi: 10.1093/annonc/mdx716. [Epub ahead of print]

BACKGROUND: Coagulation activation and venous thromboembolism (VTE) are hallmarks of malignant disease and represent a major cause of morbidity and mortality in cancer. Coagulation inhibition with low molecular weight heparin (LMWH) may improve survival specifically in small cell lung cancer (SCLC) patients by preventing VTE and tumor progression; however, randomized trials with well-defined patient populations are needed to obtain conclusive data. The aim of RASTEN was to investigate the survival effect of LMWH enoxaparin in a homogenous population of SCLC patients. **PATIENTS AND METHODS:** We performed a randomized, multicenter, open-label trial to investigate the addition of enoxaparin at a supraprophylactic dose (1 mg/kg) to standard treatment in patients with newly diagnosed SCLC. The primary outcome was overall survival (OS), and secondary outcomes were progression-free survival (PFS), incidence of VTE and hemorrhagic events. **RESULTS:** In RASTEN, 390 patients were randomized over an 8-year period (2008-2016), of which 186 and 191 were included in the final analysis in the LMWH and control arm, respectively. We found no evidence of a difference in OS or PFS by the addition of enoxaparin (HR 1.11; 95% CI: 0.89-1.38, P=0.36 and HR 1.18; 95% CI: 0.95-1.46, P=0.14, respectively). Subgroup analysis of patients with limited and extensive disease did not show reduced mortality by enoxaparin. The incidence of VTE was significantly reduced in the LMWH arm (HR 0.31; 95% CI: 0.11-0.84, P=0.02). Hemorrhagic events were more frequent in the LMWH-treated group but fatal bleedings occurred in both arms. **CONCLUSION:** LMWH enoxaparin in addition to standard therapy did not improve OS in SCLC atients, despite being administered at a supraprophylactic dose and despite resulting in a significant reduction in VTE incidence. Addition of LMWH cannot be generally recommended in the management of SCLC patients, and predictive biomarkers of VTE and LMWH-associated bleeding in cancer patients are warranted. ClinicalTrials.gov: NCT00717938.

Paclitaxel as third-line chemotherapy for small cell lung cancer failing both etoposide- and camptothecin-based chemotherapy. Kim SH1, Kim MJ, Kim YJ, Chang H, Kim JW, Lee JO, Lee KW, Kim JH, Bang SM, Lee JS. Medicine (Baltimore). 2017 Oct;96(42):e8176. doi: 10.1097/MD.0000000000008176.

Paclitaxel has been shown to have clinical activity in the treatment of small cell lung cancer (SCLC). However, its role as third-line chemotherapy for SCLC after both etoposide- and camptothecin-based

regimens has not been clarified.All patients with refractory SCLC who were treated with paclitaxel-based regimen as third-line chemotherapy between 2005 and 2011 in Seoul National University Bundang Hospital were reviewed retrospectively. Forty patients previously treated with both etoposide- and camptothecin-based chemotherapy were included. The median age of the enrolled patients was 67 years (range, 35-86 years). Most patients (77.5%) received cisplatin plus etoposide as first-line therapy, and camptothecins such as irinotecan or topotecan as second-line therapy. Of 34 patients with measurable lesions, 8 patients (23.5%) achieved partial response and 9 (26.5%) had stable disease. The median progression-free survival (PFS) and overall survival (OS) were 2.5 and 5.9 months, respectively. Predictive factors for OS were performance status (PS) (PS <2 vs ≥2; P=.001), the presence of liver metastasis (P<.001), and number of metastatic sites (<3 vs ≥3; P=.047) in univariate analysis. PS and liver metastasis also remained statistically significant in multivariate analysis. Grade 3 or 4 hematologic toxicity was 20% for neutropenia, and 10% for thrombocytopenia. Other common non-hematological toxicities were peripheral neuropathy and mild liver enzyme elevation.Paclitaxel-based chemotherapy showed modest activity in SCLC patients refractory to both etoposide- and camptothecin-based chemotherapy. PS and presence of liver metastasis were predictive of survival after paclitaxel chemotherapy.

Antitumor activity of lurbinectedin (PM01183) and doxorubicin in relapsed small-cell lung cancer: results from a phase I study. Calvo E1, Moreno V2, Flynn M3, et al. Ann Oncol. 2017 Oct 1;28(10):2559-2566. doi: 10.1093/annonc/mdx357.
BACKGROUND: Lurbinectedin (PM01183) has synergistic antitumor activity when combined with doxorubicin in mice with xenografted tumors. This phase I trial determined the recommended dose (RD) of doxorubicin (bolus) and PM01183 (1-h intravenous infusion) on day 1 every 3 weeks (q3wk), and obtained preliminary evidence of antitumor activity for this combination in small-cell lung cancer (SCLC). **PATIENTS AND METHODS:** Patients with advanced solid tumors received doxorubicin and PM01183 following a standard dose escalation design and expansion at the RD. Twenty-seven patients had relapsed SCLC: 12 with sensitive disease (platinum-free interval ≥90 days) and 15 with resistant disease (platinum-free interval <90 days). **RESULTS:** Doxorubicin 50 mg/m2 and PM01183 4.0 mg flat dose was the RD. In relapsed SCLC, treatment tolerance at the RD was manageable. Transient and reversible myelosuppression (including neutropenia, thrombocytopenia, and febrile neutropenia) was the main toxicity, managed with dose adjustment and colony-stimulating factors. Fatigue (79%), nausea/vomiting (58%), decreased appetite (53%), mucositis (53%), alopecia (42%), diarrhea/constipation (42%), and asymptomatic creatinine (68%) and transaminase increases (alanine aminotransferase 42%; aspartate aminotransferase 32%) were common, and mostly mild or moderate. Complete (n = 2, 8%) and partial response (n = 13, 50%) occurred in relapsed SCLC, mostly at the RD. Response rates at second line were 91.7% in sensitive disease [median progression-free survival (PFS)=5.8 months] and 33.3% in resistant disease (median PFS = 3.5 months). At third line, response rate was 20.0% (median PFS = 1.2 months), all in resistant disease. **CONCLUSION:** Doxorubicin 50 mg/m2 and PM01183 4.0 mg flat dose on day 1 q3wk has shown remarkable activity, mainly in second line, with manageable tolerance in relapsed SCLC, leading to further evaluation of this combination within an ongoing phase III trial.

Receipt of thoracic radiation therapy and radiotherapy dose are correlated with outcomes in a retrospective study of three hundred and six patients with extensive stage small-cell lung cancer.
Li-Ming X1, Zhao LJ2, Simone CB 2nd3, et al. Radiother Oncol. 2017 Oct 24. pii: S0167-8140(17)32634-8. doi: 10.1016/j.radonc.2017.10.005. [Epub ahead of print]
BACKGROUND: The importance of the thoracic radiation therapy (TRT) dose has not been clearly defined in extensive stage small-cell lung cancer (ES-SCLC) and it is unclear whether improved TRT

dose translates into a survival benefit. **METHODS:** 306 patients with ES-SCLC were retrospectively reviewed, of which 170 received IMRT/CRT fractionation RT after ChT, and 136 received chemotherapy (ChT) alone. We adopted the time-adjusted BED (tBED) for effective dose fractionation calculation. Due to the nonrandomized nature of this study, we compared the ChT+RT with ChT groups that matched on possible confounding variables. **RESULTS:** Patients achieved 2-year OS, PFS and LC rates of 19.7%, 10.7% and 28.4%, respectively. After propensity score matching, (113 cases for each group), the rates of OS, PFS and LC at 2 years were 21.4%, 7.7% and 34.5% for ChT+TRT, and 10.3% (p<0.001), 4.6% (p<0.001) and 6.3% for ChT only (p<0.001), respectively. Among propensity score matching patients, 56 cases for each group received the high dose (tBED>50 Gy) TRT and received low dose (tBED≤50 Gy) TRT. Two-year OS, PFS and LC rates were 32.3%, 15.3% and 47.1% for the high dose compared with 17.0% (p<0.001), 12.9% (p=0.097) and 34.7% (p=0.029) for low dose radiotherapy. **CONCLUSIONS:** TRT added to ChT improved ES-SCLC patient OS. High dose TRT improved OS over lower doses. Our results suggest that high-dose thoracic radiation therapy may be a reasonable consideration in select patients with ES-SCLC.

[Intensified Beclin-1 Mediated by Low Expression of Mir-30a-5p Promotes Chemoresistance in Human Small Cell Lung Cancer.](#)

Yang X1, Bai F1, Xu Y2, Chen Y1,2, Chen L1,2. Cell Physiol Biochem. 2017 Oct 5;43(3):1126-1139. doi: 10.1159/000481754. [Epub ahead of print]

BACKGROUND/AIMS: Although small cell lung cancer (SCLC) is sensitive to initial chemotherapy, patients experience tumor recurrence and metastasis, leading to treatment failure. Autophagy as a protective pattern for cell survival in the harsh environment plays an important role in chemoresistance. However, the role of Beclin-1, a key regulator of autophagy in the drug-resistance of SCLC cells is still poorly understood. In the current study, we focused on the effect and regulation of Beclin-1 in chemoresistance of SCLC cells. **METHODS:** We analyzed the levels of Beclin-1 in etoposide/cisplatin (EP) -resistant and -sensitive cell lines, as well as the relationship between Beclin-1 and patients' chemosensitivity. The function of Beclin-1 in chemoresistant SCLC cells in vitro was measured by MTT, WB, colony formation and flow cytometric analysis. Further rescue experiment was performed after co-transfected with siBeclin-1 and miR-30a mimics or inhibitor. **RESULTS:** Beclin-1 was upregulated in drug-resistant cells and patients with lower sensitivity to etoposide/cisplatin therapy. Downregulated Beclin-1 attenuated drug sensitivity and colony formation ability of chemoresistant cells. Moreover, inhibition of Beclin-1 resulted in a dramatic decline of autophagy and increase of apoptosis in drug-resistant cells, accompanied by a remarkable reduction in S phase and a raise in G2/M phase of cell cycle. The transfection with miR-30a-5p mimics exhibited an opposite effect. In addition, inhibition of Beclin-1 could partly reverse the effect induced by miR-30a-5p suppression in drug-sensitive cells. **CONCLU-SION:** Beclin-1 regulated by miR-30a-5p plays a notable role in the drug-resistance of SCLC. Inhibition of Beclin-1 by induction of miR-30a-5p may improve the therapeutic outcome via resensitizing the drug-resistant cells to chemotherapy in SCLC.

[Small-cell lung cancer: what we know, what we need to know and the path forward.](#)

Gazdar AF1,2, Bunn PA3, Minna JD1,4. Nat Rev Cancer. 2017 Oct 27. doi: 10.1038/nrc.2017.87. [Epub ahead of print]

Small-cell lung cancer (SCLC) is a deadly tumour accounting for approximately 15% of lung cancers and is pathologically, molecularly, biologically and clinically very different from other lung cancers. While the majority of tumours express a neuroendocrine programme (integrating neural and endocrine properties), an important subset of tumours have low or absent expression of this programme. The probable initiating molecular events are inactivation of TP53 and RB1, as well as frequent disruption of several signalling networks, including Notch signalling. SCLC, when diagnosed, is usually widely metastatic and initially responds to cytotoxic therapy but nearly always rapidly relapses with resistance to

further therapies. There were no important therapeutic clinical advances for 30 years, leading SCLC to be designated a 'recalcitrant cancer'. Scientific studies are hampered by a lack of tissue availability. However, over the past 5 years, there has been a worldwide resurgence of studies on SCLC, including comprehensive molecular analyses, the development of relevant genetically engineered mouse models and the establishment of patient-derived xenografts. These studies have led to the discovery of new potential therapeutic vulnerabilities for SCLC and therefore to new clinical trials. Thus, while the past has been bleak, the future offers greater promise.

Glycobiomarker, Fucosylated Short-Form Secretogranin III Levels Are Increased in Serum of Patients with Small Cell Lung Carcinoma. Togayachi A, Iwaki J, Kaji H, et al. J Proteome Res. 2017 Oct 12. doi: 10.1021/acs.jproteome.7b00484. [Epub ahead of print]
Secretogranin III (SgIII) is a member of the chromogranin/secretogranin family of neuroendocrine secretory proteins. Granins are expressed in endocrine and neuroendocrine cells and subsequently processed into bioactive hormones. Although granin-derived peptide expression is correlated with neuroendocrine carcinomas, little is known about SgIII. We previously identified SgIII by a comparative glycoproteomics approach for elucidation of glycobiomarker candidates in lung carcinoma. Here, we examined the expression, secretion, and glycosylation of SgIII to identify novel biomarkers of small cell lung carcinoma (SCLC). In comparative immunohistochemical analysis and secretion profiling, SgIII was observed in all types of lung cancer. However, low-molecular-weight SgIII (short-form SgIII) was specifically found in SCLC culture medium. Glycoproteomics analysis showed that a fucosylated glycan was attached to the first of three potential N-glycosylation sites and an unfucosylated glycan was detected on the second site; however, the third site was not glycosylated. Next, we performed lectin capture with a fucose-binding lectin and detected short-form SgIII specifically in the sera of patients with SCLC. The results suggested an association between the fucosylated glycoform of short-form SgIII and SCLC. Thus, fucosylated short-form SgIII may be a valuable biomarker for SCLC and could be used to monitor development of the disease. All MS data are available via ProteomeXchange and jPOST with identifiers

The Prognosis of Small Cell Lung Cancer in Patients with Pulmonary Fibrosis. Matsumoto Y1, Ohara S2, Furukawa R2, Usui K2. Anticancer Res. 2017 Oct;37(10):5791-5795.
BACKGROUND/AIM: The purpose of this study was to assess the prognosis of small cell lung cancer (SCLC) based on the underlying pulmonary disease. **PATIENTS AND METHODS:** A total of 204 patients with SCLC were reviewed and categorized into three groups: normal, emphysema and fibrosis. **RESULTS:** The median overall survival duration (OS) in patients with normal lungs (n=57), with emphysema (n=105) and fibrosis (n=42) was 21.3, 16.4 and 10.8 months (p=0.063). In limited-stage disease (LD), the median OS in patients with fibrosis (7.4 months) was shorter than normal (52.7 months) or emphysema patients (26.4 months) (p=0.034). In extensive-stage disease (ED), the median OS in patients with fibrosis (12.7 months) was not significantly different from normal (11.4 months) or emphysema patients (13.5 months) (p=0.600). **CONCLUSION:** Patients with fibrosis had a poorer prognosis than normal or emphysema patients in LD-SCLC, but the coexistence of pulmonary fibrosis did not affect the prognostic outcomes in ED-SCLC.

Common TDP1 polymorphisms in relation to survival among small cell lung cancer patients: a multicenter study from the International Lung Cancer Consortium. Lohavanichbutr P1, Sakoda LC2, Amos CI3, et al. Clin Cancer Res. 2017 Oct 3. pii: clincanres.1401.2017. doi: 10.1158/1078-0432.CCR-17-1401. [Epub ahead of print]
PURPOSE: DNA topoisomerase inhibitors are commonly used for treating small cell lung cancer (SCLC). Tyrosyl-DNA phosphodiesterase (TDP1) repairs DNA damage caused by this class of drugs and may therefore influence treatment outcome. In this study, we investigated whether common TDP1 single

nucleotide polymorphisms (SNPs) are associated with overall survival among SCLC patients. **EXPERIMENTAL DESIGN:** Two TDP1 SNPs (rs942190 and rs2401863) were analyzed in 890 patients from 10 studies in the International Lung Cancer Consortium (ILCCO). The Kaplan-Meier method and Cox regression analyses were used to evaluate genotype associations with overall mortality at 36 months post-diagnosis, adjusting for age, sex, race, and tumor stage. **RESULTS:** Patients homozygous for the minor allele (GG) of rs942190 had poorer survival compared to those carrying AA alleles, with a hazard ratio (HR) of 1.36 (95% confidence interval (CI): 1.08-1.72, p-value=0.01), but no association with survival was observed for patients carrying the AG genotype (HR=1.04, 95% CI:0.84-1.29, p-value=0.72). For rs2401863, patients homozygous for the minor allele (CC) tended to have better survival than patients carrying AA alleles (HR=0.79, 95% CI: 0.61-1.02, p-value=0.07). Results from the Genotype Tissue Expression (GTEx) Project, the Encyclopedia of DNA Elements (ENCODE), and the ePOSSUM web application support the potential function of rs942190. **CONCLUSIONS:** We found the rs942190 GG genotype to be associated with relatively poor survival among SCLC patients. Further investigation is needed to confirm the result and to determine whether this genotype may be a predictive marker for treatment efficacy of DNA topoisomerase inhibitors.

[HSP90 inhibitor (NVP-AUY922) enhances the anti-cancer effect of BCL-2 inhibitor (ABT-737) in small cell lung cancer expressing BCL-2.](#)
Yang H1, Lee MH2, Park I1, et al. Cancer Lett. 2017 Oct 4;411:19-26. doi: 10.1016/j.canlet.2017.09.040. [Epub ahead of print]
Small cell lung cancer (SCLC) cannot be efficiently controlled using existing chemotherapy and radiotherapy approaches, indicating the need for new therapeutic strategies. Although ABT-737, a B-cell lymphoma-2 (BCL-2) inhibitor, exerts anticancer effects against BCL-2-expressing SCLC, monotherapy with ABT-737 is associated with limited clinical activity because of the development of resistance and toxicity. Here, we examined whether combination therapy with ABT-737 and heat shock protein 90 (HSP90) inhibitor NVP-AUY922 exerted synergistic anticancer effects on SCLC. We found that the combination of ABT-737 and NVP-AUY922 synergistically induced the apoptosis of BCL-2-expressing SCLC cells. NVP-AUY922 downregulated the expression of AKT and ERK, which activate MCL-1 to induce resistance against ABT-737. The synergistic effect was also partly due to blocking NF-κB activation, which induces anti-apoptosis protein expressions. However, interestingly, targeting BCL-2 and MCL-1 or BCL2 and NF-κB did not induce the cytotoxicity. In conclusion, our study showed that combination of BCL2 inhibitor with HSP90 inhibitor increased activity in in vitro and in vivo study in only BCL-2 expressing SCLC compared to either single BCL2 inhibitor or HSP inhibitor. The enhanced activity might be led by blocking several apoptotic pathways simultaneously rather than a specific pathway.

PALLIATIVE AND SUPPORTIVE CARE

[Risk of rash associated with vandetanib treatment in non-small-cell lung cancer patients: A meta-analysis of 9 randomized controlled trials.](#) Liu Y1, Qi M, Hou S, Shao L, Zhang J, Li Y, Liu Q.
Medicine (Baltimore). 2017 Oct;96(43):e8345. doi: 10.1097/MD.0000000000008345.
BACKGROUND: Vandetanib is a promising anticancer target agent for treating advanced carcinomas, such as non-small-cell lung cancer (NSCLC) and breast cancer. Rash is a frequently reported adverse event of vandetanib. We conducted this meta-analysis to determine the incidence rate and overall risks of all-grade and high-grade rash with vandetanib in NSCLC patients. **METHODS:** PubMed, Embase, Web of Science, American Society of Clinical Oncology, and Cochrane Library were systematically searched to identify studies with vandetanib and rash in NSCLC patients. Data were extracted to calculate the pooled incidence of all-grade and high-grade (grade ≥3) rash caused by vandetanib treatment. **RESULTS:**

Nine randomized controlled trials involving 4893 patients met the inclusion criteria and were included in this meta-analysis. The overall incidence of all-grade and high-grade rash caused by vandetanib treatment was 46% (95% CI: 37.1%, 54.8%), and 3.2% (95% CI: 1.4%, 5.1%), respectively. The risk ratios (RR) of all-grade and high-grade rash for vandetanib treatment versus control treatment were 2.35 (95% CI: 1.20, 4.61; P<.001) and 4.68 (95% CI 1.42, 15.37; P<.001), respectively. Subgroup analysis suggested that the increased risk of all-grade rash was clear across all subgroups, including first-line/second-line therapy, phase 2/phase 3 trial, sample size </>200, a dosage of 100 or 300mg, and monotherapy/combination therapy. However, for the high-grade rash, vandetanib did not increase the risk of rash when it was used in first-line therapy, or in a phase II trial, or in a trial with sample size <200. **CONCLUSIONS:** This study suggests that vandetanib was associated with a significantly increased risk of rash. Therefore, early recognition and appropriate monitoring should be taken when NSCLC patients were treated with vandetanib.

[Reducing Symptom Distress in Patients With Advanced Cancer Using an e-Alert System for Caregivers: Pooled Analysis of Two Randomized Clinical Trials.](#) Gustafson DH1, DuBenske LL2, Atwood AK1, et al. J Med Internet Res. 2017 Nov 14;19(11):e354. doi: 10.2196/jmir.7466.
BACKGROUND: Symptom distress in patients toward the end of life can change rapidly. Family caregivers have the potential to help patients manage those symptoms, as well as their own stress, if they are equipped with the proper resources. Electronic health (eHealth) systems may be able to provide those resources. Very sick patients may not be able to use such systems themselves to report their symptoms but family caregivers could. **OBJECTIVE:** The aim of this paper was to assess the effects on cancer patient symptom distress of an eHealth system that alerts clinicians to significant changes in the patient's symptoms, as reported by a family caregiver. **METHODS:** A pooled analysis from two randomized clinical trials (NCT00214162 and NCT00365963) compared outcomes at 12 months for two unblinded groups: a control group (Comprehensive Health Enhancement Support System [CHESS]-Only) that gave caregivers access to CHESS, an online support system, and an experimental group (CHESS+CR [Clinician Report]), which also had CHESS but with a CR that automatically alerted clinicians if symptoms exceeded a predetermined threshold of severity. Participants were dyads (n=235) of patients with advanced lung, breast, or prostate cancer and their respective family caregivers from 5 oncology clinics in the United States of America. The proportion of improved patient threshold symptoms was compared between groups using area-under-the-curve analysis and binomial proportion tests. The proportion of threshold symptoms out of all reported symptoms was also examined. **RESULTS:** When severe caregiver-reported symptoms were shared with clinicians, the symptoms were more likely to be subsequently reported as improved than when the symptoms were not shared with clinicians (P<.001). Fewer symptom reports were completed in the group of caregivers whose reports went to clinicians than in the CHESS-Only group (P<.001), perhaps because caregivers, knowing their reports might be sent to a doctor, feared they might be bothering the clinician. **CONCLUSIONS:** This study suggests that an eHealth system designed for caregivers that alerts clinicians to worrisome changes in patient health status may lead to reduced patient distress.

[Managing, making sense of and finding meaning in advanced illness: a qualitative exploration of the coping and wellbeing experiences of patients with lung cancer.](#) Harrop E1, Noble S1, Edwards M1, Sivell S1, Moore B2, Nelson A1. Sociol Health Illn. 2017 Oct 16. doi: 10.1111/1467-9566.12601. [Epub ahead of print]
Coping plays an essential role in maintaining the wellbeing of patients with cancer. A number of different coping responses and strategies have been identified in the literature. The value and relevance of meaning based coping theory has also been emphasised, including Antonovosky's Sense of Coherence (SoC) theory. Ten patients with advanced lung cancer were interviewed up to three times. A total of twenty in

depth interviews were carried out, fully transcribed and data were analysed following a methodology of Interpretative Phenomenological Analysis. Three broad domains were identified to categorise the core life concerns of participants; making sense of and managing one's illness; maintaining daily life and relationships and confronting the future. Within these domains multiple coping themes are identified, which to varying degrees help to maintain patient wellbeing and quality of life. This article considers the relevance of SoC theory for understanding the coping experiences of patients with advanced cancer, and identifies resources and factors likely to support patient coping, with implications for health and social care services.

[Psychological distress and coping strategies among women with incurable lung cancer: a qualitative study.](#) Liao YC1, Liao WY2, Sun JL3, Ko JC4, Yu CJ2. Support Care Cancer. 2017 Oct 10. doi: 10.1007/s00520-017-3919-x. [Epub ahead of print]
PURPOSE: Limited research has focused on women with lung cancer (LC) although they are recognized as the most vulnerable to psychological distress. This study explored in-depth the psychological distress experienced by women with incurable LC and analyzed the coping strategies with which they manage that distress. **METHODS:** A qualitative methodology with in-depth interviews was employed for 34 women with advanced or recurrent LC. An inductive data-driven thematic analysis was applied to analyze transcripts. **RESULTS:** Psychological distress was an iterative process for the women. Four themes were identified: shock regarding the diagnosis, distress regarding cancer treatment and its side effects, the facing of a recurrent or progressive disease, and persistent struggle with the life-limiting disease. Various coping strategies applied by the women to manage psychological distress were grouped into four themes: relying upon social support, focusing on positive thoughts, avoidance-based strategies, and religious faith and acceptance. **CONCLUSIONS:** Women with incurable LC experienced substantial iterative psychological distress throughout the illness, regardless of length of illness at time of interview. They applied multiple forms of coping. The findings enrich the limited existing literature on this understudied population and provide direction for the future development of interventions to improve their psychological well-being.

[Objective and subjective financial burden and its associations with health-related quality of life among lung cancer patients.](#) Chen JE1, Lou VW1,2, Jian H3, Zhou Z3, Yan M3, Zhu J4, Li G4, He Y5. Support Care Cancer. 2017 Nov 6. doi: 10.1007/s00520-017-3949-4. [Epub ahead of print]
PURPOSE: The purpose of this study is to examine the effect of financial burden, using objective and subjective indicators, on the health-related quality of life (HRQOL) in lung cancer patients. **METHOD:** A total of 227 patients diagnosed with lung cancer (from the inpatient unit of the department of internal medicine-chest oncology, in Shanghai Chest Hospital, China) participated in the study. Financial information was measured by direct medical costs, direct nonmedical costs, healthcare-cost-to-income ratio, and perceived financial difficulty. HRQOL was measured using the Functional Assessment of Cancer Therapy-Lung (FACT-L) scale. **FINDINGS:** Catastrophic health spending, defined as a healthcare-cost-to-income ratio of more than 40%, was reported in 72.7% of the participants, whereas 37.0% reported that healthcare costs exceeded annual household income. Financial difficulty was perceived in 83.7% of the participants. Patients whose healthcare costs exceeded their annual household income and who perceived financial difficulty reported a clinically meaningful difference in overall HRQOL (> 6 points on the FACT-L) compared with participants without catastrophic health spending or perceived financial difficulty. Healthcare costs did not show a significant effect on HRQOL. **CONCLUSION:** Healthcare costs exceeding total annual household income and perceived financial difficulty are associated with poorer HRQOL in lung cancer patients. Subjective indicator of financial burden has a stronger effect on quality of life than objective indicators. **IMPLICATION:** Health-cost-to-income ratio and perceived financial difficulty can be implied as objective and subjective indicators of

financial burden to identify the patients who may need additional assistance. Communication on deciding on cost-effective treatments can be facilitated.

[Preventing chemotherapy-induced nausea and vomiting in patients with lung cancer: efficacy of NEPA (netupitant-palonosetron), the first combination antiemetic.](#) Hesketh PJ1, Palmas M2, Nicolas P3. Support Care Cancer. 2017 Oct 28. doi: 10.1007/s00520-017-3936-9. [Epub ahead of print]
PURPOSE: Patients receiving platinum-based chemotherapy are at high risk of chemotherapy-induced nausea and vomiting (CINV), a distressing side effect of treatment. This post-hoc subgroup analysis of two pivotal trials evaluated the efficacy of NEPA in preventing CINV in subsets of patients with lung cancer who received cisplatin or carboplatin. **METHODS:** In each study, the efficacy endpoints complete response (CR; defined as no emetic episodes and no rescue medication) and no significant nausea (NSN; defined as a score of < 25 mm on a visual analog scale of 0-100 mm) during the acute (0-24 h), delayed (25-120 h), and overall (0-120 h) phases post-chemotherapy in cycle 1 (study 1) and cycles 1-4 (study 2) were assessed. Safety was evaluated by recording treatment-emergent adverse events (AEs) and treatment-related AEs. **RESULTS:** NEPA treatment resulted in high CR rates across the acute, delayed, and overall phases (cisplatin: > 88% overall CR; carboplatin: > 75% overall CR), with higher CR rates for NEPA-treated patients than those receiving palonosetron; moreover, CR rates were sustained over multiple chemotherapy cycles (> 75%). High rates of NSN observed during cycle 1 (> 79%) were also maintained over multiple chemotherapy cycles. NEPA was well tolerated in all patients. **CONCLUSIONS:** NEPA appears to be effective and well tolerated in patients with lung cancer receiving platinum-based chemotherapy, across the acute, delayed, and overall phases and throughout multiple cycles. As a highly effective oral combination antiemetic agent administered as a single dose once per cycle, NEPA may offer a convenient, simplified prophylactic antiemetic.

["Lost to Follow-up" Among Adult Cancer Survivors.](#) Gill A1, Gosain R, Bhandari S, Gosain R, Gill G, Abraham J, Miller K. Am J Clin Oncol. 2017 Oct 12. doi: 10.1097/COC.0000000000000408. [Epub ahead of print]
BACKGROUND: Follow-up cancer care is important for patients who have received IV chemotherapy but some patients discontinue their care and are lost to follow-up (LFU) at the cancer center where they were treated. The purpose of this study was to determine what proportion of cancer survivors are LFU at 5 years after treatment, the timing of LFU, and the characteristics of those who do not continue survivorship care. **METHODS:** Adult patients with cancer who were treated with chemotherapy at a large community teaching hospital in 2006 and 2007 were identified and linked with State tumor registry data. Hospital medical records were reviewed to obtain information on demographics, diagnosis, treatment, and date of last follow-up visit. Characteristics of patients with ≥5 years of follow-up care were compared with those who were LFU. **RESULTS:** In total, 487 patients received chemotherapy and 304 died (62%) during the 5-year follow-up period. Among the 183 cancer patients who were known to be alive at 5 years, 92 (50%) were LFU and 50% (46/92) of this LFU group were LFU within 1 year of diagnosis. At 5 years, follow-up care was continuing for 55% of women, compared with 39% of men. The highest proportion of follow-up was observed among lung cancer patients (84%), followed by patients with breast cancers (63%) and gastrointestinal cancers (40%). Patients with hematological cancers had the lowest follow-up proportion at 5 years (29%) (P<0.05). Follow-up was not significantly associated with age (P=0.48), insurance status(P=0.29), and race(P=0.06). **CONCLUSIONS:** It is estimated that 65% of the cancer survivors in the United States are ≥5 years beyond their diagnosis but there is little data on oncology follow-up rates. In our retrospective study of 183 patients who were treated with chemotherapy only 49.7% continue to follow-up at their treatment center. LFU has important implications in planning long-term care strategies for cancer survivors and in survivorship research.

[**A randomized, double-blind, placebo-controlled, multicenter study of a ginger extract in the management of chemotherapy-induced nausea and vomiting (CINV) in patients receiving high-dose cisplatin.**](#) Bossi P1, Cortinovis D2, Fatigoni S3, et al. Ann Oncol. 2017 Oct 1;28(10):2547-2551. doi: 10.1093/annonc/mdx315.

BACKGROUND: The activity of ginger in the management of chemotherapy-induced nausea and vomiting (CINV) has been suggested, but design inadequacies, heterogeneity of the population, small numbers and poor quality of tested products limit the possibility to offer generalizable results. **PATIENTS AND METHODS:** We conducted a randomized, double-blind, placebo-controlled, multicenter study in patients planned to receive ≥2 chemotherapy cycles with high dose (>50 mg/m2) cisplatin. Patients received ginger 160 mg/day (with standardized dose of bioactive compounds) or placebo in addition to the standard antiemetic prophylaxis for CINV, starting from the day after cisplatin administration. CINV was assessed through daily visual-analogue scale and Functional Living Index Emesis questionnaires. The main objective was protection from delayed nausea; secondary end points included intercycle nausea and nausea anticipatory symptoms. **RESULTS:** In total, 121 patients received ginger and 123 placebo. Lung (49%) and head and neck cancer (HNC; 35%) were the most represented tumors. No differences were reported in terms of safety profile or compliance. The incidence of delayed, intercycle and anticipatory nausea did not differ between the two arms in the first cycle and second cycle. A benefit of ginger over placebo in Functional Living Index Emesis nausea score differences (day 6-day 1) was identified for females (P = 0.048) and HNC patients (P = 0.038). **CONCLUSIONS:** In patients treated with high-dose cisplatin, the daily addition of ginger, even if safe, did not result in a protective effect on CINV. The favorable effect observed on nausea in subgroups at particular risk of nausea (females; HNC) deserves specific investigation.

COMPLEMENTARY & ALTERNATIVE THERAPY

[**The efficacy of the Kampo medicine rikkunshito for chemotherapy-induced anorexia (RICH trial): study protocol for a randomized controlled trial.**](#) Inoue T1, Takagi H1,2, Owada Y1, et al. Trials. 2017 Oct 18;18(1):485. doi: 10.1186/s13063-017-2227-6.

BACKGROUND: Cisplatin is a key drug in lung cancer therapy. However, cisplatin is also well known to induce gastrointestinal disorders, such as chemotherapy-induced nausea and vomiting, anorexia, and weight loss. These symptoms sometimes affect patients' quality of life and make continuation of chemotherapy difficult. Anorexia is a cause of concern for patients with cancer because a persistent loss of appetite progresses to cancer cachexia. Although evidence-based management for chemotherapy has recently been established, there is room for improvement. **METHODS/DESIGN:** This placebo-controlled, double-blind, randomized trial will aim to determine the efficacy of the traditional Japanese Kampo medicine rikkunshito (TJ-43) for preventing anorexia caused by cisplatin-including chemotherapy in patients with lung cancer. Patients with lung cancer who plan to receive cisplatin-including chemotherapy will be recruited. Patients who provide written consent will be randomly allocated to receive either TJ-43 (arm A) or placebo (arm B) for one course of chemotherapy (21 or 28 consecutive days). Investigators and patients will be masked to the treatment assignment throughout the trial. The primary endpoint will be evaluated as the change in dietary intake from day 0 (the day before the start of chemotherapy) to day 7 of cisplatin-including chemotherapy. The two arms of the trial will comprise 30 patients each. From November 2014, a total of 60 patients will be recruited, and recruitment for the study is planned to be complete by October 2017. **DISCUSSION:** This trial is designed to examine the efficacy of rikkunshito (TJ-43) for reducing anorexia and maintaining food intake caused by cisplatin-including chemotherapy in patients with lung cancer.

[Chinese medicine formula "Shenqi San" extract inhibits proliferation of human lung adenocarcinoma A549 cells via inducing apoptosis.](#) Xia Y1, Shi L2, Ai ZZ3, Zhang DZ3, Liu YW1, You PT4. J Huazhong Univ Sci Technolog Med Sci. 2017 Oct;37(5):766-771. doi: 10.1007/s11596-017-1802-0. Epub 2017 Oct 20.

The main purpose of this study was to investigate the active components of the Chinese medicine formula Shenqi San (SS) by high performance liquid chromatography with diode array detector and electrospray ionization-hybrid quadrupole time-of-flight mass spectrum (HPLC-DADESI- QTOF-MS), and demonstrate the anticancer mechanism of SS on human lung adenocarcinoma A549 cells by evaluating the cell proliferation and apoptosis induction. The chloroform extraction of SS (CE-SS) was extracted from SS, while HPLC-DAD-ESI-QTOF-MS assay was performed to identify components of CE-SS. MTT assay was used to quantify the proliferation of A549 cells with the treatment of CE-SS. Apoptosis analysis was carried out by detecting phosphatidylserine (PS) externalization using the Annexin V-FITC Apoptosis Detection Kit and the stained cells were analyzed with a flow cytometer. DAPI staining assay was carried out to observe morphological characteristics of apoptotic cells. Western blotting was used to detect the expression of important signaling proteins including caspase-3, -8, -9, p53, Bax and Bcl-2. Eight compounds were identified through HPLC-DAD-ESI-QTOF-MS analysis and 3-pyridine carboxylic acid, barbatin C, scutebarbatine F and barbatine D might be the main compounds responsible for the antitumor effect of CE-SS. CE-SS suppressed the proliferation of lung cancer A549 cells in a time- and dose-dependent manner. By Annexin V-FITC/PI double staining, we found that treatment with CE-SS induced apoptosis in A549 cells. After 24-h exposure to CE-SS, the expression of cleaved-caspase-9, cleaved-caspase-8 and cleaved-caspase-3 protein was activated, the expression of p53 protein increased while the ratio of Bax/Bcl-2 also increased. This study identified the eight compounds of CE-SS, and demonstrated their anticancer effect on human lung adenocarcinoma A549 cells via induction of apoptosis.

MISCELLANEOUS WORKS

[Trends in Adult Cancer-Related Emergency Department Utilization: An Analysis of Data From the Nationwide Emergency Department Sample.](#) Rivera DR1, Gallicchio L1, Brown J2, Liu B1, Kyriacou DN3, Shelburne N1. JAMA Oncol. 2017 Oct 12;3(10):e172450. doi: 10.1001/jamaoncol.2017.2450. Epub 2017 Oct 12.

IMPORTANCE: The emergency department (ED) is used to manage cancer-related complications among the 15.5 million people living with cancer in the United States. However, ED utilization patterns by the population of US adults with cancer have not been previously evaluated or described in published literature. **OBJECTIVE:** To estimate the proportion of US ED visits made by adults with a cancer diagnosis, understand the clinical presentation of adult patients with cancer in the ED, and examine factors related to inpatient admission within this population. **DESIGN, SETTING, AND RTICIPANTS:** Nationally representative data comprised of 7 survey cycles (January 2006-December 2012) from the Nationwide Emergency Department Sample were analyzed. Identification of adult (age ≥18 years) cancer-related visits was based on Clinical Classifications Software diagnoses documented during the ED visit. Weighted frequencies and proportions of ED visits among adult patients with cancer by demographic, geographic, and clinical characteristics were calculated. Weighted multivariable logistic regression was used to examine the associations between inpatient admission and key demographic and clinical variables for adult cancer-related ED visits. **MAIN OUTCOMES AND MEASURES:** Adult cancer-related ED utilization patterns; identification of primary reason for ED visit; patient-related factors associated with inpatient admission from the ED. **RESULTS:** Among an estimated 696 million weighted adult ED visits from January 2006 to December 2012, 29.5 million (4.2%) were made by a patient with a cancer diagnosis. The most common cancers associated with an ED visit were breast, prostate, and lung cancer,

and most common primary reasons for visit were pneumonia (4.5%), nonspecific chest pain (3.7%), and urinary tract infection (3.2%). Adult cancer-related ED visits resulted in inpatient admissions more frequently (59.7%) than non-cancer-related visits (16.3%) (P < .001). Septicemia (odds ratio [OR], 91.2; 95% CI, 81.2-102.3) and intestinal obstruction (OR, 10.94; 95% CI, 10.6-11.4) were associated with the highest odds of inpatient admission. **CONCLUSIONS AND RELEVANCE:** Consistent with national prevalence statistics among adults, breast, prostate, and lung cancer were the most common cancer diagnoses presenting to the ED. Pneumonia was the most common reason for adult cancer-related ED visits with an associated high inpatient admission rate. This analysis highlights cancer-specific ED clinical presentations and the opportunity to inform patient and system-directed prevention and management strategies.

Lung Cancer Messages on Twitter: Content Analysis and Evaluation.

Sutton J1, Vos SC2, Olson MK2, Woods C3, Cohen E4, Ben Gibson C5, Phillips NE5, Studts JL6, Eberth JM7, Butts CT8. J Am Coll Radiol. 2017 Nov 15. pii: S1546-1440(17)31283-8. doi: 10.1016/j.jacr.2017.09.043. [Epub ahead of print]

PURPOSE: The aim of this project was to describe and evaluate the levels of lung cancer communication across the cancer prevention and control continuum for content posted to Twitter during a 10-day period (September 30 to October 9) in 2016. **METHODS:** Descriptive and inferential statistics were used to identify relationships between tweet characteristics in lung cancer communication on Twitter and user-level data. Overall, 3,000 tweets published between September 30 and October 9 were assessed by a team of three coders. Lung cancer-specific tweets by user type (individuals, media, and organizations) were examined to identify content and structural message features. The study also assessed differences by user type in the use of hashtags, directed messages, health topic focus, and lung cancer-specific focus across the cancer control continuum. **RESULTS:** Across the universe of lung cancer tweets, the majority of tweets focused on treatment and the use of pharmaceutical and research interventions, followed by awareness and prevention and risk topics. Among all lung cancer tweets, messages were most consistently tweeted by individual users, and personal behavioral mobilizing cues to action were rare. **CONCLUSIONS:** Lung cancer advocates, as well as patient and medical advocacy organizations, with an interest in expanding the reach and effectiveness of social media efforts should monitor the topical nature of public tweets across the cancer continuum and consider integrating cues to action as a strategy to increase engagement and behavioral activation pertaining to lung cancer reduction efforts.

Evaluating Molecular Biomarkers for the Early Detection of Lung Cancer: When Is a Biomarker Ready for Clinical Use? An Official American Thoracic Society Policy Statement.
Mazzone PJ, Sears CR, Arenberg DA, et al. Am J Respir Crit Care Med. 2017 Oct 1;196(7):e15-e29. doi: 10.1164/rccm.201708-1678ST.

BACKGROUND: Molecular biomarkers have the potential to improve the current state of early lung cancer detection. The goal of this project was to develop a policy statement that provides guidance about the level of evidence required to determine that a molecular biomarker, used to support early lung cancer detection, is appropriate for clinical use. **METHODS:** An ad hoc project steering committee was formed, to include individuals with expertise in the early detection of lung cancer and molecular biomarker development, from inside and outside of the Assembly on Thoracic Oncology. Key questions, generated from the results of a survey of the project steering committee, were discussed at an in-person meeting. Results of the discussion were summarized in a policy statement that was circulated to the steering committee and revised multiple times to achieve consensus. **RESULTS:** With a focus on the clinical applications of lung cancer screening and lung nodule evaluation, the policy statement outlines categories of results that should be reported in the early phases of molecular biomarker development, discusses the level of evidence that would support study of the clinical utility, describes the outcomes that should be

proven to consider a molecular biomarker clinically useful, and suggests study designs capable of assessing these outcomes. **CONCLUSIONS:** The application of molecular biomarkers to assist with the early detection of lung cancer has the potential to substantially improve our ability to select patients for lung cancer screening, and to assist with the characterization of indeterminate lung nodules. We have described relevant considerations and have suggested standards to apply when determining whether a molecular biomarker for the early detection of lung cancer is ready for clinical use.

[Pulmonary Nodules: A Small Problem for Many, Severe Distress for Some, and How to Communicate About It.](#) Slatore CG1, Wiener RS2. Chest. 2017 Oct 21. pii: S0012-3692(17)32915-X. doi: 10.1016/j.chest.2017.10.013. [Epub ahead of print]

Every year, millions of patients are diagnosed with pulmonary nodules, and as increasing numbers of people undergo lung cancer screening, even more patients will be found to have a nodule. The vast majority of patients cannot benefit from the detection of a pulmonary nodule since most are benign. Accordingly, it is important to develop strategies to minimize harm, in particular the distress of a "near-cancer" diagnosis. In other settings, communication strategies are critical mediators of patient-centered outcomes for those with and at-risk of cancer. We have conducted multiple studies to characterize the experience of patients with the diagnosis and evaluation of incidental pulmonary nodules, measure patient-centered outcomes for patients with pulmonary nodules, and determine the association of patient-clinician communication practices with those outcomes. We have learned that a substantial proportion of patients experience distress and inadequate communication about pulmonary nodules and their evaluation, and yet many clinicians are unaware of the degree to which some patients are affected by the finding of a pulmonary nodule. In this review, we provide a comprehensive summary of our results and provide suggestions for how clinicians can best provide high quality communication for their patients.

[The role of patient and physician advocacy in reducing wait times for cancer care: a qualitative analysis.](#) Mathews M1, Bulman D1, Ryan D1. CMAJ Open. 2017 Oct 17;5(4):E773-E778. doi: 10.9778/cmajo.20170039.

BACKGROUND: There is growing interest in the role of physician as health advocate; however, few studies have documented advocacy from the patient's perspective. To address this gap, we examined the experiences of patients with cancer from the onset of symptoms to the start of treatment in Newfoundland and Labrador and aimed to describe wait times and efforts to improve timeliness of care from the patients' perspective. **METHODS:** We conducted qualitative interviews with 60 participants aged 19 years or more with breast, colorectal, lung or prostate cancer who were recruited from a survey of patients with cancer that was carried out as an earlier part of a larger study. All survey participants had received care at regional cancer clinics in Newfoundland and Labrador and were selected by means of purposive sampling based on their type of cancer, level of satisfaction with care and place of residence (urban, semiurban or rural). Interviews were transcribed verbatim and coded by means of a thematic approach. **RESULTS:** Participants described actions taken by themselves, their families/friends or members of their health care team to reduce their wait for a diagnosis and/or treatment. In all instances, participants believed that these actions resulted in more timely care. Participants reported that "insider knowledge" of health care professionals (whether friends, family members or members of the care team) was particularly valuable in reducing delays. **INTERPRETATION:** The use of advocacy was relatively commonplace. The role of advocacy, whether it originates from patient or caregiver, is important to ensure access to timely, good-quality cancer care.

[Real-World Treatment Sequences and Outcomes Among Patients With Non-Small Cell Lung Cancer (RESOUNDS) in the United States: Study Protocol.](#) Hess LM1, Kern DM2, Carter GC1,

Winfree K1, Wang L2, Sontag A1, Oton AB1. JMIR Res Protoc. 2017 Oct 11;6(10):e195. doi: 10.2196/resprot.7750.

BACKGROUND: Survival outcomes are related to treatment choices in a line of therapy and to treatment sequences across all lines of therapy. **OBJECTIVE:** The Real-World Treatment Sequences and Outcomes among Patients with NSCLC (RESOUNDS) study is designed to (1) evaluate treatment sequences used for patients who receive at least two lines of therapy for non-small cell lung cancer (NSCLC) in the United States and (2) evaluate patient outcomes in terms of progression-free and overall survival related to treatment sequencing. Additional objectives include the evaluation of symptoms, comorbidities, and health care resource utilization and costs. **METHODS:** Patients will be censored at loss to follow-up due to leaving the health plan or reaching the end of the study period. **RESULTS:** This study is ongoing. **CONCLUSIONS:** The RESOUNDS cohort study is a novel approach to building a comprehensive dataset that mimics a prospective observational study using linked patient-level data from four real-world data sources. This study will provide timely information on the sequencing of treatments for patients with NSCLC.

[Lung Cancer Mortality Associated With Smoking and Smoking Cessation Among People Living With HIV in the United States.](#) Reddy KP1,2,3, Kong CY3,4, Hyle EP1,3,5, et al. JAMA Intern Med. 2017 Nov 1;177(11):1613-1621. doi: 10.1001/jamainternmed.2017.4349.

IMPORTANCE: Lung cancer has become a leading cause of death among people living with human immunodeficiency virus (HIV) (PLWH). Over 40% of PLWH in the United States smoke cigarettes; HIV independently increases the risk of lung cancer. **OBJECTIVE:** To project cumulative lung cancer mortality by smoking exposure among PLWH in care. **DESIGN:** Using a validated microsimulation model of HIV, we applied standard demographic data and recent HIV/AIDS epidemiology statistics with specific details on smoking exposure, combining smoking status (current, former, or never) and intensity (heavy, moderate, or light). We stratified reported mortality rates attributable to lung cancer and other non-AIDS-related causes by smoking exposure and accounted for an HIV-conferred independent risk of lung cancer. Lung cancer mortality risk ratios (vs never smokers) for male and female current moderate smokers were 23.6 and 24.2, respectively, and for those who quit smoking at age 40 years were 4.3 and 4.5. In sensitivity analyses, we accounted for nonadherence to antiretroviral therapy (ART) and for a range of HIV-conferred risks of death from lung cancer and from other non-AIDS-related diseases (eg, cardiovascular disease). **MAIN OUTCOMES AND MEASURES:** Cumulative lung cancer mortality by age 80 years (stratified by sex, age at entry to HIV care, and smoking exposure); total expected lung cancer deaths, accounting for nonadherence to ART. **RESULTS:** Among 40-year-old men with HIV, estimated cumulative lung cancer mortality for heavy, moderate, and light smokers who continued to smoke was 28.9%, 23.0%, and 18.8%, respectively; for those who quit smoking at age 40 years, it was 7.9%, 6.1%, and 4.3%; and for never smokers, it was 1.6%. Among women, the corresponding mortality for current smokers was 27.8%, 20.9%, and 16.6%; for former smokers, it was 7.5%, 5.2%, and 3.7%; and for never smokers, it was 1.2%. ART-adherent individuals who continued to smoke were 6 to 13 times more likely to die from lung cancer than from traditional AIDS-related causes, depending on sex and smoking intensity. Due to greater AIDS-related mortality risks, individuals with incomplete ART adherence had higher overall mortality but lower lung cancer mortality. Applying model projections to the approximately 644 200 PLWH aged 20 to 64 in care in the United States, 59 900 (9.3%) are expected to die from lung cancer if smoking habits do not change. **CONCLUSIONS AND RELEVANCE:** Those PLWH who adhere to ART but smoke are substantially more likely to die from lung cancer than from AIDS-related causes.

[Survival As a Quality Metric of Cancer Care: Use of the National Cancer Data Base to Assess Hospital Performance.](#) Shulman LN1, Palis BE1, McCabe R1, Mallin K1, Loomis A1, Winchester D1,

McKellar D1. J Oncol Pract. 2017 Nov 1:JOP2016020446. doi: 10.1200/JOP.2016.020446. [Epub ahead of print]

PURPOSE: Survival is considered an important indicator of the quality of cancer care, but the validity of different methodologies to measure comparative survival rates is less well understood. We explored whether the National Cancer Data Base (NCDB) could serve as a source of unadjusted and risk-adjusted cancer survival data and whether these data could be used as quality indicators for individual hospitals or in the aggregate by hospital type. **METHODS:** The NCDB, an aggregate of > 1,500 hospital cancer registries, was queried to analyze unadjusted and risk-adjusted hazards of death for patients with stage III breast cancer (n = 116,787) and stage IIIB or IV non-small-cell lung cancer (n = 252,392). Data were analyzed at the individual hospital level and by hospital type. **RESULTS:** At the hospital level, after risk adjustment, few hospitals had comparative risk-adjusted survival rates that were statistically better or worse. By hospital type, National Cancer Institute-designated comprehensive cancer centers had risk-adjusted survival ratios that were statistically significantly better than those of academic cancer centers and community hospitals. **CONCLUSION:** Using the NCDB as the data source, survival rates for patients with stage III breast cancer and stage IIIB or IV non-small-cell lung cancer were statistically better at National Cancer Institute-designated comprehensive cancer centers when compared with other hospital types. Compared with academic hospitals, risk-adjusted survival was lower in community hospitals. At the individual hospital level, after risk adjustment, few hospitals were shown to have statistically better or worse survival, suggesting that, using NCDB data, survival may not be a good metric to determine relative quality of cancer care at this level.