Caring Ambassadors Lung Cancer Program
October and November Literature Review, 2016

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Mitochondria-Targeted Hydroxyapatite Nanoparticles for Selective Growth Inhibition of Lung Cancer in Vitro and in Vivo. Sun Y, Chen Y, Ma X, Yuan Y, Liu C, Kohn J1, Qian J. ACS Appl Mater Interfaces. 2016 Oct 5;8(39):25680-25690. Epub 2016 Sep 21.

Lung cancer is the leading cause of cancer-related mortality worldwide. Most patients have metastases at the time of diagnosis, thus demanding development of more effective and specific agents. In this study, the specific anticancer effect of hydroxyapatite nanoparticles (HAPNs) to human lung cancer cells (A549) and the underlying mechanisms were investigated, using normal bronchial epithelial cells (16HBE) as the control. Rod-shaped HAPNs (∼10 nm in width and 50 nm in length) were prepared by aqueous precipitation method. Without any further functionalization and drug loading, HAPNs selectively inhibited cancer-cell proliferation. Their efficient mitochondrial targeting correlated strongly with decreased mitochondrial membrane potential and induction of mitochondria-dependent apoptosis in A549 cells. Caveolae-mediated endocytosis via lysosome trafficking was observed to be a prominent internalization pathway for HAPNs in both A549 and 16HBE cells. However, more nanoparticles were taken up into A549 cells. HAPNs triggered a sustained elevation of intracellular calcium concentration ($[Ca2+]i$) in cancer cells but only a transitory increase in normal control cells. In a nude mouse lung cancer model with xenotransplanted A549 cells, HAPN treatment demonstrated nearly 40% tumor growth inhibition without apparent side effect. These results demonstrated that the enhanced cellular uptake and mitochondrial targeting of HAPNs, together with the prolonged elevation of $[Ca2+]i$ in A549 cells, could result in the cancer-specific cytotoxicity of HAPNs. Thus, HAPNs might be a promising agent or mitochondria-targeted delivery system for effective lung cancer therapy.

Early 18F-FDG uptake as a reliable imaging biomarker of T790M-mediated resistance but not MET amplification in non-small cell lung cancer treated with EGFR tyrosine kinase inhibitors. De Rosa V1, Iommelli F1, Monti M2, Mainolfi CG2, Fonti R1, Del Vecchio S3. EJNMMI Res. 2016 Dec;6(1):74. Epub 2016 Oct 10.

BACKGROUND: The two main mechanisms of resistance to EGFR tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC) are the occurrence of T790M secondary mutation in the kinase

domain of EGFR and MET amplification. The aim of the present study was to test whether early changes of 18F-fluorodeoxyglucose (18F-FDG) uptake in animal models bearing erlotinib-resistant NSCLC may have different imaging patterns of response to erlotinib depending on the molecular mechanisms underlying resistance. Animal tumor models were developed using NSCLC H1975 cells bearing the T790M mutation and H1993 cells with MET amplification. Nude mice bearing erlotinib-resistant H1975 and H1993 xenografts (four animals for each cell line and for each treatment) were subjected to 18F-FDG PET/CT scan before and immediately after treatment (50 mg/kg p.o. for 3 days) with erlotinib, WZ4002, crizotinib, or vehicle. A three-dimensional region of interest analysis was performed to determine the percent change of 18F-FDG uptake in response to treatment. At the end of the imaging studies, tumors were removed and analyzed for glycolytic and mitochondrial proteins as well as levels of cyclin D1. **RESULTS:** Imaging studies with 18F-FDG PET/CT in H1975 tumor-bearing mice showed a reduction of 18F-FDG uptake of 25.87 % ± 8.93 % after treatment with WZ4002 whereas an increase of 18F-FDG uptake up to 23.51 % ± 9.72 % was observed after treatment with erlotinib or vehicle. Conversely, H1993 tumors showed a reduction of 18F-FDG uptake after treatment with both crizotinib (14.70 % ± 1.30 %) and erlotinib (18.40 % ± 9.19 %) and an increase of tracer uptake in vehicle-treated (56.65 % ± 5.65 %) animals. The in vivo reduction of 18F-FDG uptake was always associated with downregulation of HKII and p-PKM2 Tyr105 glycolytic proteins and upregulation of mitochondrial complexes (subunits I-IV) in excised tumors. **CONCLUSIONS:** 18F-FDG uptake is a reliable imaging biomarker of T790M-mediated resistance and its reversal in NSCLC whereas it may not be accurate in the detection of MET-mediated resistance.

Novel synthetic chalcones induce apoptosis in the A549 non-small cell lung cancer cells harboring a KRAS mutation. Wang Y1, Hedblom A2, Koerner SK1, Li M2, Jernigan FE1, Wegiel B3, Sun L4. Bioorg Med Chem Lett. 2016 Oct 24. pii: S0960-894X(16)31102-7. doi: 10.1016/j.bmcl.2016.10.063. [Epub ahead of print]
A series of novel chalcones were synthesized by the Claisen-Schmidt condensation reaction of tetralones and 5-/6-indolecarboxaldehydes. Treatment of human lung cancer cell line harboring KRAS mutation (A549) with the chalcones induced dose-dependent apoptosis. Cell cycle analyses and Western blotting suggested the critical role of the chalcones in interrupting G2/M transition of cell cycle. SAR study demonstrated that substituent on the indole N atom significantly affects the anticancer activity of the chalcones, with methyl and ethyl providing the more active compounds (EC50: 110-200nM), Compound 1g was found to be >4-fold more active in the A549 cells (EC50: 110nM) than in prostate (PC3) or pancreatic cancer (CLR2119, PAN02) cells. Furthermore, compound 1l selectively induced apoptosis of lung cancer cells A549 (EC50: 0.55μM) but did not show measurable toxicity in the normal lung bronchial epithelial cells (hBEC) at doses as high as 10μM, indicating specificity towards cancer cells.

An UPLC-MS/MS method for the quantitation of alectinib in rat plasma. Huang XX1, Li YX1, Li XY1, Hu XX1, Tang PF1, Hu GX2. J Pharm Biomed Anal. 2017 Jan 5;132:227-231. doi: 10.1016/j.jpba.2016.10.010. Epub 2016 Oct 14.
Currently, crizotinib is the first generation drug, which has been used in the treatment of ALK-rearranged non-small cell lung cancer (NSCLC). However, more and more patients are found in crizotinib-resistance. In the last year, alectinib has been approved for treatment of patients with crizotinib-resistance. In this study, we aim to develop and validate a simple, rapid and sensitive tandem mass spectrometry (UHPLC-MS/MS) method for determination of alectinib in rat plasma. Diazepam was chosen as an internal standard (IS). Protein precipitation by acetonitrile was utilized to prepare plasma samples. Chromatographic separation was achieved on a RRHD Eclipse Plus C18 (2.1×50mm, 1.8μ) column with a gradient mobile phase consisting of acetonitrile and water (containing 0.1% formic acid). The analytes were detected by an electrospray ionization (ESI) source in positive mode. A dynamic multiple reaction

monitoring (MRM) method was developed to detect specific precursor and product ions. The target fragment ions were m/z 483.2→396.1 for alectinib and m/z 285.0→192.9 for diazepam (IS). Linear calibration plots were achieved in the range of 1-500ng/ml for alectinib (R2=0.997) in rat plasma. Mean recoveries of alectinib in rat plasma ranged from 84.2% to 92.2%. The intra- and inter-day precision was below 9.3% and accuracy was from -1.4% to 12.1%. No obvious matrix effect was found. This method shows a good performance: accuracy, precision and stability. It has been fully validated and successfully applied to pharmacokinetic study of alectinib.

[Peperomin E reactivates silenced tumor suppressor genes in lung cancer cells by inhibition of DNA methyltransferase.](#) Wang XZ1, Cheng Y1, Wang KL1, et al. Cancer Sci. 2016 Oct;107(10):1506-1519. doi: 10.1111/cas.13029. Epub 2016 Oct 7.
Advanced lung cancer has poor prognosis owing to its low sensitivity to current chemotherapy agents. Therefore, discovery of new therapeutic agents is urgently needed. In this study, we investigated the antitumor effects of peperomin E, a secolignan isolated from Peperomia dindygulensis, a frequently used Chinese folk medicine for lung cancer treatment. The results indicate that peperomin E has antiproliferative effects, promoting apoptosis and cell cycle arrest in non-small-cell lung cancer (NSCLC) cell lines in a dose-dependent manner, while showing lower toxicity against normal human lung epidermal cells. Peperomin E inhibited tumor growth in A549 xenograft BALB/c nude mice without significant secondary adverse effects, indicating that it may be safely used to treat NSCLC. Furthermore, the mechanisms underlying the anticancer effects of peperomin E have been investigated. Using an in silico target fishing method, we observed that peperomin E directly interacts with the active domain of DNA methyltransferase 1 (DNMT1), potentially affecting its genome methylation activity. Subsequent experiments verified that peperomin E decreased DNMT1 activity and expression, thereby decreasing global methylation and reactivating the epigenetically silenced tumor suppressor genes including RASSF1A, APC, RUNX3, and p16INK4, which in turn activates their mediated pro-apoptotic and cell cycle regulatory signaling pathways in lung cancer cells. The observations herein report for the first time that peperomin E is a potential chemotherapeutic agent for NSCLC. The anticancer effects of peperomin E may be partly attributable to its ability to demethylate and reactivate methylation-silenced tumor suppressor genes through direct inhibition of the activity and expression of DNMT1.

[The Prognostic Value of PLR in Lung Cancer, a Meta-analysis Based on Results from a Large Consecutive Cohort.](#) Ding N1, Pang Z1, Shen H2, Ni Y2, Du J1,3, Liu Q1. Sci Rep. 2016 Oct 5;6:34823. doi: 10.1038/srep34823.
Recently, many studies have been conducted to explore prognostic value of platelet to lymphocyte ratio (PLR) for patients with lung cancer, while the results remain controversial. We collected pretreatment, clinicopathological and follow-up data of 1388 lung cancer patients receiving surgery between 2006 and 2011 in our hospital, and reviewed relevant articles from Embase, Pubmed, Web of science databases, then performed a meta-analysis to clarify the relationship between PLR and prognosis of lung cancer patients. Finally, 11 articles with our study were included, results indicated elevated PLR was negatively related to overall survival (HR = 1.33, 95% CI: 1.10-1.62), but not related to progress-free survival (HR = 1.21, 95% CI: 0.97-1.49). Subgroup analysis suggested high PLR was correlated with poor survival in non-small cell lung cancer (HR = 1.43, 95% CI: 1.14-1.78), but not in small cell lung cancer (HR = 1.10, 95% CI: 0.76-1.58). Besides, for patients treated by chemotherapy or radiotherapy (HR = 1.66, 95% CI: 1.15-2.38) and patients in late stage (HR = 1.41, 95% CI: 1.19-1.68), PLR had significantly prognostic value. Additionally, the result was significant for patients when cut-off value of PLR was between 150 and 200 (HR = 1.47, 95% CI: 1.18-1.82). **In Conclusion**, this meta-analysis revealed that elevated PLR was associated with poor prognosis in lung cancer.

[**Reduced decorin expression in the tumor stroma correlates with tumor proliferation and predicts poor prognosis in patients with I-IIIA non-small cell lung cancer.**](#) Hong X1, Yang Z1, Wang M1, Wang L2, Xu Q3. Tumour Biol. 2016 Oct 10. [Epub ahead of print]

Decorin, chiefly synthesized by tumor stroma, is known as a tumor suppressor. However, the clinical and prognostic significance in lung cancer remained unclear. Here, decorin and Ki67 expression was detected by immunohistochemistry (IHC) in I-IIIA non-small cell lung cancer (NSCLC) tissues (n = 264) in comparison to adjacent normal tissues (n = 40). The relationship between the expression of decorin and clinical characteristics, as well as Ki67 index and prognosis, was analyzed. Decorin expression was decreased in both the stroma (P < 0.001) and the tumor cells (P = 0.038) in NSCLC specimens. There was the lowest stromal expression of decorin in patients with G3 adenocarcinoma and higher Ki67 index in the stromal decorin-negative group. The Kaplan-Meier survival analysis demonstrated that lack of decorin in the stroma was correlated with a shorter DFS and OS (P = 0.005 and P = 0.010, respectively), while there was no significant association between decorin expression in the tumor cells and outcome. Multivariate analysis showed that reduced expression of decorin in the stroma was an independent prognostic factor for poor outcome including DFS (HR = 5.685, 95 % CI 0.493-0.933; P = 0.017) and OS (HR = 6.579, 95 % CI 0.484-0.908; P = 0.010). Negative decorin in the stroma combined with high Ki67 index predicted poorer outcomes for I-IIIA NSCLC patients. Our results provide data on decorin expression in both the stroma and cancer cells in NSCLC and reveal that reduced expression of stromal decorin correlates with high Ki67 index and has prognostic significance for poor outcome in I-IIIA NSCLC. Our data suggest that evaluating stromal decorin expression might be useful in assessing the prognosis and malignant potential.

SCREENING, DIAGNOSIS AND STAGING

[**Biopsy Procedures and Molecular Testing Utilization and Related Costs in Patients with Metastatic Lung Cancer.**](#) Shinde R1, Cao X1, Kothari S1. J Manag Care Spec Pharm. 2016 Oct;22(10):1194-203. doi: 10.18553/jmcp.2016.15404. Epub 2016 Sep 2.

BACKGROUND: Epidermal growth factor receptor (EGFR) gene mutations and anaplastic lymphoma kinase (ALK) gene rearrangements are key therapeutic targets for biomarker-driven treatment with an EGFR or ALK tyrosine kinase inhibitor (TKI) in patients with metastatic non-small cell lung cancer (NSCLC). To appropriately guide treatment decisions, since 2011, the National Comprehensive Cancer Network and the American Society of Clinical Oncology therefore recommend EGFR and ALK analysis in tumor samples obtained at the time of diagnosis in patients with non-squamous NSCLC. Currently, there are limited data on utilization patterns and cost of biopsy procedures and biomarker tests in patients with metastatic NSCLC who receive an EGFR or ALK TKI. **OBJECTIVES:** To (a) describe utilization patterns and costs associated with biopsy procedures and biomarker testing in patients with NSCLC who received erlotinib or crizotinib between 2009 and 2012 and (b) investigate the timing of these procedures relative to the erlotinib or crizotinib index date. **METHODS:** Adult patients with metastatic lung cancer were identified by ICD-9-CM diagnostic codes within the Truven Health Analytic MarketScan database. Patients were included in the analysis if they had an index erlotinib or crizotinib claim between January 1, 2009, and September 30, 2012 (index period) and were continuously enrolled for ≥ 12 months before the index claim. Because there is no specific ICD-9-CM diagnostic code for NSCLC, patients with metastatic lung cancer who received erlotinib or crizotinib were considered to have metastatic NSCLC. Using CPT and ICD-9-CM codes, lung biopsy procedures performed during the 24 months before or 12 months after the index claim date were identified. For every patient, biomarker testing claims for EGFR and ALK were identified using the molecular pathology stacked CPT code during the 2 months before or 1 month after the index date. The frequency of claims for biopsy procedures and biomarker testing was analyzed descriptively. The overall summary measures for biomarker testing, especially frequency of EGFR testing

in patients receiving erlotinib, was also described as before and after 2011, the year when biomarker testing became part of the guidelines. Per patient and overall costs for biopsy procedures and biomarker testing were calculated from payer and patient perspectives. **RESULTS:** Of the 4,926 identified patients, 4,801 (97.5%) received erlotinib, and 125 (2.5%) received crizotinib. Biopsy procedure claims were identified for 3,579 (72.7%) patients, including 3,503 (73.0%) erlotinib recipients and 76 (60.8%) crizotinib recipients. Biomarker testing claims were identified for 675 (13.7%) patients, including 634 (13.2%) erlotinib recipients and 41 (32.8%) crizotinib recipients. Overall, most biomarker testing procedures (476 of 741) were identified in 435 (of 675) patients after year 2011. Also, among erlotinib recipients, percentage of patients receiving EGFR testing was increased over the index period. Per patient mean (SD) numbers of biopsy procedures and biomarker tests were 1.2 (1.1) and 0.2 (0.4), respectively. In the outpatient setting, per patient mean (SD) cost per biopsy procedure was $1,223 ($1,899) from the payer perspective and $60 ($147) from the patient perspective, whereas in the inpatient setting, it was $8,163 ($18,712) and $180 ($691), respectively. Among patients receiving at least 1 biomarker test, the per patient mean (SD) cost for the overall population was $891 ($1,062) and $43 ($229); for erlotinib recipients, it was $906 ($1,084) and $42 ($228); and for crizotinib recipients, it was $664 ($576) and $55 ($243) in payer and patient perspectives, respectively. **CONCLUSIONS:** This study provides insight into the use and cost of biopsy and biomarker testing procedures in patients with metastatic NSCLC. The low frequency of biomarker testing highlights the need for more awareness of testing to guide treatment decisions in these patients. Costs associated with biopsy procedures and biomarker testing provide insight into the economic impact on metastatic NSCLC patients treated with targeted therapy. **DISCLOSURES:** This study was sponsored by Merck & Co. Shinde is a study manager working for Merck under contract with AllSourcePPS, an Agile 1 company in Huntington Beach, California. Cao and Kothari are employees of Merck & Co., Kenilworth, New Jersey. Study concept and design were contributed primarily by Shinde and Kothari. Data analysis was performed by Cao. Data interpretation was performed by Shinde, Cao, and Kothari. Shinde wrote the manuscript with assistance from Cao and Kothari. The revision was completed primarily by Shinde and Kothari.

[Development of a programmed cell death ligand-1 immunohistochemical assay validated for analysis of non-small cell lung cancer and head and neck squamous cell carcinoma.](#) Rebelatto MC1, Midha A2, Mistry A3, et al. Diagn Pathol. 2016 Oct 8;11(1):95.
BACKGROUND: A high-quality programmed cell-death ligand 1 (PD-L1) diagnostic assay may help predict which patients are more likely to respond to anti-programmed cell death-1 (PD-1)/PD-L1 antibody-based cancer therapy. Here we describe a PD-L1 immunohistochemical (IHC) staining protocol developed by Ventana Medical Systems Inc. and key analytical parameters of its use in formalin-fixed, paraffin-embedded (FFPE) samples of non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma (HNSCC). **METHODS:** An anti-human PD-L1 rabbit monoclonal antibody (SP263) was optimized for use with the VENTANA OptiView DAB IHC Detection Kit on the automated VENTANA BenchMark ULTRA platform. The VENTANA PD-L1 (SP263) Assay was validated for use with FFPE NSCLC and HNSCC tissue samples in a series of studies addressing sensitivity, specificity, robustness, and precision. Samples from a subset of 181 patients from a Phase 1/2 study of durvalumab (NCT01693562) were analyzed to determine the optimal PD-L1 staining cut-off for enriching the probability of responses to treatment. The scoring algorithm was defined using statistical analysis of clinical response data from this clinical trial and PD-L1 staining parameters in HNSCC and NSCLC tissue. Inter-reader agreement was established by three pathologists who evaluated 81 NSCLC and 100 HNSCC samples across the range of PD-L1 expression levels. **RESULTS:** The VENTANA PD-L1 (SP263) Assay met all pre-defined acceptance criteria. For both cancer types, a cut-off of 25 % of tumor cells with PD-L1 membrane staining of any intensity best discriminated responders from nonresponders. Samples with staining above this value were deemed to have high PD-L1 expression, and those with

staining below it were deemed to have low or no PD-L1 expression. Inter-reader agreement on PD-L1 status was 97 and 92 % for NSCLC and HNSCC, respectively. **CONCLUSIONS:** These results highlight the robustness and reproducibility of the VENTANA PD-L1 (SP263) Assay and support its suitability for use in the evaluation of NSCLC and HNSCC FFPE tumor samples using the devised ≥25 % tumor cell staining cut-off in a clinical setting. The clinical utility of the PD-L1 diagnostic assay as a predictive biomarker will be further validated in ongoing durvalumab studies.

[**Patients' Attitudes Regarding Lung Cancer Screening and Decision Aids: A Survey and Focus Group Study.**](#) Crothers K1, Kross E2, Reisch LM3, Shahrir SF4, Slatore C5,6, Zeliadt SB7,8, Triplette M9, Meza R10, Elmore JG11. Ann Am Thorac Soc. 2016 Sep 21. [Epub ahead of print]
RATIONALE: Little is known about vulnerable patients' perceptions and understanding of, and preferences for lung cancer screening decision aids. **OBJECTIVES:** To determine, in a low-income, racially diverse population, participants' experience, preferences and reactions to web-based and paper decision aids, and 2) understanding of harms and benefits of lung cancer screening. **METHODS:** We enrolled outpatients at an urban county hospital in 6 focus group discussions that included review of a web-based and a paper-based lung-cancer screening decision aid. Participants completed surveys before and after the focus groups. **MEASUREMENTS AND MAIN RESULTS:** 45 patients participated (mean age 61; 76% current smokers, 24% former smokers); 27% had not completed high school; 50% had an annual income ≤$15,000; 42% were non-white; and 96% reported chronic illness requiring ≥3 healthcare visits yearly. Comparing the proportion with correct answers on pre- and postsurveys, participants' understanding of lung cancer screening increased, particularly of the harms of screening including the potential for false-positives, extra testing, and complications. However, after conclusion of the focus groups, over 50% believed that screening lowered the chance of getting lung cancer. Five major themes emerged from qualitative analyses. **PARTICIPANTS:** 1) were not aware of the purpose of lung cancer screening; 2) want to know about the benefits and harms; 3) felt physicians need to communicate more effectively; 4) found decision aids helpful and influential for decision-making about screening; and 5) wanted the discussion to be personalized and tailored. Participants expressed surprise that the magnitude of their lung cancer risk and benefits of screening were lower than anticipated. **CONCLUSIONS:** Vulnerable patients find lung cancer screening decision aids helpful and generally show increased knowledge after reviewing decision aids, particularly of harms. Our results can inform future implementation efforts.

[**Biomarkers for the Clinical Use of PD-1/PD-L1 Inhibitors in Non-Small-Cell Lung Cancer: A Review.**](#) Sacher AG1, Gandhi L2. JAMA Oncol. 2016 Sep 1;2(9):1217-22. doi: 10.1001/jamaoncol.2016.0639.
IMPORTANCE: The development of programmed cell death 1 (PD-1)/PD-1 ligand 1 (PD-L1) checkpoint inhibitors has changed the landscape of non-small-cell lung cancer (NSCLC) therapy, with 2 approvals from the US Food and Drug Administration of PD-1 inhibitors for second-line therapy. However, the rational use of these agents has been limited by the lack of a definitive predictive biomarker. **OBSERVATIONS:** Tumor PD-L1 expression is associated with an increased likelihood of NSCLC response to these agents, although responses can still occur at a low rate in PD-L1-negative tumors. The use of PD-L1 as a predictive biomarker for use of PD-1/PD-L1 inhibitors is limited by the multitude of PD-L1 antibodies, assays, scoring systems, and thresholds for positivity currently used. Alternative biomarkers such as tumor neoantigens identified through whole-exome sequencing and clinical parameters (eg, smoking or oncogene driver status) may also have predictive value. Biomarkers that can direct the rational use of PD-1/PD-L1 checkpoint inhibitors are crucial given the risk of life-threatening immune-related complications associated with these therapies and the reality that most patients still do not benefit from their use. **CONCLUSIONS AND RELEVANCE:** The refinement of

existing biomarkers and identification of novel predictive biomarkers will be key to ensuring the effective and safe use of these agents. Since most patients still do not benefit from these agents, it is critical to continue to work to define the select patient population who will derive durable benefit from PD-1/PD-L1 inhibition and identify markers that could have predictive value for combination therapies that could expand the population who benefit.

[Mutation profiles in early-stage lung squamous cell carcinoma with clinical follow-up and correlation with markers of immune function.](#) Choi M1, Kadara H2, Zhang J3, et al. Ann Oncol. 2016 Sep 29. pii: mdw437. [Epub ahead of print]

BACKGROUND: Lung squamous cell carcinoma (LUSC) accounts for 20-30% of non-small cell lung cancers (NSCLCs). There are limited treatment strategies for LUSC in part due to our inadequate understanding of the molecular underpinnings of the disease. We performed whole-exome sequencing (WES) and comprehensive immune profiling of a unique set of clinically annotated early-stage LUSCs to increase our understanding of the pathobiology of this malignancy. **METHODS:** Matched pairs of surgically resected stage I-III LUSCs and normal lung tissues (n=108) were analyzed by WES. Immunohistochemistry and image analysis-based profiling of ten immune markers was done on a subset of LUSCs (n=91). Associations among mutations, immune markers and clinicopathological variables were statistically examined using ANOVA and Fisher's exact test. Cox proportional hazards regression models were used for statistical analysis of clinical outcome. **RESULTS:** This early-stage LUSC cohort displayed an average of 209 exonic mutations per tumor. Fourteen genes exhibited significant enrichment for somatic mutation: TP53, MLL2, PIK3CA, NFE2L2, CDH8, KEAP1, PTEN, ADCY8, PTPRT, CALCR, GRM8, FBXW7, RB1 and CDKN2A Among mutated genes associated with poor recurrence-free survival, MLL2 mutations predicted poor prognosis in both TP53 mutant and wild type LUSCs. We also found that in treated patients, FBXW7 and KEAP1 mutations were associated with poor response to adjuvant therapy, particularly in TP53-mutant tumors. Analysis of mutations with immune markers revealed that ADCY8 and PIK3CA mutations were associated with markedly decreased tumoral PD-L1 expression, LUSCs with PIK3CA mutations exhibited elevated CD45ro levels and CDKN2A-mutant tumors displayed an up-regulated immune response. **CONCLUSION(S):** Our findings pinpoint mutated genes that may impact clinical outcome as well as personalized strategies for targeted immunotherapies in early-stage LUSC.

[How Patients View Lung Cancer Screening: The Role of Uncertainty in Medical Decision Making.](#) Schapira MM1,2, Aggarwal C3, Akers S4, et al. Ann Am Thorac Soc. 2016 Sep 27. [Epub ahead of print]

RATIONALE: Radiographic lung cancer screening guidelines and coverage requirements warrant a shared decision making process. Guidance is needed regarding how to conduct shared decision making effectively. A useful organizing theme should include consideration of a patient's response to and tolerance of uncertainty associated with lung cancer screening. **OBJECTIVES:** The objectives of this study are to: 1) describe how patients respond to specific categories of uncertainty in the context of lung cancer screening; and 2) inform strategies for addressing concerns about uncertainty as part of the shared decision making. **METHODS:** We performed two series of structured interviews on participants in a convenience sample of current or former cigarette smokers recruited from primary care and pulmonary practices in Philadelphia. An interview guide included prompts related to benefits, harms, and responses to general and specific types of uncertainty (stochastic, statistical, and evidentiary) associated with lung cancer screening. Interviews were audio-recorded, transcribed, and independently coded by 2 investigators. An inductive analysis was conducted and major themes were identified. **MEASURE-MENTS AND MAIN RESULTS:** Twenty-two (22) adults participated in the study. Sixty-eight percent (68%) were male, 72% were Black or African American, and 50% met United States Preventive Services Task Force criteria for lung cancer screening. The primary themes to emerge from our study were: 1) the

desire to decrease uncertainty may motivate lung cancer screening decisions; 2) uncertainty is an attribute of health states that impacts how patients weigh benefits and harms of lung cancer screening; 3) patient understanding and tolerance of uncertainty varies across stochastic, statistical, and evidentiary uncertainty; and 4) provider-patient communication may mitigate intolerance of uncertainty in the context of lung cancer screening. **CONCLUSIONS:** A systematic approach to understanding and addressing patients' concerns about uncertainty in the context of lung cancer screening can guide a patient-centered approach to shared decision making. The results of this study can inform provider-patient communication strategies regarding the decision to perform radiographic lung cancer screening.

[Primary Care Provider and Patient Perspectives on Lung Cancer Screening: A Qualitative Study.](#)
Kanodra NM1, Pope C2, H Halbert C3, Silvestri GA4, Rice LJ5, Tanner NT6,7. Ann Am Thorac Soc. 2016 Sep 27. [Epub ahead of print]
RATIONALE: The United States Preventive Services Task Force (USPSTF) recommends annual low-dose computed tomography (LDCT) for lung cancer screening in high-risk individuals. Preventive health care is predominantly provided by primary care providers (PCPs). Successful implementation of a screening program requires acceptance and participation from both providers and patients, with available collaboration with pulmonologists. **OBJECTIVES:** To identify perceptions and perspectives on lung cancer screening and implementation among PCPs and eligible Veteran patients at high-risk for lung cancer. **METHODS:** We conducted a qualitative study using grounded theory in which 28 Veterans and 13 PCPs completed a questionnaire and participated in focus groups. Sessions were recorded, transcribed verbatim and analyzed with NVivo 10 software. Counts and percentages were used to report questionnaire results. **MEASUREMENTS AND MAIN RESULTS:** While 58% percent of providers were aware of lung cancer screening guidelines, many could not recall the exact patient eligibility criteria. Most patients were willing to undergo LDCT screening and identified smoking as a risk factor for lung cancer; but they did not recall their PCP explaining the reason for the testing. All providers assessed smoking behavior, but only 23% referred active smokers to formal cessation services. Patients volunteered their hurdles with smoking cessation while discussing risk factors for cancer. PCPs cited time constraints as a reason for lack of appropriate counseling and shared decision-making. Both parties were willing to explore modalities and decision aid tools to improve shared decision-making; however, while patients were interested in individual risk prediction, few PCPs believed statistical approaches to counseling would confuse patients. **CONCLUSIONS:** While patients and providers are receptive to LDCT screening, efforts are needed to improve guideline knowledge and adherence among providers. System level interventions are necessary to facilitate time and resources for shared decision-making and smoking cessation counseling and treatment. Further research is needed to identify optimal strategies for effective lung cancer screening in the community.

[Circulating tumor DNA detection in lung cancer patients before and after surgery.](#) Guo N1,2, Lou F3, Ma Y4, et al. Sci Rep. 2016 Sep 19;6:33519. doi: 10.1038/srep33519.
Circulating tumor DNA (ctDNA) in peripheral blood is a "liquid biopsy" that contains representative tumor information including gene mutations. Additionally, repeated ctDNA samples can be easily obtained to monitor response to treatment and disease progression, which may be especially valuable to lung cancer patients with tumors that cannot be easily biopsied or removed. To investigate the changes in ctDNA after surgical tumor resection, tumor and blood samples obtained before and after surgery were collected prospectively from 41 non-small lung cancer (NSCLC) patients. Somatic driver mutations in tumor DNA (tDNA) and pre- and post-op plasma ctDNA sample pairs were identified by targeted sequencing in several genes including EGFR, KRAS, and TP53 with an overall study concordance of 78.1% and sensitivity and specificity of 69.2% and 93.3%, respectively. Importantly, the frequency of 91.7% of ctDNA mutations decreased after surgery and these changes were observed as little as 2 days

post-op. Moreover, the presence of ctDNA had a higher positive predictive value than that of six tumor biomarkers in current clinical use. This study demonstrates the use of targeted sequencing to reliably identify ctDNA changes in response to treatment, indicating a potential utility of this approach in the clinical management of NSCLC.

[Society of Behavioral Medicine supports implementation of high quality lung cancer screening in high-risk populations.](#) Watson KS1,2,3, Blok AC4, Buscemi J5,6, et al. Transl Behav Med. 2016 Sep 19. [Epub ahead of print]
The Society of Behavioral Medicine (SBM) supports the United States Preventive Services Task Force (USPSTF) recommendation of low-dose computed tomography (LDCT) screening of the chest for eligible populations to reduce lung cancer mortality. Consistent with efforts to translate research findings into real-world settings, SBM encourages health-care providers and health-care systems to (1) integrate evidence-based tobacco treatment as an essential component of LDCT-based lung cancer screening, (2) examine the structural barriers that may impact screening uptake, and (3) incorporate shared decision-making as a clinical platform to facilitate consultations and engagement with individuals at high risk for lung cancer about the potential benefits and harms associated with participation in a lung cancer screening program. We advise policy makers and legislators to support screening in high-risk populations by continuing to (1) expand access to high quality LDCT-based screening among underserved high-risk populations, (2) enhance cost-effectiveness by integrating evidence-based tobacco treatments into screening in high-risk populations, and (3) increase funding for research that explores implementation science and increased public awareness and access of diverse populations to participate in clinical and translational research.

[Cytology smears as excellent starting material for next-generation sequencing-based molecular testing of patients with adenocarcinoma of the lung.](#) Velizheva NP1, Rechsteiner MP1, Wong CE1, et al. Cancer Cytopathol. 2016 Sep 16. doi: 10.1002/cncy.21771. [Epub ahead of print]
BACKGROUND: Molecular testing of lung adenocarcinomas (ADCs) is crucial for therapy stratification of patients. Because of the often limited diagnostic material, the authors aimed to explore the suitability of cytology smears for next-generation sequencing (NGS) and compared the results with concurrent histological specimens or cell blocks. **METHODS:** A total of 16 formalin-fixed paraffin-embedded (FFPE) ADCs with known genetic alterations were used as the first cohort for targeted DNA and RNA sequencing. In the second cohort of 8 cases, 8 cytological smears were compared with matching histological specimens or cell blocks for the study. For NGS library amplification, commercially available panels for DNA and RNA sequencing were applied. The Ion Torrent Personal Genome Machine and the Ion Reporter workflow (version 5.0) were used for sequencing. **RESULTS:** All DNA libraries derived from FFPE and non-formalin-fixed cytological smear samples produced acceptable quality metrics, thereby enabling successful targeted DNA sequencing (100% performance). Targeted RNA sequencing failed in 1 FFPE case and 1 cytology probe by not reaching enough mapped fusion reads (92% performance rate). All previously detected mutations and gene rearrangements could be confirmed (sensitivity of 100%), whereas specificity of the DNA-based NGS assay reached 96%. **CONCLUSIONS:** The results of the current study demonstrated the suitability of non-formalin cytology specimens for the simultaneous NGS testing of lung ADCs using amplicon resequencing panels. These assays allowed for the input of cytological smears equal to concurrent histology or cell blocks and proved to be accurate in the detection of therapeutically actionable somatic mutations and gene rearrangements.

[Assessing PDL-1 and PD-1 in Non-Small Cell Lung Cancer: A Novel Immunoscore Approach.](#)
Paulsen EE1, Kilvaer TK2, Khanehkenari MR3, et al. Clin Lung Cancer. 2016 Oct 5. pii: S1525-7304(16)30235-2. doi: 10.1016/j.cllc.2016.09.009. [Epub ahead of print]

INTRODUCTION: Immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) or its ligand, PD-L1, have gained momentum in the treatment of non-small cell lung cancer (NSCLC). However, their prognostic significance remains controversial. The present study evaluated the expression of PD-L1 and PD-1 and their potential role in an Immunoscore, supplementing the TNM classification of NSCLC. **MATERIALS AND METHODS:** Tissue microarrays constructed from tumor tissue samples from 2 cohorts of a total of 536 patients (University Hospital of North Norway, n = 285; Nordland Hospital, n = 251) with primary resected stage I to IIIA NSCLC. PD-L1 and PD-1 were evaluated by immunohistochemistry in the primary tumor and metastatic lymph node tissue. **RESULTS:** In univariate analysis, a high density of PD-L1+ immune cells in the stromal compartment (S-PD-L1) and PD-1+ intraepithelial tumor infiltrating lymphocytes (T-PD-1) was associated with favorable disease-specific survival (DSS; S-PD-L1, P = .004; T-PD-1, P = .012), both limited to the squamous cell carcinoma histologic subgroup (S-PD-L1, P = .002; T-PD-1, P = .034). A combined low S-PD-L1 and T-PD-1 was associated with poor survival in all patients (DSS: hazard ratio [HR], 1.81; 95% confidence interval [CI], 1.37-2.40; P < .001) at both centers and for all pathologic stages. In multivariate analysis, S-PD-L1 and T-PD-1 were independent positive prognostic factors, and combined low scores remained an independent prognosticator for poor survival (DSS: HR, 1.72; 95% CI, 1.29-2.28; P < .001; disease-free survival, P = .001; overall survival, P = .005). **CONCLUSION:** Our study identified S-PD-L1 and T-PD-1 as independent positive prognostic factors for NSCLC patients. Their combination added significant prognostic impact within each pathologic stage and hence are feasible to include in a TNM Immunoscore.

[Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration for Mediastinal Staging in a Community Medical Center.](#) Warren WA1,2,3, Hagaman JT2,3,4,5. Ann Am Thorac Soc. 2016 Oct;13(10):1802-1807.

RATIONALE: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and positron emission tomography (PET)-computed tomography (CT) are valuable tools for lung cancer staging. Data from tertiary referral centers suggest that these modalities are superior to mediastinoscopy in mediastinal staging. **OBJECTIVES:** To validate EBUS-TBNA for lung cancer staging in a community center with operators with various levels of experience. **METHODS:** At an 800-bed community hospital, we reviewed all cases where EBUS-TBNA and PET-CT were performed for mediastinal staging by one of seven private practice pulmonologists. Cases were reviewed with lymph node dissection by mediastinoscopy after negative EBUS-TBNA. **MEASUREMENTS AND MAIN RESULTS:** Of the 333 cases that were reviewed, 44 underwent mediastinoscopy after negative EBUS-TBNA. Four patients were positive for malignancy at stations 4R and 7 lymph nodes. In none of these cases did EBUS-TBNA reveal lymphoid tissue confirming the sample location. PET-CT showed mediastinal lymph nodes with increased avidity in two of the false-negative cases. EBUS-TBNA plus PET-CT had a sensitivity, specificity, and negative predictive value of 98.86, 100, and 94.87%, respectively, compared with mediastinoscopy for detecting metastasis. **CONCLUSIONS:** EBUS-TBNA is accurate in detecting mediastinal metastasis of lung cancer in the community setting. PET-CT without uptake in lymph nodes reduces the likelihood of malignancy but cannot rule out mediastinal involvement.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[A Risk Score to Assist Selecting Lobectomy Versus Sublobar Resection for Early Stage Non-Small Cell Lung Cancer.](#) Gulack BC1, Jeffrey Yang CF1, Speicher PJ1, et al. Ann Thorac Surg. 2016 Sep 1. pii: S0003-4975(16)30739-1. doi: 10.1016/j.athoracsur.2016.06.032. [Epub ahead of print]

BACKGROUND: The long-term survival benefit of lobectomy over sublobar resection for early-stage non-small cell lung cancer must be weighed against a potentially increased risk of perioperative mortality. The objective of the current study was to create a risk score to identify patients with favorable short-term outcomes following lobectomy. **METHODS:** The 2005-2012 American College of Surgeons National Surgical Quality Improvement Program database was queried for patients undergoing a lobectomy or sublobar resection (either segmentectomy or wedge resection) for lung cancer. A multivariable logistic regression model was utilized to determine factors associated with 30-day mortality among the lobectomy group and to develop an associated risk score to predict perioperative mortality. **RESULTS:** Of the 5,749 patients who met study criteria, 4,424 (77%) underwent lobectomy, 1,098 (19%) underwent wedge resection, and 227 (4%) underwent segmentectomy. Age, chronic obstructive pulmonary disease, previous cerebrovascular event, functional status, recent smoking status, and surgical approach (minimally invasive versus open) were utilized to develop the risk score. Patients with a risk score of 5 or lower had no significant difference in perioperative mortality by surgical procedure. Patients with a risk score greater than 5 had significantly higher perioperative mortality after lobectomy (4.9%) as compared to segmentectomy (3.6%) or wedge resection (0.8%, p < 0.01). **CONCLUSIONS:** In this study, we have developed a risk model that predicts relative operative mortality from a sublobar resection as compared to a lobectomy. Among patients with a risk score of 5 or less, lobectomy confers no additional perioperative risk over sublobar resection.

[Timing of Surgery after Neoadjuvant Chemoradiation in Locally Advanced Non-Small Cell Lung Cancer.](#) Gao SJ1, Corso CD1, Wang EH1, Blasberg JD2, Detterbeck FC2, Boffa DJ2, Decker RH1, Kim

INTRODUCTION: A subset of patients with potentially resectable clinical stage IIIA non-small cell lung cancer (NSCLC) are managed with trimodality therapy. However, little data exist to guide the timing of surgery after neoadjuvant therapy. This study examined whether the time interval between neoadjuvant chemoradiation (NCRT) and surgical resection impacts overall survival. **METHODS:** Clinical stage IIIA disease (T1-3 N2) NSCLC patients who underwent neoadjuvant chemoradiation therapy were identified in the National Cancer Data Base (NCDB) between 2004-2012 and categorized based on the interval between chemoradiation and surgery (0 to ≤3, 3 to ≤6, 6 to ≤9, and 9 to ≤12 weeks). Other clinical stages were excluded. Kaplan-Meier method and log-rank tests were used to compare overall survival and a bootstrapped Cox proportional hazards model was used to determine significant contributors to overall survival. **RESULTS:** Of the 1623 patients identified, 7.9% underwent surgery 0 to ≤3 weeks, 50.5% underwent surgery 3 to ≤6 weeks, 31.9% underwent surgery 6 to ≤9 weeks, and 9.6% underwent surgery 9 to ≤12 weeks after NCRT. Multivariate survival analysis demonstrated no significant difference in survival in those who underwent surgery within 6 weeks of NCRT. However, significant drops in overall survival were observed in those who had surgery 6 to ≤9 weeks (HR: 1.33, 95% CI: 1.01-1.76, P=0.043) and 9 to ≤12 weeks (HR: 1.44, 95% CI: 1.04-2.01, P=0.030) after NCRT. **CONCLUSIONS:** The findings from this retrospective study suggest that overall survival may be significantly lower in clinical stage IIIA N2 NSCLC patients who undergo surgery later than 6 weeks after NCRT. These results discourage unnecessary delays in surgery.

[Upstaging and survival after robotic-assisted thoracoscopic lobectomy for non-small cell lung cancer.](#) Toosi K1, Velez-Cubian FO2, Glover J1, et al. Surgery. 2016 Sep 21. pii: S0039-6060(16)30419-6. doi: 10.1016/j.surg.2016.08.003. [Epub ahead of print]

BACKGROUND: Mediastinal involvement in resected non-small-cell lung cancer mandates adjuvant therapy and affects survival. This study investigated lymph node dissection efficacy, lymph node metastasis detection, and survival after robotic-assisted lobectomy for non-small-cell lung cancer. **METHODS:** We retrospectively analyzed patients who underwent robotic-assisted lobectomy for non-small-cell lung cancer. Survival was assessed through chart reviews, Social Security Death Registry, and

national obituary searches. Kaplan-Meier survival curves by clinical and pathologic stage were compared by log-rank and Cox regression analysis. **RESULTS:** In 249 patients (mean age, 67.8 ± 0.6 years), mean individual mediastinal lymph nodes retrieved was 7.7 ± 0.3 lymph nodes, with mean of 13.9 ± 0.4 N1+ mediastinal lymph nodes. There were 159 (63.9%) clinical stage I versus 134 (53.8%) pathologic stage I patients, with 67 (26.9%) patients upstaged (20 cN0 to pN1; 17 cN0 to pN2; 4 cN1 to pN2) and 37 (14.9%) downstaged. One-year and 3-year survival rates, respectively, changed between clinical stage I (clinical stage I, 91% and 70%; clinical stage II, 80% and 64%; clinical stage III, 78% and 57%; clinical stage IV, 71% and 45%) and pathologic stage (pathologic stage I, 92% and 75%; clinical stage II, 83% and 73%; pathologic stage III, 75% and 44%; and pathologic stage IV, 67% and 0%). **CONCLUSION:** Mediastinal lymph node dissection during robotic-assisted lobectomy adequately assesses lymph node stations and detects occult lymph node metastasis. Stage-specific survival is affected by upstaging.

Brain Metastases: Surgical treatment and overall survival. D'Andrea G1, Palombi L2, Minniti G3, Pesce A4, Marchetti P2. World Neurosurg. 2016 Sep 22. pii: S1878-8750(16)30884-1. doi: 10.1016/j.wneu.2016.09.054. [Epub ahead of print]
OBJECTIVE: Brain metastases occur between 10 and 40% of patients with cancer and are more common than primary brain tumors (30-40%) and their incidence is growing because of the improvements in control of systemic disease, the prolonged survival and the better radiological detection. Modern treatment of brain metastases dramatically changed their expected prognosis that traditionally has been considered very poor referring such patients only to palliation because their terminal stage, and new prognostic indexes have been proposed to evaluate them. The aim of our study was to determine the long-term incidence of surgery on overall survival (OS) in patients with brain metastases from dissimilar primary tumors and to identify the prognostic variables associated with a prolonged survival. Surgical resection should be considered the primary option for brain metastases and together with stereotactic radiosurgery must be evaluated for single brain metastases and also for multiple lesions up to 3.
METHODS: We retrospectively reviewed a consecutive series of patients operated between January 2010 and October 2014 for cerebral metastases from lung, kidney, breast and gastrointestinal cancers plus melanoma. Among the variables, we include age, sex, histology, location of lesions and specific treatments that these patients have undergone including chemotherapy, radiotherapy and surgery, individually or in combination of them. At admission, all the patients underwent an oncological evaluation considering their general health conditions according to specific scales (ECOCG) and their prognostic classification according with the Radiation Therapy Oncology Group (RTOG) one.
RESULTS: None worsened after surgery and, at discharge, 19 (26.76%) patients demonstrated an unchanged postoperative neurological examination while 52 patients (73.23%) showed an improvement (chi2 34.84, p-value < 0.0001). The expected overall survival, considering all tumor subtypes, was 372.24 months but the patients in our series obtained an overall survival of 787 months, more than twice than expected; specifically, the average expected survival of each patient was of 5.24 months while the obtained was 11.08 (p-value 0.000008). **CONCLUSION:** We believe that surgery is a safe and effective procedure for cerebral metastases and should not be considered an aggressive treatment in such disease because in our series 55% of the patients had a survival longer than 6 months and a significant improvement in term of obtained vs expected survival.

Sublobar Resection Margin Width Does Not Affect Recurrence of Clinical N0 Non-small Cell Lung Cancer Presenting as GGO-Predominant Nodule of 3 cm or Less. Moon Y1, Lee KY2, Moon SW1, Park JK3. World J Surg. 2016 Oct 7. [Epub ahead of print]
BACKGROUND: Sublobar resection of lung cancer may benefit patients with lung cancer presenting as ground-glass opacity (GGO) nodules. The purpose of this study was to evaluate the effect of margin width on recurrence after sublobar resection in patients with clinical N0 non-small cell lung cancer presenting as

GGO-predominant nodule. **METHODS:** We conducted a retrospective chart review of 91 patients treated for clinical N0 non-small cell lung cancer ≤3 cm by sublobar resection with clear resection margins. We assigned them to two groups: GGO-predominant tumor and solid-predominant tumor. Each group was subdivided into two groups according to the margin width: resection margin ≤5 mm and resection margin >5 mm. We analyzed the clinicopathological findings and survival among these four groups. **RESULTS:** There was no recurrence in GGO-predominant tumors after sublobar resection. Margin width did not influence the recurrence in GGO-predominant tumors. In the cases of solid-predominant tumor, 5-year recurrence-free survival after sublobar resection according to margin width ≤5 and >5 mm was 24.2 and 79.6 %, respectively (p < 0.001). Therefore, narrow margin width (resection margin ≤5 mm) was a significant risk factor for recurrence of solid-predominant tumors (hazard ratio 3.868, 95 % confidence interval 1.177-12.714, p = 0.026). **CONCLUSIONS:** The width between the tumor and resection margin does not affect the recurrence after R0 sublobar resection in patients with clinical N0 GGO-predominant lung cancer ≤3 cm. By contrast, margin width is a significant risk factor for recurrence after sublobar resection in patients with clinical N0 solid-predominant lung cancer.

[The impact of resection method and patient factors on quality of life among stage IA non-small cell lung cancer surgical patients.](#) Schwartz RM1, Yip R2, Flores RM3, Olkin I4, Taioli E5, Henschke C2; I-ELCAP Investigators. J Surg Oncol. 2016 Oct 28. doi: 10.1002/jso.24478. [Epub ahead of print]
BACKGROUND AND OBJECTIVES: Given the increased number of treatment options for stage IA lung cancer patients, there is a growing body of literature that focuses on comparing each option's relative impact on quality of life (QoL). The current study seeks to further understand the differences in these patients' QoL according to surgical approach. **METHODS:** Screening-diagnosed first primary pathologic stage IA non-small-cell lung cancer surgical patients from the I-ELCAP cohort who answered a baseline and 1-year follow-up QoL questionnaire (SF-12) were included in the analysis. Thoracotomy patients (N = 85) were compared with VATS patients (N = 15) using paired t-tests and analysis of variance tests. **RESULTS:** Multivariate analyses indicated no differences in QoL change between the two groups from pre- to post-surgery. Physical and emotional role functioning significantly improved among VATS patients and worsened among thoracotomy patients. Among thoracotomy patients, a significant decrease in post-surgical physical QoL was observed only in those who underwent lobectomy (-3.3; 95% CI: -5.1,-1.5), not limited resection. **CONCLUSIONS:** Although the sample size is small, preliminary findings underscore that changes in overall QoL are similar in VATS and thoracotomy stage IA lung cancer patients. Extension of the resection may be a more relevant factor on QoL post-surgery.

[Perioperative physical exercise interventions for patients undergoing lung cancer surgery: What is the evidence?](#) Mainini C1, Rebelo PF1, Bardelli R1, et al. SAGE Open Med. 2016 Oct 19;4:2050312116673855. eCollection 2016.
Surgical resection appears to be the most effective treatment for early-stage non-small cell lung cancer. Recent studies suggest that perioperative pulmonary rehabilitation improves functional capacity, reduces mortality and postoperative complications and enhances recovery and quality of life in operated patients. Our aim is to analyse and identify the most recent evidence-based physical exercise interventions, performed before or after surgery. We searched in MEDLINE, EMBASE, CINAHL, Cochrane Library and PsycINFO. We included randomised controlled trials aimed at assessing efficacy of exercise-training programmes; physical therapy interventions had to be described in detail in order to be reproducible. Characteristics of studies and programmes, results and outcome data were extracted. Six studies were included, one describing preoperative rehabilitation and three assessing postoperative intervention. It seems that the best preoperative physical therapy training should include aerobic and strength training with a duration of 2-4 weeks. Although results showed improvement in exercise performance after preoperative pulmonary rehabilitation, it was not possible to identify the best preoperative intervention

due to paucity of clinical trials in this area. Physical training programmes differed in every postoperative study with conflicting results, so comparison is difficult. Current literature shows inconsistent results regarding preoperative or postoperative physical exercise in patients undergoing lung resection. Even though few randomised trials were retrieved, treatment protocols were difficult to compare due to variability in design and implementation. Further studies with larger samples and better methodological quality are urgently needed to assess efficacy of both preoperative and postoperative exercise programmes.

Total or partial vertebrectomy for lung cancer invading the spine. Oka S1, Matsumiya H1, Shinohara S1 et al. Ann Med Surg (Lond). 2016 Oct 15;12:1-4. eCollection 2016.
BACKGROUND: Surgery for lung cancer invading the spine remains challenging associated with high morbidity and mortality. However, recent advances in surgical techniques as well as in perioperative care may improve outcomes of lung cancer surgery with vertebrectomy. We describe our surgical approach and assess the outcome lung cancer invading the spine. **METHODS:** We retrospectively reviewed our recent experiences of lung cancer with vertebral invasion, in which we have performed total or partial vertebrectomy from January 2011 through April 2015. **RESULTS:** We experienced eight patients who were treated with partial or total vertebrectomy for lung cancer. Vertebral invasion was evaluated by chest CT and MRI findings. All cases were no distant metastasis. N factors were all patients N0 revealed by chest CT and PET-CT. Two patients were treated preoperative induction therapy (CDDP + TS-1, Radiation 50 Gy). For the surgery, total vertebrectomy was performed two patients, hemi vertebrectomy was two patients, transverse-process resection was four patients. In all of eight cases, complete resection were perfomed with total or partial vertebrectomy. Morbidity was observed in six patients (75%); no mortality occurred. Six patients (75%) were survived after surgery (range: 12-62 months) and four patients (50%) were no recurrence. Five years overall survival rate was 71.4%. **CONCLUSIONS:** In our experience, Lung cancer surgery combined with vertebrectomy is highly aggressive surgery associated with high morbidity. But, this procedure is a promising treatment option for selected patients, for example N0M0 disease with lung cancer invading the spine.

Addition of Surgery After Radiation Significantly Improves Survival in Stage IIIB Non-small Cell Lung Cancer: A Population-Based Analysis. Herskovic A1, Chitti B2, Christos P3, Wernicke AG1, Parashar B4. World J Surg. 2016 Oct 14. [Epub ahead of print]
OBJECTIVES: Limited work, either retrospective or prospective, has been done to investigate whether or not there is a cause-specific mortality (CSM) or all-cause mortality (ACM) benefit to adding surgery following neoadjuvant treatment for Stage IIIB NSCLC. **METHODS:** We extracted patients with Stage IIIB NSCLC from the Survival, Epidemiology, and End Results Program (SEER) database treated from 2004 to 2012 with either radiation alone or radiation followed by surgery. Other variables extracted were age, sex, race, and tumor location. The impact of patient and treatment variables on CSM and ACM was explored using Cox multivariable regression analysis. **RESULTS:** A total of 14,065 patients were extracted from the SEER database. On multivariable analysis, even after adjustment for age, gender, race, and site, radiation followed by surgery was associated with a reduction in cause-specific mortality compared to radiation alone (adjusted HR 0.46; 95 % CI 0.41, 0.52; p < 0.0001). Median overall survival was 11 months in the radiotherapy alone arm versus 29 months in the radiotherapy plus surgery arm (p < 0.0001 by log-rank test). After adjustment for these same factors, radiation followed by surgery was also associated with a reduction in all-cause mortality compared with radiation alone (adjusted HR 0.47; 95 % CI 0.42, 0.52; p < 0.0001). Median cause-specific survival was 12 months in the radiotherapy alone arm versus 33 months in the radiotherapy plus surgery arm (p < 0.0001 by log-rank test). **DISCUSSION:** In the SEER database, there appears to be both a CSM and ACM benefit to adding surgery following radiation for Stage IIIB NSCLC.

Role of Postoperative Radiotherapy in Pathologic Stage IIIA (N2) Non-Small Cell Lung Cancer in a Prospective Nationwide Oncology Outcomes Database. Herskovic A1, Mauer E2, Christos P2, Nagar H1. J Thorac Oncol. 2016 Oct 13. pii: S1556-0864(16)31145-5. doi: 10.1016/j.jtho.2016.09.135. [Epub ahead of print]

BACKGROUND: The role of postoperative radiotherapy (PORT) in the treatment of pathologic stage IIIA (N2) non-small cell lung cancer (NSCLC) remains controversial. We investigated practice patterns and outcomes for these patients in a prospectively maintained nationwide oncology outcomes database.
METHODS: Patients with known histologies of pathologic stage IIIA (N2) NSCLC who underwent surgery with negative margins and received adjuvant multiagent chemotherapy from 2004-2013 were identified from the National Cancer DataBase (NCDB) and stratified by the use of PORT. Multivariable logistic regression modelling was used to examine factors associated with receiving PORT and multivariable proportional hazards regression was used to examine the association of treatment and mortality, adjusting for demographic, socioeconomic and clinicopathologic factors. Landmark analysis and covariate balancing propensity score (CBPS) weighting were also explored to account for immortal time bias and non-randomization. **FINDINGS:** A total of 2,691 patients were identified with median follow-up of 32.32 months. In multivariable analysis, improved overall survival (OS) was associated with multiple factors, including younger age, female sex, lower Charlson-Deyo comorbidity index, histology (squamous better than adenocarcinoma), smaller tumor size, lower pathologic T stage, surgical procedure (pneumonectomy or lobectomy better than sublobar resection), and receiving PORT (all P<0.05). Prior to landmark analysis, the hazard ratio (HR) showed an OS benefit for patients receiving PORT (adjusted HR 0.83, [95% CI, 0.72 to 0.95]; P=0.008). This benefit remained significant after CBPS weighting (HR 0.81, [95% CI, 0.70 to 0.94]; P=0.005), almost significant after landmark analysis (adjusted HR 0.84, [95% CI, 0.69 to 1.007]; P=0.059), and significant after landmark analysis with CBPS weighting (HR 0.77, [95% CI, 0.63 to 0.94]; P=0.009). Median survival past landmark time was 27.43 months in the PORT group and 25.86 months in the non-PORT group. Factors significantly associated with receiving PORT were facility location, facility type, Charlson-Deyo comorbidity index, and grade (all P<0·05).
INTERPRETATION: Improved survival is associated with receipt of PORT for patients with pathologic stage IIIA (N2) NSCLC treated with complete resection and multiagent chemotherapy.

NSCLC - CHEMOTHERAPY

Feasibility of Concomitant Chemoradiotherapy in Daily Practice for Patients with NSCLC Stage III. VAN DER Meer FS1, Schramel FM2, VAN Vulpen M3, El Sharouni SY3. Anticancer Res. 2016 Sep;36(9):4673-6.

BACKGROUND: In patients with non-small cell lung cancer (NSCLC), approximately 25% have locally advanced disease. For patients with irresectable (N2-3 or T4) or inoperable disease, treatment consists of chemoradiotherapy. Concomitant chemoradiotherapy improves survival compared to sequential chemoradiotherapy in these patients. **PATIENTS AND METHODS:** Treatment plans and completion of treatment was evaluated for all patients treated at the St. Antonius Hospital from 2008-2011 for NSCLC stage IIIA/B not eligible for surgery. **RESULTS:** Between 2008 and 2011, 180 patients with NSCLC stage III were treated at our hospital. A total of 152 patients were not eligible for surgery; in 78 (51%) patients, primary treatment was chemoradiotherapy; 31 (20%) were planned for concomitant treatment. The most frequent reasons for refraining from concomitant chemoradiotherapy were limitations of radiotherapy constraints and condition of the patients (87%). **CONCLUSION:** Although concomitant chemoradiotherapy is the standard-of-care in patients with stage IIIA/B NSCLC ineligible for surgery, the majority (80%) of the patients were treated otherwise.

[**Efficacy of crizotinib and pemetrexed-based chemotherapy in Chinese NSCLC patients with ROS1 rearrangement.**](#) Zhang L1, Jiang T1, Zhao C2, et al. Oncotarget. 2016 Oct 12. doi: 10.18632/oncotarget.12612. [Epub ahead of print]

BACKGROUND: ROS1 rearrangement is a novel molecular subgroup of non-small-cell lung cancer (NSCLC). This study aimed to investigate the efficacy of crizotinib and pemetrexed-based chemotherapy in Chinese NSCLC patients with ROS1 rearrangement. **RESULTS:** A total of 2309 patients received ROS1 fusion detection and 51(2.2%) patients had ROS1 rearrangement. There was no significant difference between ROS1 fusion-positive and fusion-negative cohorts in demographic data. For the ROS1 fusion-positive patients, crizotinb-treated group had a higher overall response rate (ORR, 80.0%), disease control rate (DCR, 90.0%) and longer progression-free survival (PFS, 294 days) compared with the rates in pemetrexed-treated group (ORR, 40.8%; DCR, 71.4%; PFS, 179 days) and non-pemetrexed-treated group (ORR, 25.0%; DCR, 47.7%; PFS, 110 days). Besides, ORR, DCR and PFS were similar in three major ROS1 fusion partners. For the first-line treatment, patients received pemetrexed had a significant longer PFS than those received non-pemetrexed chemotherapy (209 vs. 146 days, P = 0.0107). In pemetrexed-treated cohorts, ROS1-positive patients with low TS expression had a statistically significant longer PFS than those with high TS expression (184 vs. 110 days, P = 0.0105). **MATERIALS AND METHODS:** We retrospectively identified patients with NSCLC who were screened for ROS1 fusion using multiplex reverse transcription-polymerase chain reaction (RT-PCR) from October 2013 to February 2016. The thymidylate synthase (TS) mRNA levels were tested using quantitative real-time RT-PCR. **CONCLUSIONS:** Crizotinib was also highly active at treating Chinese NSCLC patients with ROS1 rearrangement. TS expression could predict the efficacy of pemetrexed-based therapy in ROS1 fusion-positive patients.

[**Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study.**](#)
Gomez DR1, Blumenschein GR Jr2, Lee JJ3, et al. Lancet Oncol. 2016 Oct 24. pii: S1470-2045(16)30532-0. doi: 10.1016/S1470-2045(16)30532-0. [Epub ahead of print]

BACKGROUND: Evidence from retrospective studies suggests that disease progression after first-line chemotherapy for metastatic non-small-cell lung cancer (NSCLC) occurs most often at sites of disease known to exist at baseline. However, the potential effect of aggressive local consolidative therapy for patients with oligometastatic NSCLC is unknown. We aimed to assess the effect of local consolidative therapy on progression-free survival. **METHODS:** In this multicentre, randomised, controlled, phase 2 study, eligible patients from three hospitals had histological confirmation of stage IV NSCLC, three or fewer metastatic disease lesions after first-line systemic therapy, an Eastern Cooperative Oncology Group performance status score of 2 or less, had received standard first-line systemic therapy, and had no disease progression before randomisation. First-line therapy was four or more cycles of platinum doublet therapy or 3 or more months of EGFR or ALK inhibitors for patients with EGFR mutations or ALK rearrangements, respectively. Patients were randomly assigned (1:1) to either local consolidative therapy ([chemo]radiotherapy or resection of all lesions) with or without subsequent maintenance treatment or to maintenance treatment alone, which could be observation only. Maintenance treatment was recommended based on a list of approved regimens, and observation was defined as close surveillance without cytotoxic treatment. Randomisation was not masked and was balanced dynamically on five factors: number of metastases, response to initial therapy, CNS metastases, intrathoracic nodal status, and EGFR and ALK status. The primary endpoint was progression-free survival analysed in all patients who were treated and had at least one post-baseline imaging assessment. The study is ongoing but not recruiting participants. This study is registered with ClinicalTrials.gov, number NCT01725165. **FINDINGS:** Between Nov 28, 2012, and Jan 19, 2016, 74 patients were enrolled either during or at the completion of first-line systemic

therapy. The study was terminated early after randomisation of 49 patients (25 in the local consolidative therapy group and 24 in the maintenance treatment group) as part of the annual analyses done by the Data Safety Monitoring Committee of all randomised trials at MD Anderson Cancer Center, and before a planned interim analysis of 44 events. At a median follow-up time for all randomised patients of 12·39 months (IQR 5·52-20·30), the median progression-free survival in the local consolidative therapy group was 11·9 months (90% CI 5·7-20·9) versus 3·9 months (2·3-6·6) in the maintenance treatment group (hazard ratio 0·35 [90% CI 0·18-0·66], log-rank p=0·0054). Adverse events were similar between groups, with no grade 4 adverse events or deaths due to treatment. Grade 3 adverse events in the maintenance therapy group were fatigue (n=1) and anaemia (n=1) and in the local consolidative therapy group were oesophagitis (n=2), anaemia (n=1), pneumothorax (n=1), and abdominal pain (n=1, unlikely related). **INTERPRETATION:** Local consolidative therapy with or without maintenance therapy for patients with three or fewer metastases from NSCLC that did not progress after initial systemic therapy improved progression-free survival compared with maintenance therapy alone. These findings suggest that aggressive local therapy should be further explored in phase 3 trials as a standard treatment option in this clinical scenario.

Safety and efficacy of nivolumab and standard chemotherapy drug combination in patients with advanced non-small-cell lung cancer: a four arms phase Ib study. Kanda S1, Goto K2, Shiraishi H2, et al. Ann Oncol. 2016 Oct 20. pii: mdw416. [Epub ahead of print]
BACKGROUND: The human IgG4 monoclonal antibody nivolumab targets programmed cell death-1 (PD-1) and promotes antitumor response by blocking the interaction of PD-1 with its ligands. This single-center phase Ib study investigated the tolerability, safety, and pharmacokinetics of nivolumab combined with standard chemotherapy in patients with advanced non-small-cell lung cancer (NSCLC).
PATIENTS AND METHODS: Patients who had stage IIIB without indication for definitive radiotherapy, stage IV, or recurrent NSCLC were eligible. Regimens were nivolumab 10 mg/kg + gemcitabine/cisplatin (arm A), pemetrexed/cisplatin (arm B), paclitaxel/carboplatin/bevacizumab (arm C), or docetaxel (arm D). Regimens A, B, and D were repeated every 3 weeks for up to four cycles and regimen C was repeated for up to six cycles; nivolumab alone (arm A), with pemetrexed (arm B), bevacizumab (arm C), or docetaxel (arm D) was continued every 3 weeks as maintenance therapy until disease progression or unacceptable toxicity. Dose-limiting toxicity (DLT) was evaluated during the first treatment cycle. **RESULTS:** As of March 2014, six patients were enrolled in each arm. The combination of nivolumab 10 mg/kg and chemotherapy was well tolerated. DLT was observed in only one patient in arm A (alanine aminotransferase increased). Select adverse events (those with a potential immunologic cause) of any grade were observed in six, four, six, and five patients in arms A, B, C, and D, respectively. Three, three, six, and one patient achieved partial response while median progression-free survival was 6.28, 9.63 months, not reached, and 3.15 months in arms A, B, C, and D, respectively. **CONCLUSIONS:** Combination of nivolumab 10 mg/kg and chemotherapy showed an acceptable toxicity profile and encouraging antitumor activity in patients with advanced NSCLC.

Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. Reck M1, Rodríguez-Abreu D1, Robinson AG1, Hui R1, et al. N Engl J Med. 2016 Oct 8. [Epub ahead of print]
BACKGROUND: Pembrolizumab is a humanized monoclonal antibody against programmed death 1 (PD-1) that has antitumor activity in advanced non-small-cell lung cancer (NSCLC), with increased activity in tumors that express programmed death ligand 1 (PD-L1). **METHODS**: In this open-label, phase 3 trial, we randomly assigned 305 patients who had previously untreated advanced NSCLC with PD-L1 expression on at least 50% of tumor cells and no sensitizing mutation of the epidermal growth factor receptor gene or translocation of the anaplastic lymphoma kinase gene to receive either pembrolizumab (at a fixed dose of 200 mg every 3 weeks) or the investigator's choice of platinum-based

chemotherapy. Crossover from the chemotherapy group to the pembrolizumab group was permitted in the event of disease progression. The primary end point, progression-free survival, was assessed by means of blinded, independent, central radiologic review. Secondary end points were overall survival, objective response rate, and safety. **RESULTS:** Median progression-free survival was 10.3 months (95% confidence interval [CI], 6.7 to not reached) in the pembrolizumab group versus 6.0 months (95% CI, 4.2 to 6.2) in the chemotherapy group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.37 to 0.68; P<0.001). The estimated rate of overall survival at 6 months was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group (hazard ratio for death, 0.60; 95% CI, 0.41 to 0.89; P=0.005). The response rate was higher in the pembrolizumab group than in the chemotherapy group (44.8% vs. 27.8%), the median duration of response was longer (not reached [range, 1.9+ to 14.5+ months] vs. 6.3 months [range, 2.1+ to 12.6+]), and treatment-related adverse events of any grade were less frequent (occurring in 73.4% vs. 90.0% of patients), as were grade 3, 4, or 5 treatment-related adverse events (26.6% vs. 53.3%). **CONCLUSIONS**: In patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy.

[Immune-modulating effects of bevacizumab in metastatic non-small-cell lung cancer patients.](#)
Martino EC1, Misso G2, Pastina P1, et al. Cell Death Discov. 2016 Oct 3;2:16025. eCollection 2016.
The mPEBev is an anticancer regimen which combines a chemotherapy doublet, based on cisplatin and oral etoposide (mPE), with bevacizumab (mPEBev), a mAb targeting the vasculo-endothelial growth factor (VEGF). In previous studies, this regimen showed powerful anti-angiogenetic effects and significant antitumor activity in metastatic non-small-cell lung cancer (mNSCLC) patients. We also recorded the best benefit in patients exhibiting low-systemic inflammatory profile at baseline. On these bases, we hypothesized that mPEBev antitumor activity could be partially related to bevacizumab-associated immunological effects. For this reason, we performed an immunological monitoring in 59 out of 120 stage IIIb-IV NSCLC patients enrolled in the BEVA2007 phase II trial, who received fractioned cisplatin (30 mg/sqm days 1-3q21) and oral etoposide (50 mg, days 1-15q21) (mPE doublet) ±bevacizumab. In this group of patients, 12 received the mPE doublet alone and 47 the doublet in combination with bevacizumab (5 mg/kg on the day 3q21; mPEBev regimen). Blood cell counts, serum analysis, multiplex cytokine assay and immunocytofluorimetric analysis, performed on baseline and post-treatment on blood samples from these patients, revealed that bevacizumab addition to the doublet decreased levels of pro-angiogenic (VEGF, Angiostatin-1 and Follistatin) and inflammatory cytokines (interferon (IFN)γ, IL4 and IL17), improved in vivo and in vitro cytotoxic T-lymphocytes (CTL) response and promoted dendritic cell activation. These results suggest that the mPEBev regimen improve the micro-environmental conditions for an efficient antigen-specific CTL response, making it a feasible candidate regimen to be assessed in combination with immune-checkpoint inhibitors in NSCLC patients.

[Evaluation of erlotinib treatment response in non-small cell lung cancer using metabolic and anatomic criteria.](#) Stefano A1, Russo G, Ippolito M, et al. Q J Nucl Med Mol Imaging. 2016 Sep;60(3):264-73.
BACKGROUND: In this paper the clinical value of PET for early prediction of tumor response to erlotinib in patients with advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen is evaluated. The aim was to compare the early metabolic treatment response using European Organization for Research and Treatment of Cancer (EORTC) 1999 recommendations and PET Response Criteria in Solid Tumors (PERCIST), and the standard treatment response using Response Evaluation Criteria in Solid Tumors (RECIST). **METHODS:** Twenty patients with stage IV NSCLC were enrolled prospectively. PET/CT studies were performed before, then 48 hours, and 45 days after the initiation of erlotinib treatment. The lesion with the highest uptake in each

patient was evaluated according to EORTC 1999 recommendations, PERCIST and RECIST to assess metabolic and anatomic response. Response classifications were compared statistically using Wilcoxon signed-rank test. Disease-free survival (DFS) and overall survival (OS) were calculated by the Kaplan-Meier Test. **RESULTS:** At 48 hours, the Kaplan-Meier analysis showed that EORTC proved to be a significant prognostic factor for predicting DFS and OS. At 45 days, there was a significant difference in response evaluation between RECIST and metabolic classifications. RECIST and PERCIST were significant prognostic factors for predicting DFS and OS. EORTC was not able to discriminate responder from non-responder patients. **CONCLUSIONS:** This study shows that, according to the EORTC protocol, the PET exam is able to provide early identification of patients who benefit from Erlotinib treatment. Used at the end of therapy, PERCIST could be considered an appropriate metabolic evaluation method to discriminate responders from non-responders.

Emergence of resistance to tyrosine kinase inhibitors in non-small-cell lung cancer can be delayed by an upfront combination with the HSP90 inhibitor onalespib.

Courtin A1, Smyth T1, Hearn K1, Saini HK1, Thompson NT1, Lyons JF1, Wallis NG1. Br J Cancer. 2016 Sep 27. doi: 10.1038/bjc.2016.294. [Epub ahead of print]
BACKGROUND: Tyrosine kinase inhibitors, such as crizotinib and erlotinib, are widely used to treat non-small-cell lung cancer, but after initial response, relapse is common because of the emergence of resistance through multiple mechanisms. Here, we investigated whether a frontline combination with an HSP90 inhibitor could delay the emergence of resistance to these inhibitors in preclinical lung cancer models. **METHODS:** The HSP90 inhibitor, onalespib, was combined with either crizotinib or erlotinib in ALK- or EGFR-activated xenograft models respectively (H2228, HCC827). **RESULTS:** In both models, after initial response to the monotherapy kinase inhibitors, tumour relapse was observed. In contrast, tumour growth remained inhibited when treated with an onalespib/kinase inhibitor combination. Analysis of H2228 tumours, which had relapsed on crizotinib monotherapy, identified a number of clinically relevant crizotinib resistance mechanisms, suggesting that HSP90 inhibitor treatment was capable of suppressing multiple mechanisms of resistance. Resistant cell lines, derived from these tumours, retained sensitivity to onalespib (proliferation and signalling pathways were inhibited), indicating that, despite their resistance to crizotinib, they were still sensitive to HSP90 inhibition. **CONCLUSIONS:** Together, these preclinical data suggest that frontline combination with an HSP90 inhibitor may be a method for delaying the emergence of resistance to targeted therapies.

A multicentre phase II trial of cabazitaxel in patients with advanced non-small-cell lung cancer progressing after docetaxel-based chemotherapy.
Kotsakis A1, Matikas A1, Koinis F1, et al. Br J Cancer. 2016 Sep 27;115(7):784-8. doi: 10.1038/bjc.2016.281. Epub 2016 Sep 8.
BACKGROUND: Cabazitaxel, a semisynthetic microtubule inhibitor, has shown antitumour activity in models resistant to paclitaxel and docetaxel, and it has been approved for the treatment of docetaxel-resistant prostate cancer. We investigated its activity in patients with advanced non-small-cell lung cancer (NSCLC) progressing under or after docetaxel-based regimens. **METHODS:** Patients with locally advanced unresectable or metastatic NSCLC, with an Eastern Cooperative Oncology Group performance status of 0-2, were enrolled; patients had to have received up to two prior chemotherapy regimens for the treatment of advanced disease, including one docetaxel-containing regimen. Treatment consisted of cabazitaxel (25 mg m(-2) intravenously, every 21 days) until disease progression. The primary end point was the overall response rate. **RESULTS:** Among the 46 evaluable patients, 28.3% had squamous cell carcinoma and 54.3% had adenocarcinoma. Eight (17.4%) patients had received one and 38 (82.6%) two prior chemotherapy regimens. Treatment compliance was 95%; 26 (16%) cycles were delayed because of toxicity, (n=13) and dose reduction was required in 6 (13%) patients because of haematologic toxicity. Six (13%) patients achieved a partial response and 17 (37.0%) stable disease. The median progression-

free survival and overall survival were 2.1 (95% confidence interval (CI): 1.0-3.2) and 7.4 (95% CI: 5.2-9.6) months, respectively. Grade 4 adverse events included neutropenia (n=8; 17%), febrile neutropenia (n=6; 13%) and thrombocytopenia (n=3; 6.5%). There was one treatment-related death.
CONCLUSIONS: Cabazitaxel exhibits activity in NSCLC patients pre-treated with docetaxel-based chemotherapy with a substantial but manageable toxicity profile. The drug merits further evaluation in this indication.

[Optimum treatment for mediastinal lymph node positive (N2) resectable non-small cell lung cancer: what is the role for surgery?](#) Awan M1, Sharma N2, Towe CW3, Efird JT4, Machtay M1, Biswas T1. Expert Rev Anticancer Ther. 2016 Oct 6:1-14. [Epub ahead of print]
INTRODUCTION: A third of patients with Non-Small Cell Lung Cancer (NSCLC) present with Stage III disease with mediastinal (N2) nodal involvement representing an extremely heterogeneous population with a generally poor prognosis. Areas covered: This article describes the complexity of Stage III-N2 patients reviewing the outcomes of key clinical trials while highlighting the trial designs and subtleties that have created controversy in management. Both bimodality approaches combining chemotherapy with either surgery or radiation and trimodality approaches combining chemotherapy with both local therapies are reviewed. Finally, prognostic factors and future directions are explored for the management of this population. Expert commentary: Upfront surgery is not recommended for patients with Stage III-N2 NSCLC. Neoadjuvant approaches with both chemotherapy and chemoradiation are acceptable in a multidisciplinary setting if appropriate surgery is performed by a dedicated thoracic surgeon. Non-operative candidates should receive definitive concurrent chemoradiation. Innovative approaches are necessary to improve outcomes in this population.

[Drug Dose Per Kilogram Lean Body Mass Predicts Hematologic Toxicity From Carboplatin-Doublet Chemotherapy in Advanced Non-Small-Cell Lung Cancer.](#) Sjøblom B1, Benth JŠ2, Grønberg BH3, Baracos VE4, Sawyer MB5, Fløtten Ø6, Hjermstad MJ7, Aass N8, Jordhøy M9. Clin Lung Cancer. 2016 Oct 5. pii: S1525-7304(16)30234-0. doi: 10.1016/j.cllc.2016.09.008. [Epub ahead of print]
BACKGROUND: Variations in lean body mass (LBM) have been suggested to explain variations in toxicity from systemic cancer treatment. We investigated if drug doses per kilogram of LBM were associated with severe hematologic toxicity (HT) in patients with stage IIIB/IV non-small-cell lung cancer (NSCLC) enrolled onto randomized trials comparing first-line carboplatin-doublets. **PATIENTS AND METHODS:** Patients received carboplatin (AUC [area under the plasma concentration vs. time curve] = 5) plus either pemetrexed 500 mg/m2, gemcitabine 1000 mg/m2, or vinorelbine 60 mg/m2. LBM was estimated from the cross-sectional muscle area at the third lumbar vertebra on computed tomographic scans. Administered doses on day 1, first cycle, were recalculated as milligram of drug per kilogram of LBM. Primary outcome was Common Terminology Criteria for Adverse Events version 3.0 grade 3/4 HT after cycle 1. **RESULTS:** Data from 424 patients were analyzed. Mean age was 65 years, 57% were men, and 78% had stage IV disease. Despite dose individualization by body surface area for the nonplatinum drugs, mean (range) doses expressed as mg/kg LBM showed ~3-fold range: gemcitabine 38.0 (22.5-61.7) mg/kg LBM, pemetrexed 19.1 (8.1-27.9) mg/kg LBM, and vinorelbine 2.4 (1.4-3.6) mg/kg LBM. For these drugs, dose per kilogram of LBM was associated with HT in adjusted multivariate models (P = .004). Taking mean dose per kilogram LBM for each drug as reference, a 1% increase (odds ratio [OR] = 1.03; 95% confidence interval [CI], 1.01-1.06) or 1% decrease (OR = 0.97; 95% CI, 0.95-0.99) was associated with altered risk of grade 3/4 HT. For doses > 20% above and below mean (14% and 15% of patients, respectively) the risk of grade 3/4 HT was almost doubled (OR = 1.93, 95% CI, 1.21-3.10) and halved (OR = 0.52; 95% CI, 0.32-0.83), respectively. **CONCLUSION:** Dose per kilogram of LBM

varied considerably and was an independent predictor of HT. Computed tomography-defined LBM may provide a future basis for better dose individualization.

Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study.

Langer CJ1, Gadgeel SM2, Borghaei H3, et al. Lancet Oncol. 2016 Nov;17(11):1497-1508. doi: 10.1016/S1470-2045(16)30498-3. Epub 2016 Oct 10.

BACKGROUND: Limited evidence exists to show that adding a third agent to platinum-doublet chemotherapy improves efficacy in the first-line advanced non-small-cell lung cancer (NSCLC) setting. The anti-PD-1 antibody pembrolizumab has shown efficacy as monotherapy in patients with advanced NSCLC and has a non-overlapping toxicity profile with chemotherapy. We assessed whether the addition of pembrolizumab to platinum-doublet chemotherapy improves efficacy in patients with advanced non-squamous NSCLC. **METHODS:** In this randomised, open-label, phase 2 cohort of a multicohort study (KEYNOTE-021), patients were enrolled at 26 medical centres in the USA and Taiwan. Patients with chemotherapy-naive, stage IIIB or IV, non-squamous NSCLC without targetable EGFR or ALK genetic aberrations were randomly assigned (1:1) in blocks of four stratified by PD-L1 tumour proportion score ($<1\%$ vs $\geq1\%$) using an interactive voice-response system to 4 cycles of pembrolizumab 200 mg plus carboplatin area under curve 5 mg/mL per min and pemetrexed 500 mg/m2 every 3 weeks followed by pembrolizumab for 24 months and indefinite pemetrexed maintenance therapy or to 4 cycles of carboplatin and pemetrexed alone followed by indefinite pemetrexed maintenance therapy. The primary endpoint was the proportion of patients who achieved an objective response, defined as the percentage of patients with radiologically confirmed complete or partial response according to Response Evaluation Criteria in Solid Tumors version 1.1 assessed by masked, independent central review, in the intention-to-treat population, defined as all patients who were allocated to study treatment. Significance threshold was $p<0\cdot025$ (one sided). Safety was assessed in the as-treated population, defined as all patients who received at least one dose of the assigned study treatment. This trial, which is closed for enrolment but continuing for follow-up, is registered with ClinicalTrials.gov, number NCT02039674. **FINDINGS:** Between Nov 25, 2014, and Jan 25, 2016, 123 patients were enrolled; 60 were randomly assigned to the pembrolizumab plus chemotherapy group and 63 to the chemotherapy alone group. 33 (55%; 95% CI 42-68) of 60 patients in the pembrolizumab plus chemotherapy group achieved an objective response compared with 18 (29%; 18-41) of 63 patients in the chemotherapy alone group (estimated treatment difference 26% [95% CI 9-42%]; p=0·0016). The incidence of grade 3 or worse treatment-related adverse events was similar between groups (23 [39%] of 59 patients in the pembrolizumab plus chemotherapy group and 16 [26%] of 62 in the chemotherapy alone group). The most common grade 3 or worse treatment-related adverse events in the pembrolizumab plus chemotherapy group were anaemia (seven [12%] of 59) and decreased neutrophil count (three [5%]); an additional six events each occurred in two (3%) for acute kidney injury, decreased lymphocyte count, fatigue, neutropenia, and sepsis, and thrombocytopenia. In the chemotherapy alone group, the most common grade 3 or worse events were anaemia (nine [15%] of 62) and decreased neutrophil count, pancytopenia, and thrombocytopenia (two [3%] each). One (2%) of 59 patients in the pembrolizumab plus chemotherapy group experienced treatment-related death because of sepsis compared with two (3%) of 62 patients in the chemotherapy group: one because of sepsis and one because of pancytopenia. **INTERPRETATION:** Combination of pembrolizumab, carboplatin, and pemetrexed could be an effective and tolerable first-line treatment option for patients with advanced non-squamous NSCLC. This finding is being further explored in an ongoing international, randomised, double-blind, phase 3 study.

[Multi-institutional experience of stereotactic body radiotherapy for large (≥5 centimeters) non-small cell lung tumors.](#) Verma V1, Shostrom VK2, Kumar SS3, et al. Cancer. 2016 Oct 14. doi: 10.1002/cncr.30375. [Epub ahead of print]

BACKGROUND: Stereotactic body radiotherapy (SBRT) is the standard of care for patients with nonoperative, early-stage non-small cell lung cancer (NSCLC) measuring < 5 cm, but its use among patients with tumors measuring ≥5 cm is considerably less defined, with the existing literature limited to small, single-institution reports. The current multi-institutional study reported outcomes evaluating the largest such population reported to date. **METHODS:** Clinical/treatment characteristics, outcomes, toxicities, and patterns of failure were assessed in patients with primary NSCLC measuring ≥5 cm without evidence of distant/lymph node metastasis who underwent SBRT using ≤5 fractions. Statistics included Kaplan-Meier survival analyses and univariate/multivariate Cox proportional hazards models. **RESULTS:** A total of 92 patients treated from 2004 through 2016 were analyzed from 12 institutions. The median follow-up was 12 months (15 months in survivors). The median age and tumor size among the patients were 73 years (range, 50-95 years) and 5.4 cm (range, 5.0-7.5 cm), respectively. The median dose/fractionation was 50 Gray/5 fractions. The actuarial local control rates at 1 year and 2 years were 95.7% and 73.2%, respectively. The disease-free survival rate was 72.1% and 53.5%, respectively, at 1 year and 2 years. The 1-year and 2-year disease-specific survival rates were 95.5% and 78.6%, respectively. The median, 1-year, and 2-year overall survival rates were 21.4 months, 76.2%, and 46.4%, respectively. On multivariate analysis, lung cancer history and pre-SBRT positron emission tomography maximum standardized uptake value were found to be associated with overall survival. Posttreatment failures were most commonly distant (33% of all disease recurrences), followed by local (26%) and those occurring elsewhere in the lung (23%). Three patients had isolated local failures. Grade 3 to 4 toxicities included 1 case (1%) and 4 cases (4%) of grade 3 dermatitis and radiation pneumonitis, respectively (toxicities were graded according to the Common Terminology Criteria for Adverse Events [version 4.0]). Grades 2 to 5 radiation pneumonitis occurred in 11% of patients. One patient with a tumor measuring 7.5 cm and a smoking history of 150 pack-years died of radiation pneumonitis. **CONCLUSIONS:** The results of the current study, which is the largest study of patients with NSCLC measuring ≥5 cm reported to date, indicate that SBRT is a safe and efficacious option.

[Postoperative radiotherapy for non-small cell lung cancer.](#) Burdett S1, Rydzewska L, Tierney J, et al. Cochrane Database Syst Rev. 2016 Sep 29;9:CD002142. [Epub ahead of print]

BACKGROUND: The role of postoperative radiotherapy (PORT) in the treatment of patients with completely resected non-small cell lung cancer (NSCLC) was not clear. A systematic review and individual participant data meta-analysis was undertaken to evaluate available evidence from randomised controlled trials (RCTs). These results were first published in Lung Cancer in 2013. **OBJECTIVES:** To evaluate the effects of PORT on survival and recurrence in patients with completely resected NSCLC. To investigate whether predefined patient subgroups benefit more or less from PORT. **SEARCH METHODS:** We supplemented MEDLINE and CANCERLIT searches (1965 to 8 July 2016) with information from trial registers, handsearching of relevant meeting proceedings and discussion with trialists and organisations. **SELECTION CRITERIA:** We included trials of surgery versus surgery plus radiotherapy, provided they randomised participants with NSCLC using a method that precluded prior knowledge of treatment assignment. **DATA COLLECTION AND ANALYSIS:** We carried out a quantitative meta-analysis using updated information from individual participants from all randomised trials. We sought data on all participants from those responsible for the trial. We obtained updated individual participant data (IPD) on survival and date of last follow-up, as well as details on treatment allocation, date of randomisation, age, sex, histological cell type, stage, nodal status and performance

status. To avoid potential bias, we requested information on all randomised participants, including those excluded from investigators' original analyses. We conducted all analyses on intention-to-treat on the endpoint of survival. **MAIN RESULTS:** We identified 14 trials evaluating surgery versus surgery plus radiotherapy. Individual participant data were available for 11 of these trials, and our analyses are based on 2343 participants (1511 deaths). Results show a significant adverse effect of PORT on survival, with a hazard ratio of 1.18, or an 18% relative increase in risk of death. This is equivalent to an absolute detriment of 5% at two years (95% confidence interval (CI) 2% to 9%), reducing overall survival from 58% to 53%. Subgroup analyses showed no differences in effects of PORT by any participant subgroup covariate.We did not undertake analysis of the effects of PORT on quality of life and adverse events. Investigators did not routinely collect quality of life information during these trials, and it was unlikely that any benefit of PORT would offset the observed survival disadvantage. We considered risk of bias in the included trials to be low. **AUTHORS' CONCLUSIONS:** Results from 11 trials and 2343 participants show that PORT is detrimental to those with completely resected non-small cell lung cancer and should not be used in the routine treatment of such patients. Results of ongoing RCTs will clarify the effects of modern radiotherapy in patients with N2 tumours.

[Stereotactic ablative body radiotherapy for non-small cell lung cancer: setup reproducibility with novel arms-down immobilisation.](#) Moore K1, Paterson C2, Hicks J2, Harrow S2, McJury M3. Br J Radiol. 2016 Oct 6:20160227. [Epub ahead of print]
OBJECTIVES: A clinical evaluation of the intrafraction and interfraction set up accuracy of a novel thermoplastic mould immobilisation device and patient position in early stage lung cancer being treated with stereotactic radiotherapy at the Beatson West of Scotland Cancer Centre. **METHODS:** 35 patients were immobilised in a novel, arms-down position, with a 4 point Klarity clear thermoplastic mould fixed to a SinMed head and neck board. A knee support was also used for patient comfort and support. Pre-treatment and post treatment kV (CBCT) images were fused with the planning CT scan to determine intra- and interfraction motion. A total of 175 cone-beam CT scans were analysed in the longitudinal, vertical and lateral directions. **RESULTS:** The mean intrafraction errors were 0.05 mm +/- 0.77 (lateral), 0.44 +/- 1.2 mm (superior-inferior) and -1.44 +/- 1.35 mm (anterior-posterior) respectively. Mean composite 3-D displacement vector was 2.14 +/- 1.2 mm. Interfraction errors were -0.66 +/- 2.35 mm (lateral), -0.13 +/- 3.11 mm (superior-inferior), and 0.00 +/- 2.94 mm (anterior-posterior), with 3-D vector 4.08 +/- 2.73 mm. **CONCLUSIONS:** Setup accuracy for lung image-guided SABR using a unique immobilisation device where patient have arms by their side, has been shown to be safe and favourably comparable to other published setup data where more complex and cumbersome devices were utilised. There was no arm toxicity reported and low arm doses. Advances in knowledge: We report on the accuracy of a novel patient immobilisation device.

[To gate or not to gate - dosimetric evaluation comparing Gated vs. ITV-based methodologies in stereotactic ablative body radiotherapy (SABR) treatment of lung cancer.](#) Kim J1, Wu Q2, Zhao B2, Wen N2, Ajlouni M2, Movsas B2, Chetty IJ2. Radiat Oncol. 2016 Sep 22;11(1):125.
BACKGROUND: To compare retrospectively generated gated plans to conventional internal target volume (ITV)-based plans and to evaluate whether gated radiotherapy provides clinically relevant dosimetric improvements to organs-at-risk (OARs). **METHODS:** Evaluation was performed of 150 stereotactic ablative radiotherapy treatment plans delivered to 128 early-stage (T1-T3 (<5 cm)) NSCLC patients. To generate gated plans, original ITV-based plans were re-optimized and re-calculated on the end-exhale phase and using gated planning target volumes (PTV). Gated and ITV-based plans were produced for 3 × 18 Gy and 4 × 12 Gy fractionation regimens. Dose differences between gated and ITV-based plans were analyzed as a function of both three-dimensional motion and tumor volume. OARs were analyzed using RTOG and AAPM dose constraints. **RESULTS:** Differences between gated and ITV-

based plans for all OAR indices were largest for the 3 × 18 Gy regimen. For this regimen, MLD differences calculated by subtracting the gated values from the ITV-based values (ITV vs. Gated) were 0.10 ± 0.56 Gy for peripheral island (N = 57), 0.16 ± 0.64 Gy for peripheral lung-wall seated (N = 57), and 0.10 ± 0.64 Gy for central tumors (N = 36). Variations in V20 were similarly low, with the greatest differences occurring in peripheral tumors (0.20 ± 1.17 %). Additionally, average differences (in 2Gy-equivalence) between ITV and gated lung indices fell well below clinical tolerance values for all fractionation regimens, with no clinically meaningful differences observed from the 4 × 12 Gy regimen and rarely for the 3 × 18 Gy regimen (<2 % of cases). Dosimetric differences between gated and ITV-based methods did generally increase with increasing tumor motion and decreasing tumor volume. Dose to ribs and bronchial tree were slightly higher in gated plans compared to ITV-based plans and slightly lower for esophagus, heart, spinal cord, and trachea. **CONCLUSIONS:** Analysis of 150 SABR-based lung cancer treatment plans did not show a substantial benefit for the gating regimen when compared to ITV-based treatment plans. Small benefits were observed only for the largest tumor motion (exceeding 2 cm) and the high dose treatment regimen (3 × 18 Gy), though these benefits did not appear to be clinically relevant.

[New approach in lung cancer radiotherapy offers better normal tissue sparing.](#) Mihaylov IB1. Radiother Oncol. 2016 Sep 27. pii: S0167-8140(16)34306-7. doi: 10.1016/j.radonc.2016.09.008. [Epub ahead of print]
PURPOSE: Medical images are more than pictures. They contain additional quantitative information which can be interrogated, quantified, and utilized. Besides anatomical information computed tomography (CT) imaging data provide electron density information. Radiotherapy use of this density information is limited to its application only in dose calculations. The direct product of dose, density, and volume forms a quantity called integral dose. The integral dose delivered to a volume of interest is the total energy deposited in that volume. Here it is hypothesized that minimization of the integral dose is advantageous in radiotherapy planning. The purpose of this work is to study the incorporation of quantitative imaging information in radiotherapy inverse optimization through total energy minimization (Energy hereafter). **DESIGN:** Twenty lung patient plans were studied. For each patient density was quantified on voxel-by-voxel basis through image gray value-to-density conversion curves. Energy-based objective function was used for inverse radiotherapy plan optimization. The obtained plans were evaluated in the light of current standard of care, based on dose-volume (DVH) optimization approach. **RESULTS:** The statistical significance analyses of the results indicated that the doses to normal tissue were between 14% and 45% lower, when Energy-based optimization was used instead of DVH-based optimization. **CONCLUSION:** Incorporation of quantitative imaging information, through CT derived density, in the optimization cost function allows reduction of dose to normal tissue for NSCLC cases. Energy-based radiotherapy plans result in lower normal tissue dose and potentially lower complication rates compared to standard of care. Copyright © 2016 Elsevier Ireland Ltd. All rights reserved.

[Radiation Therapy Plus Anti-Programmed Death Ligand 1 Immunotherapy: A Review on Overall Survival.](#) Krcik EM. Radiol Technol. 2016 Sep;88(1):123-8.
PURPOSE: To analyze current preclinical trials and early clinical trials on the effects of concomitant anti-programmed death ligand 1 (anti-PD-L1) immunotherapy and radiation therapy on progression-free survival (PFS) and overall survival (OS) for advanced melanoma and metastatic non-small cell lung cancer (NSCLC) patients. **METHODS:** A literature review was conducted to find current articles about radiation and anti-PD-L1 combinatorial therapy to gain knowledge about T-lymphocyte (T-cell) mediated immune responses, preclinical mouse tumor trials, and early clinical trials. **RESULTS:** Several preclinical studies involving mice tumor strains and 2 early clinical trials observed an increase in PFS and OS when testing radiation therapy given in combination with anti-PD-L1 immunotherapy. Abscopal

effects of tumor regression and control were notable in some studies. **DISCUSSION:** Low doses of radiation enhance the immune system by increasing T-cell activity. Radiation also increases levels of PD-L1 that inhibit tumor-fighting capabilities of T-cells. Anti-PD-L1 immunotherapy given in combination with radiation therapy has been tested in preclinical studies and hypothesized to increase PFS and OS in patients with advanced melanoma and metastatic NSCLC. **CONCLUSION:** Anti-PD-L1 immunotherapy boosts the immune effects of radiation therapy on tumor regression by eradicating the limiting effects of PD-L1 on the immune system. The combination therapies have the potential to benefit metastatic patients who qualify for the treatment.

[**Institutional Enrollment and Survival Among NSCLC Patients Receiving Chemoradiation: NRG Oncology Radiation Therapy Oncology Group (RTOG) 0617.**](#) Eaton BR1, Pugh SL2, Bradley et al. J Natl Cancer Inst. 2016 May 19;108(9). pii: djw034. doi: 10.1093/jnci/djw034. Print 2016 Sep.
BACKGROUND: The purpose of this analysis is to evaluate the effect of institutional accrual volume on clinical outcomes among patients receiving chemoradiation for locally advanced non-small cell lung cancer (LA-NSCLC) on a phase III trial. **METHODS:** Patients with LA-NSCLC were randomly assigned to 60 Gy or 74 Gy radiotherapy (RT) with concurrent carboplatin/paclitaxel +/- cetuximab on NRG Oncology RTOG 0617. Participating institutions were categorized as low-volume centers (LVCs) or high-volume centers (HVCs) according to the number of patients accrued ($\leq$3 vs > 3). All statistical tests were two-sided. **RESULTS:** Range of accrual for LVCs (n = 195) vs HVCs (n = 300) was 1 to 3 vs 4 to 18 patients. Baseline characteristics were similar between the two cohorts. Treatment at a HVC was associated with statistically significantly longer overall survival (OS) and progression-free survival (PFS) compared with treatment at a LVC (median OS = 26.2 vs 19.8 months; HR = 0.70, 95% CI = 0.56 to 0.88, P = .002; median PFS: 11.4 vs 9.7 months, HR = 0.80, 95% CI = 0.65-0.99, P = .04). Patients treated at HVCs were more often treated with intensity-modulated RT (54.0% vs 39.5%, P = .002), had a lower esophageal dose (mean = 26.1 vs 28.0 Gy, P = .03), and had a lower heart dose (median = V5 Gy 38.2% vs 54.1%, P = .006; V50 Gy 3.6% vs 7.3%, P < .001). Grade 5 adverse events (AEs) (5.3% vs 9.2%, P = .09) and RT termination because of AEs (1.3% vs 4.1%, P = .07) were less common among patients treated at HVCs. HVC remained independently associated with longer OS (P = .03) when accounting for other factors. **CONCLUSION:** Treatment at institutions with higher clinical trial accrual volume is associated with longer OS among patients with LA-NSCLC participating in a phase III trial.

[**Intensity-Modulated Radiation Therapy May Improve Local-Regional Tumor Control for Locally Advanced Non-Small Cell Lung Cancer Compared With Three-Dimensional Conformal Radiation Therapy.**](#) Wang J1, Zhou Z1, Liang J1, et al. Oncologist. 2016 Sep 14. pii: theoncologist.2016-0155. [Epub ahead of print]
BACKGROUND: Consistent results are lacking as regards the comparative effectiveness of intensity-modulated radiotherapy (IMRT) versus three-dimensional conformal radiotherapy (3DCRT) in patients with locally advanced non-small cell lung cancer (LA-NSCLC). **PATIENTS AND METHODS:** Patients treated with definitive radiotherapy (RT) between 2002 and 2010 were retrospectively reviewed. Overall survival (OS), local-regional progression-free survival (LRPFS), distant metastasis-free survival (DMFS), and progression-free survival (PFS) were compared among patients irradiated with different techniques. The association between RT technique and survival indexes was assessed in a Cox proportional hazard regression model. Propensity score matching (PSM) was used to balance known confounding factors. **RESULTS:** A total of 652 patients were eligible for analysis, including 206 with 3DCRT and 446 with IMRT. The median OS of the 3DCRT and IMRT groups were 19.4 and 23.3 months, with the 5-year rate of 13% and 19%, respectively (p = .043). Multivariate analysis identified IMRT as an independent favorable factor associated with LRPFS and DMFS. PSM analysis further verified the beneficial effect of IMRT on LRPFS. No difference in OS or PFS was observed between the two techniques. Subgroup

analysis revealed that IMRT might be differentially more effective in both OS and LRPFS among patients who were female, nonsmokers, with adenocarcinoma, or without weight loss. There was a significant reduction of lung toxicity and similar esophagus toxicity in the IMRT group when compared with the 3DCRT group. **CONCLUSION:** IMRT may confer superior LRPFS and comparable OS than can be achieved with 3DCRT in LA-NSCLC, along with the reduction of pulmonary toxicity. **IMPLICATIONS FOR PRACTICE:** Based on the largest number of patients from a single institution, the present study demonstrated that intensity-modulated radiotherapy (IMRT) could provide superior local-regional progression-free survival and similar overall survival compared with the traditional three-dimensional conformal radiotherapy (3DCRT) for stage III non-small cell lung cancer (NSCLC). IMRT was also found to be associated with the significantly decreased incidence of pulmonary toxicity. These results suggest that IMRT should be considered a surrogate for 3DCRT in locally advanced NSCLC and might be the preferred option for a female nonsmoker with adenocarcinoma and a potentially high risk of pulmonary toxicity from radiotherapy.

Definitive Upfront Stereotactic Ablative Radiotherapy Combined with Image-Guided, Intensity Modulated Radiotherapy (IG-IMRT) or IG-IMRT Alone for Locally Advanced Non-Small Cell Lung Cancer. Chi A1, Wen S2, Monga M3, Almubarak M4, He X5, Rojanasakul Y5, Tse W6, Remick SC4. PLoS One. 2016 Sep 9;11(9):e0162453. doi: 10.1371/journal.pone.0162453. eCollection 2016. **BACKGROUND:** Image-guided (IG) intensity-modulated radiotherapy (IMRT) enables maximal tumor margin reduction for the sparing of organs at risk (OARs) when used to treat locally advanced non-small cell lung cancer (NSCLC) with definitive chemo-radiation. It also allows for the incorporation of stereotactic ablative radiotherapy (SABR) into the treatment regimen. Here, we describe our initial experience in combining definitive upfront SABR to the primary lesion with chemo-radiation delivered with conventionally fractionated IG-IMRT to the remaining regional disease; along with clinical outcome following chemo-radiation with conventionally fractionated IG-IMRT alone in the treatment of locally advanced NSCLC. **METHODS:** The clinical outcome of 29 patients with locally advanced NSCLC who underwent conventionally fractionated IG-IMRT, or definitive upfront SABR followed by IG-IMRT combined with chemotherapy (induction, concurrent, or both) was retrospectively reviewed. **RESULTS:** After a median follow up of 23.7 months, the median overall survival (OS) and progression-free survival (PFS) were 19.8 and 11.3 months, respectively. The 2 year local, regional, and distant control was 60%, 62%, and 38%, respectively. No local failure was observed in 3 patients following SABR + IG-IMRT while 6/26 patients failed locally following IG-IMRT alone. SABR + IG-IMRT was well tolerated. No ≥ grade 3 radiation-related toxicity was observed. **CONCLUSION:** Definitive upfront SABR followed by IG-IMRT in selected patients with locally advanced NSCLC warrants further investigation in future clinical trials, while chemo-radiation with IG-IMRT alone was well tolerated.

Peer Review of Radiotherapy Planning: Quantifying Outcomes and a Proposal for Prospective Data Collection. Mackenzie J1, Graham G2, Olivotto IA3. Clin Oncol (R Coll Radiol). 2016 Sep 12. pii: S0936-6555(16)30275-8. doi: 10.1016/j.clon.2016.08.012. [Epub ahead of print] **AIMS:** The Canadian Partnership for Quality Radiotherapy quality assurance guidelines recommend that radiation oncologist peer review of curative radiotherapy plans takes place ideally before the first fraction of treatment is delivered. This study documented and evaluated the outcomes of weekly, disease site-specific, radiotherapy peer review, quality assurance rounds at the Tom Baker Cancer Centre in Calgary, Canada with a view to making recommendations about the optimal timing and documentation of peer review during the radiotherapy planning processes. **MATERIALS AND METHODS:** Outcomes of each case reviewed at (i) breast, (ii) head and neck (including thyroid and cutaneous cases) and (iii) lung team quality assurance rounds from 6 January to 5 May 2015 were recorded prospectively. Each radiotherapy plan was assigned an outcome: A for plans with no suggested changes; B for satisfactory, but where

issues were raised to consider for future patients; or C when a change was recommended before the first or next fraction. The B outcomes were further subdivided into B1 for a case-specific concern and B2 for a policy gap. Plans were assessed after contour definition and before the plan was formulated (post-contouring reviews) and/or assessed when the plan was complete (post-planning reviews). **RESULTS:** 209 radiotherapy plans prescribed by 20 radiation oncologists were peer reviewed at 43 quality assurance meetings. 93% were curative-intent and 7% were palliative. 83% of plans were reviewed before delivery of the first treatment fraction. There were a total of 257 case reviews: 60 at the post-contouring stage, 197 at the post-planning stage, including 46 patients reviewed at both time points. Overall rates of A, B1, B2 and C outcomes were 78%, 9%, 4% and 9%, respectively. The most common reason for a B or C outcome was related to target volume definition. Only 56% of C outcomes at the post-planning stage would have been detected at the post-contouring stage. Results varied between tumour site groups. **CONCLUSIONS:** 9% of radiotherapy plans reviewed had changes suggested before delivery to the patient. Review at the post-planning stage after plan completion was necessary to detect all suggested changes, but for head and neck cases, all C outcomes could have been detected at the post-contouring stage. More widespread implementation of radiotherapy peer review in the UK is recommended.

[Cost of Intensity-modulated Radiation Therapy for Older Patients with Stage III Lung Cancer.](#)
Kale MS1, Mhango G1, Bonomi M2, Federman A1, Sigel K1, Rosenzweig KE3, Wisnivesky JP1,4. Ann Am Thorac Soc. 2016 Sep;13(9):1593-9. doi: 10.1513/AnnalsATS.201603-156OC.
RATIONALE: In the treatment of stage III non-small cell lung cancer (NSCLC), three-dimensional conformal radiotherapy (3D-RT) is the standard method for radiation delivery; however, intensity-modulated radiotherapy (IMRT) has been rapidly adopted. These two modalities may lead to similar survival, warranting a closer scrutiny of the costs involved. **OBJECTIVES:** The purpose of this study is to compare radiotherapy-related and total costs of older patients with NSCLC treated with 3D-RT versus IMRT. **METHODS:** We conducted a population-based study of all Medicare beneficiaries aged 65 years or older in a Surveillance, Epidemiology and End Results region. Patients were diagnosed with stage III NSCLC diagnosed between 2002 and 2009. Patients received IMRT or 3D-RT in combination with chemotherapy within 4 months of diagnosis. Radiotherapy-related and total adjusted cost and survival of patients receiving 3D-RT versus IMRT were compared using propensity scores methods. **MEASURE-MENTS AND MAIN RESULTS:** Of the 2,418 patients in study, 314 (13%) received IMRT. Adjusted analyses showed no difference in overall survival (hazard ratio, 0.97; 95% confidence interval [CI], 0.85-1.12) in patients treated with 3D-RT versus IMRT. After adjusting for propensity scores, RT-related costs (estimated difference, $6,850; 95% CI, $5,532-$8,168) and total costs (estimated difference, $8,713; 95% CI, $4,376-$13,051) were significantly higher among patients undergoing IMRT. **CONCLUSIONS:** The rapid adoption of IMRT for the treatment of stage III NSCLC has occurred in the absence of evidence from prospective randomized trials. Our results show that IMRT is associated with similar survival but increased costs, underscoring the need for continued research in IMRT and other new technologies.

SMALL CELL LUNG CANCER - SCLC

[Overexpression of pro-gastrin releasing peptide promotes the cell proliferation and progression in small cell lung cancer.](#) Gong Z1, Lu R2, Xie S1, Jiang M3, Liu K3, Xiao R3, Shen J3, Wang Y3, Guo L4. Biochem Biophys Res Commun. 2016 Oct 14;479(2):312-318. doi: 10.1016/j.bbrc.2016.09.066. Epub 2016 Sep 15.
Pro-gastrin releasing peptide (ProGRP) plays the role of oncogene in small cell lung cancer (SCLC). In this study, we aim to explore the biological function of ProGRP in SCLC cells and its potential mechanism. Expression of ProGRP in SCLC tissues and cell lines were detected by

immunohistochemistry and western blot analysis, respectively. The transduced cell lines with ProGRP down-regulation were established using RNA interference technology. Cell viability, cologenic, apoptosis-associated assay and the biomarker levels determination for cell supernatant were performed in the transduced cells to elucidate the biological functions and mechanisms of ProGRP in SCLC cells. Our data showed that ProGRP protein was demonstrated a higher level in SCLC tissues and cells compared with the control, and its diagnostic efficiency was better than NSE, further, the higher levels of ProGRP were detected in the patients with extensive disease stage (P < 0.05), were also the unfavorable factor to the prognosis of SCLC patients. Additionally, the concentration of serum ProGRP is a useful biomarker in disease-monitoring of the patients with SCLC. Down-regulation of ProGRP significantly reduced SCLC cell growth, repressed colony formation, but increased cancer cell apoptosis. Additionally, repression of ProGRP also induced change in the cell cycle and output of NSE. Our data indicated that ProGRP serve as the useful biomarker in the management of SCLC and might be a potential therapeutic target.

[Prophylactic Cranial Irradiation for Patients with Surgically Resected Small Cell Lung Cancer.](#)
Xu J1, Yang H2, Fu X3, et al. J Thorac Oncol. 2016 Oct 7. pii: S1556-0864(16)31139-X. doi: 10.1016/j.jtho.2016.09.133. [Epub ahead of print]
INTRODUCTION: Data on prophylactic cranial irradiation (PCI) after complete resection of SCLC are limited. The purpose of this study was to investigate the impact of PCI in this population. **METHODS:** We retrospectively identified completely resected SCLC at the Shanghai Chest Hospital between January 2006 and January 2014. **RESULTS:** A total of 349 patients (115 patients who received PCI [the PCI-treated cohort] and 234 patients who did not [the non-PCI-treated cohort]) were included in the study. The results demonstrated that the PCI-treated cohort had longer overall survival than the non-PCI-treated cohort among patients with pathologic stage (p-stage) II (hazard ratio [HR] = 0.54, 95% confidence interval [CI]: 0.30-0.99, p = 0.047) and p-stage III (HR = 0.54, 95% CI: 0.34-0.86, p = 0.009) disease. Among patients with p-stage III disease, there was a significantly higher risk for cerebral recurrence from the time of diagnosis in the non-PCI-treated cohort (p = 0.018). With regard to patients with p-stage I disease, neither overall survival benefit (HR = 1.61, 95% CI: 0.68-3.83, p = 0.282) nor risk for cerebral recurrence (p = 0.389) was significant between the PCI-treated and non-PCI-treated cohorts. **CONCLUSIONS:** The data presented in the current study support using PCI in patients with p-stage II/III disease but not in patients with p-stage I disease. A relatively lower risk for brain metastases in p-stage I patients might explain the inferior efficacy of PCI in this population.

[EBUS may arise as an initial time saving procedure in patients who are suspected to have small cell lung cancer.](#)
Ozturk A1, Demirci NY2, Aktas Z2, Demirag F2, Alagoz A2, Alici İO2, Yilmaz A2. Clin Respir J. 2016 Sep 22. doi: 10.1111/crj.12556. [Epub ahead of print]
BACKGROUND: Small cell lung cancer (SCLC) commonly presents as hilar/mediastinal masses. In some occasions, conventional flexible bronchoscopy fails and a substantial amount of time is lost until establishing the diagnosis. **OBJECTIVE:** The aim of the study was to demonstrate the superiority of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) compared to conventional methods in establishing the diagnosis as an initial modality as well as to point out the saved time until the diagnosis. **METHODS:** We retrospectively reviewed the patients who were diagnosed as SCLC by EBUS-TBNA between April 2010 and January 2016. The demographics of the patients, smoking history were all recorded. We also compared the time between the first computed tomography (1stCT) and first diagnostic procedure (1stDP), 1stDP and final diagnosis (FDx), 1stCT and FDx, and 1stDP and EBUS procedure were also compared. **RESULTS:** One hundred and thirty-three patients were included in the study. The diagnostic yield of EBUS-TBNA was 98.5%. The mean time between the 1stCT and 1stDP; 1stDP and FDx; 1stCT and FDx; 1stDP and EBUS procedure were 7.0 ± 9.0;

11.8 ± 16.1; 18.8 ± 17.9; and 10.8 ± 16.0 days, respectively. The time between 1stCT to 1stDP was not significantly different in patients with or without previous diagnostic procedures. However, the time between 1stDP to FDx and 1stCT to FDx were significantly higher in the patients with previous procedures (P < .001). The difference in time between 1stDP to FDx and 1stCT to FDx was also similar in patients with only hilar and/or mediastinal lesions (P = .001, P = .006, respectively). **CONCLUSION:** EBUS-TBNA may be an initial diagnostic procedure in SCLC. Patients with only hilar/mediastinal masses without any endobronchial lesion could be directed to centers with the capability for performing EBUS-TBNA to have a rapid diagnosis without any time loss.

A randomized, double-blind, phase 2 trial of platinum therapy plus etoposide with or without concurrent vandetanib (ZD6474) in patients with previously untreated extensive-stage small cell lung cancer: Hoosier Cancer Research Network LUN06-113.
Sanborn RE1, Patel JD2, Masters GA3, Jayaram N4, Stephens A5, Guarino M3, Misleh J3, Wu J6, Hanna N7. Cancer. 2016 Sep 1. doi: 10.1002/cncr.30287. [Epub ahead of print]
BACKGROUND: This randomized, double-blind, phase 2 trial evaluated whether the addition of vandetanib to platinum plus etoposide for previously untreated extensive-stage small cell lung cancer (SCLC) prolonged the time to disease progression in comparison with chemotherapy alone. **METHODS:** Patients with previously untreated extensive-stage SCLC received platinum (cisplatin or carboplatin) with etoposide in combination with vandetanib (100 mg daily) or a placebo for up to 4 total cycles (no maintenance therapy). An initial safety run-in phase was conducted with the first 6 patients enrolled; all these patients received vandetanib with cisplatin and etoposide. With an overall sample size of 68 patients, the study had 80% power to detect a 3-month difference in the time to progression (TTP) from 4 to 7 months (significance level,.10 [1-sided log-rank test]). **RESULTS:** Seventy-four patients were enrolled between April 2008 and May 2013. Thirty-three patients were ultimately randomized to each arm. The baseline characteristics were well balanced, and the median number of treatment cycles was 4 for each arm. Thirty-one patients in each arm were evaluable for TTP; the median TTP was 5.62 months with vandetanib and 5.68 months with the placebo (P = .9518). The median overall survival was 13.24 months with vandetanib and 9.23 months with the placebo (P = .4577; 33 evaluable patients in each arm). Nonhematologic toxicity was increased with vandetanib versus the placebo. No correlation was seen between vascular endothelial growth factor polymorphisms and outcomes. **CONCLUSIONS:** The addition of vandetanib to platinum and etoposide did not improve outcomes for patients with newly diagnosed extensive-stage SCLC. Toxicity was increased in comparison with chemotherapy alone. Cancer 2016. © 2016 American Cancer Society.

Elevated Cellular PD1/PD-L1 Expression Confers Acquired Resistance to Cisplatin in Small Cell Lung Cancer Cells. Yan F1, Pang J1, Peng Y2, Molina JR3, Yang P4, Liu S1. PLoS One. 2016 Sep 9;11(9):e0162925. doi: 10.1371/journal.pone.0162925. eCollection 2016.
Although small cell lung cancer (SCLC) is highly responsive to chemotherapies (e.g., cisplatin-etoposide doublet), virtually almost all responsive SCLC patients experience disease recurrence characterized by drug resistance. The mechanisms underlying cisplatin resistance remain elusive. Here we report that cell-intrinsic expression of PD1 and PD-L1, two immune checkpoints, is required for sustained expansion of SCLC cells under cisplatin selection. Indeed, PD1 and PD-L1 were expressed at a higher level in lung cancer cell lines, tumor tissues, and importantly, in SCLC cells resistant to cisplatin (H69R, H82R), when compared to respective controls. Genetic abrogation of PD1 and PD-L1 in H69R and H82R cells decreased their proliferation rate, and restored their sensitivity to cisplatin. Mechanistically, PD-L1 upregulation in H69R and H82R cells was attributed to the overexpression of DNA methyltransferase 1 (DNMT1) or receptor tyrosine kinase KIT, as knockdown of DNMT1 or KIT in H69R and H82R cells led to PD-L1 downregulation. Consequently, combined knockdown of PD-L1 with KIT or DNMT1 resulted

in more pronounced inhibition of H69R and H82R cell growth. Thus, cell intrinsic PD1/PD-L1 signaling may be a predictor for poor efficacy of cisplatin treatment, and targeting the cellular PD1/PD-L1 axis may improve chemosensitization of aggressive SCLC.

[A Randomized Phase II Study of Linsitinib (OSI-906) Versus Topotecan in Patients With Relapsed Small-Cell Lung Cancer.](#) Chiappori AA1, Otterson GA2, Dowlati A3, et al. Oncologist. 2016 Sep 30. pii: theoncologist.2016-0220. [Epub ahead of print]
LESSONS LEARNED: Targeted therapy options for SCLC patients are limited; no agent, thus far, has resulted in a strategy promising enough to progress to phase III trials.Linsitinib, a potent insulin growth factor-1-receptor tyrosine kinase inhibitor, may be one agent with activity against SCLC.Despite lack of a reliable predictive biomarker in this disease, which may have partly contributed to the negative outcome reported here, linsitinib, although safe, showed no clinical activity in unselected, relapsed SCLC patients.
BACKGROUND: Treatment of relapsed small-cell lung cancer (SCLC) remains suboptimal. Insulin growth factor-1 receptor (IGF-1R) signaling plays a role in growth, survival, and chemoresistance in SCLC. Linsitinib is a potent IGF-1R tyrosine kinase inhibitor that potentially may be active against SCLC. **METHODS:** In this phase II study, 8 eligible patients were randomly assigned in a 1:2 ratio to topotecan (1.5 mg/m2 intravenously or 2.3 mg/m2 orally, daily for 5 days for 4 cycles) or linsitinib (150 mg orally twice daily until progression). The primary endpoint was progression-free survival. Patients with relapsed SCLC, platinum sensitive or resistant, performance status (PS) 0-2, and adequate hematologic, renal, and hepatic function were enrolled. Patients with diabetes, cirrhosis, and those taking insulinotropic agents were excluded. Crossover to linsitinib was allowed at progression. **RESULTS:** Fifteen patients received topotecan (8 resistant, 3 with PS 2) and 29 received linsitinib (16 resistant, 5 with PS 2). Two partial responses were observed with topotecan. Only 4 of 15 patients with topotecan and 1 of 29 with linsitinib achieved stable disease. Median progression-free survival was 3.0 (95% confidence interval [CI], 1.5-3.6) and 1.2 (95% CI, 1.1-1.4) months for topotecan and linsitinib, respectively (p = .0001). Median survival was 5.3 (95% CI, 2.2-7.6) and 3.4 (95% CI, 1.8-5.6) months for topotecan and linsitinib, respectively (p = .71). Grade 3/4 adverse events (>5% incidence) included anemia, thrombocytopenia, neutropenia/leukopenia, diarrhea, fatigue, dehydration, and hypokalemia for topotecan; and thrombocytopenia, fatigue, and alanine aminotransferase/aspartate aminotransferase elevations for linsitinib. **CONCLUSION:** Linsitinib was safe but showed no clinical activity in unselected, relapsed SCLC patients.

PALLIATIVE AND SUPPORTIVE CARE

[Impact of early Palliative Care on Caregivers of Patients with Advanced Cancer: Cluster Randomised Trial.](#) McDonald J1, Swami N2, Hannon B1, et al. Ann Oncol. 2016 Sep 29. pii: mdw438. [Epub ahead of print]
BACKGROUND: Early palliative care improves the quality of life (QOL) and satisfaction with care of patients with advanced cancer, but little is known about its effect on caregivers. Here we report outcomes of caregiver satisfaction with care and QOL from a trial of early palliative care.
PATIENT AND METHODS: Twenty-four medical oncology clinics were cluster-randomised, stratified by tumour site (lung, gastrointestinal, genitourinary, breast, gynaecological), to early palliative care team referral, or to standard oncology care with palliative care only as needed. Caregivers of patients with advanced cancer (clinical prognosis of 6-24 months, ECOG 0-2) in both trial arms completed validated measures assessing satisfaction with care (FAMCARE-19) and QOL (SF-36v2 Health Survey; Caregiver QOL-Cancer [CQOL-C]), at baseline and monthly for 4 months. We used a multilevel linear random-intercept mixed effect model to test whether there was improvement in the intervention group relative to the control group over 3 and 4 months. **RESULTS:** A total of 182 caregivers completed baseline

measures (94 intervention, 88 control); 151 caregivers (77 intervention, 74 control), completed at least one follow-up assessment. Satisfaction with care improved in the palliative intervention group compared to controls over 3 months (p=0.007) and 4 months (p=0.02). There was no significant improvement in the intervention group compared to controls for CQOL-C (3 months: p=0.92, 4 months: p=0.51), SF-36 PCS (3 months: p=0.83, 4 months: p=0.20), or SF-36 MCS (3 months: p=0.87, 4 months: p=0.60).
CONCLUSION: Early palliative care increased satisfaction with care in caregivers of patients with advanced cancer.

Weight gain as a surrogate marker of longer survival in advanced non-small cell lung cancer patients. Topkan E1. Ann Transl Med. 2016 Oct;4(19):381.
Weight loss (WL), as a key step of the irreversible and fatal cancer-related anorexia cachexia syndrome is present to some degree in 80% of non-small cell lung cancer (NSCLC) patients upon diagnosis which has been clearly proved to negatively alter patients' performance status, quality of life (QOL), response to treatment, and prognosis. However, WL is not a problem encountered only upon diagnosis but is also commonly reported during the course of aggressive chemotherapy, radiotherapy (RT) and particularly the concurrent chemoradiotherapy (C-CRT) which may further diminish QOL measures and clinical outcomes. In general, the NSCLC literature has concentrated on WL during the treatment course, but recent studies have demonstrated that it is possible to preserve or even experience weight gain (WG) during or just short after the discontinuation of various cancer treatments in approximately 40% to 45% NSCLC patients. Considering the fact that recent evidence suggest a prognostic and predictive role for WG in anticipation of longer survival times and better response rates in weight gainers, this current manuscript will specifically aim to realize the actual value of WG in locally advanced and metastatic NSCLC patients which may potentially be added to the conventional prognostic and predictive factors as a novel surrogate marker of outcomes in such patients.

Anti-PD1-induced psoriasis. A study of 21 patients. Bonigen J1, Raynaud-Donzel C2, Hureaux J3, et al. J Eur Acad Dermatol Venereol. 2016 Oct 14. doi: 10.1111/jdv.14011. [Epub ahead of print]
Nivolumab (Opdivo®), pembrolizumab (Keytruda®), atezolizumab, and pidilizumabab are anti-PD1 monoclonal antibodies. Nivolumab is licensed in advanced melanoma and second-line therapy of advanced or metastatic non-small cell lung cancer. When activated, the programmed cell death (PD)-1 is implicated in the inhibition of the immune system. Anti-PD1 removes this inhibition and allows the immune system to control tumour cell progression.1-4 Immune-mediated toxicity of this treatment have been reported, either organ-specific toxicities - i.e. pneumonia, colitis, hepatitis, hypophysitis, and thyroiditis - or skin toxicities - i.e. vitiligo, photosensitivity, lichenoid eruption. Recently, cases of anti-PD1-induced psoriasis have been reported.

Changes in Health-Related Quality of Life During Rehabilitation in Patients With Operable Lung Cancer: A Feasibility Study (PROLUCA). Sommer MS1, Trier K2, Vibe-Petersen J2, et al. Integr Cancer Ther. 2016 Oct 3. pii: 1534735416668258. [Epub ahead of print]
INTRODUCTION: Surgical resection in patients with non-small cell lung cancer (NSCLC) may be associated with significant morbidity, functional limitations, and decreased quality of life.
OBJECTIVES: The objective is to present health-related quality of life (HRQoL) changes over time before and 1 year after surgery in patients with NSCLC participating in a rehabilitation program.
METHODS: Forty patients with NSCLC in disease stage I to IIIa, referred for surgical resection at the Department of Cardiothoracic Surgery RT, Rigshospitalet, were included in the study. The rehabilitation program comprised supervised group exercise program, 2 hours weekly for 12 weeks, combined with individual counseling. The study endpoints were self-reported HRQoL (Functional Assessment of Cancer Therapy-Lung, European Organization for Research and Treatment in Cancer-Quality of Life

Questionnaire-QLQ-C30, Short-Form-36) and self-reported distress, anxiety, depression, and social support (National Comprehensive Cancer Network Distress Thermometer, Hospital Anxiety and Depression Scale, Multidimensional Scale of Perceived Social Support), measured presurgery, postintervention, 6 months, and 1 year after surgery. **RESULTS:** Forty patients were included, 73% of whom completed rehabilitation. Results on emotional well-being (P < .0001), global quality of life (P = .0032), and mental health component score (P = .0004) showed an overall statistically significant improvement during the study. **CONCLUSION:** This feasibility study demonstrated that global quality of life, mental health, and emotional well-being improved significantly during the study, from time of diagnosis until 1 year after resection, in patients with NSCLC participating in rehabilitation.
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[Factors associated with oncology patients' involvement in shared decision making during chemotherapy.](#) Colley A1, Halpern J1, Paul S2, et al. Psychooncology. 2016 Sep 20. doi: 10.1002/pon.4284. [Epub ahead of print]
OBJECTIVE: Oncology patients are increasingly encouraged to play an active role in treatment decision making. While previous studies have evaluated relationships between demographic characteristics and decision-making roles, less is known about the association of symptoms and psychological adjustment characteristics (eg, coping styles and personality traits) and decision-making roles. **METHODS:** As part of a larger study of symptom clusters, patients (n = 765) receiving chemotherapy for breast, gastrointestinal, gynecological, or lung cancer provided information on demographic, clinical, symptom, and psychological adjustment characteristics. Patient-reported treatment decision-making roles (ie, preferred role and role actually played) were assessed using the Control Preferences Scale. Differences among patients, who were classified as passive, collaborative, or active, were evaluated using $\chi 2$ analyses and analyses of variance. **RESULTS:** Over half (56.3%) of the patients reported that they both preferred and actually played a collaborative role. Among those patients with concordant roles, those who were older, those with less education and lower income, and those who were less resilient were more likely to prefer a passive role. Several psychological adjustment characteristics were associated with decision-making role, including coping style, personality, and fatalism. **CONCLUSIONS:** Oncology patients' preferences for involvement in treatment decision making are associated with demographic characteristics as well as with symptoms and psychological adjustment characteristics, such as coping style and personality. These results reaffirm the complexities of predicting patients' preferences for involvement in decision making. Further study is needed to determine if role or coping style may be influenced by interventions designed to teach adaptive coping skills.
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[A nested cohort study to identify characteristics that predict near-term disablement from lung cancer brain metastases.](#) Cheville AL1, Basford JR2, Parney I3, Yang P4, Diehn FE5. Arch Phys Med Rehabil. 2016 Sep 22. pii: S0003-9993(16)30978-9. doi: 10.1016/j.apmr.2016.08.473. [Epub ahead of print]
OBJECTIVES: To test whether the presence of patient- and imaging-level characteristics: 1) are associated with clinically meaningful changes in mobility among late stage cancer patients with metastatic brain involvement; and 2) can predict their risk of near-term functional decline. **DESIGN:** Prospective nested cohort study SETTING: Quaternary academic medical center PARTICIPANTS: The study population consisted of a nested cohort of the 66 patients with imaging confirmed brain metastases among a larger cohort of 311 patients with late stage lung cancer. **INTERVENTIONS:** Not applicable MAIN OUTCOMES: Functional evaluations with the Activity Measure for Post-Acute Care Computer Adaptive Test (AM-PAC-CAT) and symptom intensity ratings were collected at monthly intervals for up to 2 years.

RESULTS: In exploratory univariate models, whole brain radiation therapy (WBRT) and imaging findings of cerebellar or brain stem involvement were associated with large AM-PAC-CAT declines in mobility (-4.55, SE 1.12; -2.87, SE 1.0; and -3.14, SE 1.47, respectively). Also in univariate models, participants with new neurological signs or symptoms at imaging (-2.48, SE 0.99), new brain metastases (-2.14, SE 0.99), or new and expanding metastases (-2.64, SE 1.14) declined significantly. Multivariate exploratory mixed logistic models including WBRT, cerebellar/brainstem location, presence of new and expanding metastases, and worst pain intensity had excellent predictive capabilities for AM-PAC-CAT score declines of 7.5 and 10 points, C statistics >0.8. **CONCLUSIONS:** Among patients with lung cancer and brain metastases, a cerebellar/brainstem location, new and expanding metastases, and treatment with WBRT may predict severe, near-term mobility losses and indicate a need to consider rehabilitation services.

Does physical exercise improve quality of life of advanced cancer patients? Navigante A1, Morgado PC. Curr Opin Support Palliat Care. 2016 Sep 28. [Epub ahead of print]
PURPOSE OF REVIEW: We discuss the principal issues about physical activity in advanced cancer patients through the analyses of the last articles and our experience in this field. **RECENT FINDINGS:** The efficacy of exercise training intervention could improve quality of life (QOL), fatigue and well being in advanced cancer patients. Several published studies have included, nevertheless, patients with early stage of disease and more recently, populations of patients with local advanced tumors of the breast, rectum and lung, who are undergoing neoadjuvant therapy. Despite the insufficient sample of patients in these studies, physical exercise is considered to improve both cardiopulmonary function and physical muscle fitness. Cancer-related fatigue is a devastating symptom in advanced cancer patients that implies loss of mobility and independence. **SUMMARY:** Physical exercise could be a treatment to increase skeletal muscle endurance and improve well being. In palliative medicine, physical activity could be applied to medical assistance or to design prospective and controlled trials so as to evaluate possible usefulness.

Appetite Loss as an Adverse Effect During Treatment with EGFR-TKIs in Elderly Patients with Non-small Cell Lung Cancer. Inomata M1, Shimokawa K2, Tokui K2, et al. Anticancer Res. 2016
AIM: We conducted a retrospective study to investigate the frequency of appetite loss during treatment with epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) in elderly patients, aged 75 years or older, with non-small cell lung cancer harboring EGFR gene mutations. **PATIENTS AND METHODS:** Data of a total of 64 patients, including 39 relatively young (hereinafter, younger) patients and 25 elderly patients were analyzed. **RESULTS:** Appetite loss of all grades (p=0.074) and of grade 3 or greater (p=0.030) was more frequently observed in elderly patients. Diarrhea and oral mucositis were also more frequent in elderly patients, although they did not reach statistical significance. No apparent differences were observed in the frequency of aspartate aminotransferase/ alanine aminotransferase elevation, skin rash or fatigue between the two patient groups. The median (95% confidence interval) progression-free survival times were 10.8 (6.6-16.4) months and 11.8 (4.4-20.3) months in the younger and elderly patient groups, respectively. **CONCLUSION:** Our findings suggest that appetite loss is a major adverse effect in elderly patients with non-small cell lung cancer receiving treatment with EGFR-TKIs.

COMPLEMENTARY & ALTERNATIVE THERAPY

Honokiol inhibits EMT-mediated motility and migration of human non-small cell lung cancer cells in vitro by targeting c-FLIP. Lv XQ1, Qiao XR1, Su L2, Chen SZ1. Acta Pharmacol Sin. 2016 Sep 5. doi: 10.1038/aps.2016.81. [Epub ahead of print]

AIM: Honokiol (HNK) is a natural compound isolated from the magnolia plant with numerous pharmacological activities, including inhibiting epithelial-mesenchymal transition (EMT), which has been proposed as an attractive target for anti-tumor drugs to prevent tumor migration. In this study we investigated the effects of HNK on EMT in human NSCLC cells in vitro and the related signaling mechanisms. **METHODS:** TNF-α (25 ng/mL) in combination with TGF-β1 (5 ng/mL) was used to stimulate EMT of human NSCLC A549 and H460 cells. Cell proliferation was analyzed using a sulforhodamine B assay. A wound-healing assay and a transwell assay were performed to examine cell motility. Western blotting was used to detect the expression levels of relevant proteins. siRNAs were used to knock down the gene expression of c-FLIP and N-cadherin. Stable overexpression of c-FLIP L (H157-FLIP L) or Lac Z (H157-Lac Z) was also performed. **RESULTS:** Treatment with TNF-α+TGF-β1 significantly enhanced the migration of A549 and H460 cells, increased c-FLIP, N-cadherin (a mesenchymal marker), snail (a transcriptional modulator) and p-Smad2/3 expression, and decreased IκB levels in the cells; these changes were abrogated by co-treatment with HNK (30 μmol/L). Further studies demonstrated that expression level of c-FLIP was highly correlated with the movement and migration of NSCLC cells, and the downstream effectors of c-FLIP signaling were NF-κB signaling and N-cadherin/snail signaling, while Smad signaling might lie upstream of c-FLIP. **CONCLUSION:** HNK inhibits EMT-mediated motility and migration of human NSCLC cells in vitro by targeting c-FLIP, which can be utilized as a promising target for cancer therapy, while HNK may become a potential anti-metastasis drug or lead compound.

[**Comprehensive treatment with Chinese medicine in patients with advanced non-small cell lung cancer: A multicenter, prospective, cohort study.**](#) Liu J1, Lin HS2, Hou W3, et al. Chin J Integr Med. 2016 Oct 28. [Epub ahead of print]

OBJECTIVE: To determine whether additional Chinese medicine (CM) could prolong survival and improve the quality of life (QOL) in patients with advanced non-small cell lung cancer (NSCLC) compared with Western medicine (WM) alone. **METHODS:** This was a multicenter, prospective cohort study. A total of 474 hospitalized patients with stage III-IV NSCLC were recruited and divided into 2 groups. Patients in the WM group received radiotherapy, chemotherapy, and optimal supportive therapy according to the National Comprehensive Cancer Network (NCCN) guidelines. In the integrative medicine (IM) group, individualized CM (Chinese patent medicines and injections) and WM were administered. The primary end point was overall survival, and the secondary end points were time to disease progression, adverse events, and QOL. Follow-up clinical examinations and chest radiography were performed every 2 months. **RESULTS:** The median survival was 16.60 months in the IM group and 13.13 months in the WM group (P<0.01). The incidences of loss of appetite, nausea, and vomiting in the IM group were significantly lower than those in the WM group (P<0.05). The global QOL based on Functional Assessment of Cancer Therapy-Lung in the IM group was markedly higher than that in the WM group at the fourth course (P<0.05). **CONCLUSIONS:** Additional CM may prolong survival and improve the QOL patients with NSCLC. The adverse effects of radio- and chemotherapy may be attenuated if CM is used in combination with conventional treatments.

[**Combination Therapy of Gefitinib and Korean Herbal Medicines Could be a Beneficial Option for Patients with Non-Small-Cell Lung Cancer.**](#) Lee K1, Kim YS2, Son CG3, Cho JH3, Yoo HS4, Lee J5, Ryu J1, Lee N1. J Pharmacopuncture. 2016 Sep;19(3):259-263.

Lung cancer has a high mortality rate and is often diagnosed at the metastatic stage. Gefitinib is a targeted molecular therapeutic drug used to treat patients with non-small-cell lung cancer (NSCLC). Korean herbal medicines may also have therapeutic efficacy against lung cancer, reduce the side effects associated with chemotherapy, and improve patient quality of life (QOL). This case report describes the effects of a Korean herbal medicine regimen combined with gefitinib in a patient with NSCLC and bone metastasis.

The Korean herbal medicine regimen included woohwanggeosa-dan, hwanggibujeong-dan and geonchilgyebok-jeong. The computed tomography (CT) findings showed that following combination treatment, the size of the tumor was markedly decreased without serious adverse events. Moreover, the Eastern Cooperative Oncology Group (ECOG) performance status was improved and cancer-related pain was decreased. These results suggest that a combination of Korean herbal medicines and gefitinib may be an effective therapeutic option for patients with advanced NSCLC and bone metastasis. Further studies are needed to examine the mechanism and the clinical efficacy of Korean herbal medicines against NSCLC. Lung cancer has a high mortality rate and is often diagnosed at the metastatic stage. Gefitinib is a targeted molecular therapeutic drug used to treat patients with non-small-cell lung cancer (NSCLC). Korean herbal medicines may also have therapeutic efficacy against lung cancer, reduce the side effects associated with chemotherapy, and improve patient quality of life (QOL). This case report describes the effects of a Korean herbal medicine regimen combined with gefitinib in a patient with NSCLC and bone metastasis. The Korean herbal medicine regimen included woohwanggeosa-dan, hwanggibujeong-dan and geonchilgyebok-jeong. The computed tomography (CT) findings showed that following combination treatment, the size of the tumor was markedly decreased without serious adverse events. Moreover, the Eastern Cooperative Oncology Group (ECOG) performance status was improved and cancer-related pain was decreased. These results suggest that a combination of Korean herbal medicines and gefitinib may be an effective therapeutic option for patients with advanced NSCLC and bone metastasis. Further studies are needed to examine the mechanism and the clinical efficacy of Korean herbal medicines against NSCLC.

General and Genetic Toxicology of Enzyme-Treated Ginseng Extract: Toxicology of Ginseng Rh2.
Jeong MK1, Cho CK1, Yoo HS1. J Pharmacopuncture. 2016 Sep;19(3):213-224.
OBJECTIVES: Ginseng Rh2+ is enzyme-treated ginseng extract containing high amounts of converted ginsenosides, such as compound k, Rh2, Rg3, which have potent anticancer activity. We conducted general and genetic toxicity tests to evaluate the safety of ginseng Rh2+. **METHODS:** An acute oral toxicity test was performed at a high-level dose of 4,000 mg/kg/day in Sprague-Dawley (SD) rats. A 14-day range-finding study was also conducted to set dose levels for the 90-day study. A subchronic 90-day toxicity study was performed at dose levels of 1,000 and 2,000 mg/kg/day to investigate the no-observed-adverse-effect level (NOAEL) of ginseng Rh2+ and target organs. To identify the mutagenic potential of ginseng Rh2+, we conducted a bacterial reverse mutation test (Ames test) using amino-acid-requiring strains of Salmonella typhimurium and Escherichia coli (E. coli), a chromosome aberration test with Chinese hamster lung (CHL) cells, and an in vivo micronucleus test using ICR mice bone marrow as recommended by the Korean Ministry of Food and Drug Safety. **RESULTS:** According to the results of the acute oral toxicity study, the approximate lethal dose (ALD) of ginseng Rh2+ was estimated to be higher than 4,000 mg/kg. For the 90-day study, no toxicological effect of ginseng Rh2+ was observed in body-weight changes, food consumption, clinical signs, organ weights, histopathology, ophthalmology, and clinical pathology. The NOAEL of ginseng Rh2+ was established to be 2,000 mg/kg/day, and no target organ was found in this test. In addition, no evidence of mutagenicity was found either on the in vitro genotoxicity tests, including the Ames test and the chromosome aberration test, or on the in vivo in mice bone marrow micronucleus test. **CONCLUSION:** On the basis of our findings, ginseng Rh2+ is a non-toxic material with no genotoxicity. We expect that ginseng Rh2+ may be used as a novel adjuvant anticancer agent that is safe for long-term administration.

[Preventable Incidence and Mortality of Carcinoma Associated With Lifestyle Factors Among White Adults in the United States.](#) Song M1, Giovannucci E2. JAMA Oncol. 2016 Sep 1;2(9):1154-61. doi: 10.1001/jamaoncol.2016.0843.

IMPORTANCE:
Lifestyle factors are important for cancer development. However, a recent study has been interpreted to suggest that random mutations during stem cell divisions are the major contributor to human cancer. **OBJECTIVE:** To estimate the proportion of cases and deaths of carcinoma (all cancers except skin, brain, lymphatic, hematologic, and nonfatal prostate malignancies) among whites in the United States that can be potentially prevented by lifestyle modification. **DESIGN, SETTING, AND PARTICIPANTS:** This prospective cohort study analyzes cancer and lifestyle data from the Nurses' Health Study, the Health Professionals Follow-up Study, and US national cancer statistics to evaluate associations between lifestyle and cancer incidence and mortality. **EXPOSURES:** A healthy lifestyle pattern was defined as never or past smoking (pack-years <5), no or moderate alcohol drinking (≤1 drink/d for women, ≤2 drinks/d for men), BMI of at least 18.5 but lower than 27.5, and weekly aerobic physical activity of at least 75 vigorous-intensity or 150 moderate-intensity minutes. Participants meeting all 4 of these criteria made up the low-risk group; all others, the high-risk group. **MAIN OUTCOMES AND MEASURES:** We calculated the population-attributable risk (PAR) by comparing incidence and mortality of total and major individual carcinomas between the low- and high-risk groups. We further assessed the PAR at the national scale by comparing the low-risk group with the US population. **RESULTS:** A total of 89 571 women and 46 339 men from 2 cohorts were included in the study: 16 531 women and 11 731 men had a healthy lifestyle pattern (low-risk group), and the remaining 73 040 women and 34 608 men made up the high-risk group. Within the 2 cohorts, the PARs for incidence and mortality of total carcinoma were 25% and 48% in women, and 33% and 44% in men, respectively. For individual cancers, the respective PARs in women and men were 82% and 78% for lung, 29% and 20% for colon and rectum, 30% and 29% for pancreas, and 36% and 44% for bladder. Similar estimates were obtained for mortality. The PARs were 4% and 12% for breast cancer incidence and mortality, and 21% for fatal prostate cancer. Substantially higher PARs were obtained when the low-risk group was compared with the US population. For example, the PARs in women and men were 41% and 63% for incidence of total carcinoma, and 60% and 59% for colorectal cancer, respectively. **CONCLUSIONS AND RELEVANCE:** A substantial cancer burden may be prevented through lifestyle modification. Primary prevention should remain a priority for cancer control.