# Caring Ambassadors Lung Cancer Program
## Literature Review,  October 2018

## BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

**Phosphorylation of nucleolin is indispensable to its involvement in the proliferation and migration of non-small cell lung cancer cells.** Huang F1, Wu Y2, Tan H1, Guo T1, Zhang K1, Li D1, Tong Z1. Oncol Rep. 2018 Oct 12. doi: 10.3892/or.2018.6787. [Epub ahead of print]

Non-small cell lung cancer (NSCLC) is one of the mostly deadly malignancies in the world. Nucleolin is a multifunctional protein that mainly regulates ribosome biogenesis but also has other functions including modulating the transcription of mRNAs and repressing RNA polymerase II. Nucleolin is overexpressed in various cancer cells, including NSCLC cells. It can confer resistance to apoptosis and promote cell migration and blood vessel formation by directly taking part in various tumor signal transduction pathways. The activities of nucleolin are regulated mainly by intracellular localization and post-translational modifications, including phosphorylation, glycosylation, methylation, and ADP-ribosylation. Phosphorylation of nucleolin (P-nucleolin) in NSCLC cells is still not well characterized. In the present study, the levels of nucleolin and P-nucleolin were examined in lung tissue and cells and it was demonstrated that levels of the two forms of nucleolin were significantly increased in NSCLC compared with non-cancerous tissues and cells. In addition, it was demonstrated that high expression levels of nucleolin and P-nucleolin were significantly associated with poor overall survival of NSCLC patients. Doxorubicin (DOX) is a type of anthracycline that has been used in the treatment of various types of cancer, including NSCLC. Upregulation of nucleolin through exogenous expression of nucleolin promoted A549 cell proliferation and migration, while downregulation of nucleolin through expression of small interfering RNA-nucleolin attenuated A549 cell proliferation and migration. Following stimulation with DOX, A549 cell proliferation and migration decreased and the expression of P-nucleolin also decreased. In order to investigate whether P-nucleolin is indispensable to the proliferation and migration of NSCLC cells, a plasmid encoding mutant nucleolin, in which the phosphorylation site at threonine-76 was mutated to alanine, was constructed. Compared with the A549 cells transfected with wild-type nucleolin, P-nucleolin expression and cell proliferation and migration were significantly decreased in

A549 cells transfected with mutant nucleolin. These results indicate that targeting P-nucleolin may be a promising strategy for treating NSCLC patients.

**A Transcriptomic Analysis of the Development of Skeletal Muscle Atrophy in Cancer-Cachexia in Tumor-Bearing Mice.** Blackwell TA1, Cervenka I2, Khatri B3, et al. Physiol Genomics. 2018 Oct 5. doi: 10.1152/physiolgenomics.00061.2018. [Epub ahead of print]
Cancer-Cachexia (CC) is a wasting condition directly responsible for 20-40% of cancer-related deaths. The mechanisms controlling development of CC-induced muscle wasting are not fully elucidated. Most investigations focus on the post-cachectic state and do not examine progression of the condition. We recently demonstrated mitochondrial degenerations precede muscle wasting in time course progression of CC. However, the extent of muscle perturbations prior to wasting in CC is unknown. Therefore, we performed global gene expression analysis in CC-induced muscle wasting to enhance understanding of intramuscular perturbations across the development of CC. Lewis Lung Carcinoma (LLC) was injected into the hind-flank of C57BL6/J mice at 8 wks age with tumor allowed to develop for 1, 2, 3, or 4 wks and compared to PBS injected control. Muscle wasting was evident at 4 wks LLC. RNA sequencing of gastrocnemius muscle samples showed widespread alterations in LLC compared to PBS animals with largest differences seen in 4 wk LLC suggesting extensive transcriptomic alterations concurrent to muscle wasting. Commonly altered pathways included: Mitochondrial Dysfunction and Protein Ubiquitination, along with other less studied processes in this condition regulating transcription/translation and cytoskeletal structure. Current findings present novel evidence of transcriptomic shifts and altered cellular pathways in CC-induced muscle wasting.

**Overexpressed C14orf166 associates with disease progression and poor prognosis in non-small-cell lung cancer.** Zhou YW1, Li R2, Duan CJ3, Gao Y1, Cheng YD1, Zhang CF4. Biosci Rep. 2018 Sep 13;38(5). pii: BSR20180479. doi: 10.1042/BSR20180479. Print 2018 Oct 31.
Chromosome 14 ORF 166 (C14orf166), a protein involved in the regulation of RNA transcription and translation, has been reported to possess the potency to promote tumorigenesis; however, the role of C14orf166 in non-small-cell lung cancer (NSCLC) remains unknown. The purpose of the present study was to assess C14orf166 expression and its clinical significance in NSCLC. Immunohistochemical staining, quantitative real-time PCR (qRT-PCR), and Western blotting were used to detect the C14orf166 protein and mRNA expression levels in NSCLC tissues compared with adjacent normal tissues, as well as in NSCLC cells lines compared with normal human bronchial epithelial cells (HBE). Then, the correlations between the C14orf166 expression levels and the clinicopathological features of NSCLC were analyzed. Additionally, the Cox proportional hazard model was used to evaluate the prognostic significance of C14orf166. We found that C14orf166 expression increased in carcinoma tissues compared with their adjacent normal tissues at the protein (P<0.001) and mRNA levels (P<0.001). High expression of C14orf166 was significantly associated with the T stage (P=0.006), lymph node metastasis (P=0.001), advanced TNM stage (P<0.001), and chemotherapy (P<0.001). Moreover, according to the survival analysis, patients with overexpressed C14orf166 were inclined to experience a shorter overall survival and disease-free survival time (P<0.001). Multivariate COX analysis implied that C14orf166 was an independent prognostic biomarker. Taken together, our findings indicate that the overexpression of C14orf166 may contribute to the disease progression of NSCLC, represent a novel prognostic predictor and help high-risk patients make better decisions for subsequent therapy.

**Nanoscale Extracellular Vesicle-Derived DNA is Superior to Circulating Cell Free DNA for Mutation Detection in Early-Stage Non-Small Cell Lung Cancer.** Wan Y1,2, Liu B3, Lei H4,5, et al. Ann Oncol. 2018 Oct 18. doi: 10.1093/annonc/mdy458. [Epub ahead of print]

**BACKGROUND:** The comparison between relatively intact nanoscale extracellular vesicle derived DNA (nEV-DNA) and fragmented circulating cell free DNA (cfDNA) in mutation detection among patients with non-small cell lung cancer (NSCLC) has not been performed yet, and thus deserves investigation. **PATIENTS AND METHODS:** Both nEV-DNA and cfDNA was obtained from 377 NSCLC patients with known EGFR mutation status and 69 controls. The respective EGFRE19del/T790M/L858R mutation status was interrogated with amplification-refractory-mutation-system-based PCR assays (ARMS-PCR). **RESULTS:** Neither nEV-DNA nor cfDNA levels show a strong correlation with tumor volumes. There is no correlation between cfDNA and nEV-DNA levels either. The detection sensitivity of nEV-DNA and cfDNA using ARMS-PCR in early-stage NSCLC was 25.7% and 14.2%, respectively, with 96.6% and 91.7% specificity, respectively. In late-stage NSCLC, both nEV-DNA and cfDNA show ~80% sensitivity and over 95% specificity. **CONCLUSIONS:** nEV-DNA is superior to cfDNA for mutation detection in early-stage NSCLC using ARMS-PCR. However, the advantages vanish in late-stage NSCLC.

[**Prognostic and predictive role of CD8 and PD-L1 determination in lung tumor tissue of patients under anti-PD-1 therapy.**](#) Fumet JD1,2,3,4, Richard C2,3,4, Ledys F2,3,4, et al. Br J Cancer. 2018 Oct 15. doi: 10.1038/s41416-018-0220-9. [Epub ahead of print]

**BACKGROUND:** No study has evaluated the predictive and prognostic role of CD8 and PD-L1 coexpression in non-small-cell lung cancer (NSCLC). **METHODS:** We analyzed RNA sequencing and/or immunohistochemistry staining in NSCLC patients from The Cancer Genome Atlas (n = 1016), and 34 metastatic NSCLC samples not treated by immunotherapy as prognostic cohorts. As predictive aspect of CD8 and PD-L1, we used 85 NSCLC patients treated with anti-PD-1. Two validation cohorts were used including 44 NSCLC patients treated with anti-PD-1 and an external cohort with different tumor types. **RESULTS:** In prognostic cohorts, high CD8A expression was associated with longer OS (p = 0.02), while high CD274 mRNA was associated with poor prognosis (p = 0.05). In predictive cohort, high CD8 expression and CD8A mRNA were associated with longer progression-free survival (PFS) (p = 0.0002). There was no significant association between PD-L1 expression and PFS while high CD274 mRNA was associated with longer PFS (p = 0.009). A combination of CD8A and CD274 was highly predictive of outcome. These results were confirmed in the validation cohorts. This two-genes signature demonstrated similar results compared to gold standard signatures. **CONCLUSION:** CD8 represents both a prognostic and predictive factor of outcomes, while PD-L1 share different prognostic and predictive roles.

[**Exploring and comparing of the gene expression and methylation differences between lung adenocarcinoma and squamous cell carcinoma.**](#) Yang Y1, Wang M1, Liu B1. J Cell Physiol. 2018 Oct 14. doi: 10.1002/jcp.27240. [Epub ahead of print]

Lung cancer is one of the most frequently diagnosed malignant tumors and the main reason for cancer-related death around the world, whereas nonsmall cell lung cancer that consists two subtypes: lung adenocarcinoma (LUAD) and squamous cell carcinoma (LUSC) is responsible for an estimated 85% of all lung cancers. The current study aimed to explore gene expression and methylation differences between LUAD and LUSC. EdgeR was used to identify differentially regulated genes between normal and cancer in the LUAD and LUSC extracted from The Cancer Genome Atlas (TCGA), respectively, whereas SAM was used to find genes with differential methylation between normal and cancer in the LUAD and LUSC, respectively. Finally, Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis was performed to analyze the function which these genes enriched in. A total of 391 genes with opposite methylation patterns in LUAD and LUSC and four functional pathways were obtained (false discovery rate (FDR) < 0.1). These pathways mainly included fat digestion and absorption, phenylalanine metabolism, bile secretion, and so on, which were related to the airframe nutrition metabolic pathway. Moreover, two genes CTSE (cathepsin E) and solute carrier family 5 member 7 (SLC5A7) were also found, among which CTSE was overexpressed and hypomethylated in LUAD corresponding to normal

lung tissues, whereas SLC5A7 showed the opposite in LUAD. In conclusion, this study investigated the differences between the gene expression and methylation patterns in LUAD and LUSC, and explored their different biological characteristics. Further understanding of these differences may promote the discovery and development of new, accurate strategies for the prevention, diagnosis, and treatment of lung cancer.

[PorphyrinHDL: A Novel Photosensitizing Nanoparticle for Lung Cancer Therapy.](#) Ujiie H1, Ding L2, Fan R2, Kato T1, et al. Ann Thorac Surg. 2018 Oct 11. pii: S0003-4975(18)31462-0. doi: 10.1016/j.athoracsur.2018.08.053. [Epub ahead of print]

**BACKGROUND:** We have developed ultra-small porphyrin-lipoprotein nanoparticles (<20nm) called "porphyrinHDL" that have a high density of porphyrin molecules and dissociate rapidly upon tumor cell accumulation to become fluorescent and photoactive. This is introduced as a novel activatable photosensitizer for image-guided photodynamic therapy (PDT). Here, we report the studies of these nanoparticles targeted to scavenger receptor class B type I (SR-BI) expressed on lung cancer cells, as a first step towards development of a minimally-invasive treatment for peripheral lung cancer and metastatic lymph nodes of advanced lung cancer. **METHODS:** The in vitro uptake of porphyrinHDL and the corresponding PDT efficacy were evaluated in both SR-BI positive and negative lung cancer cell lines. A clinically-relevant orthotopic lung cancer model in mice was used to examine fluorescence activation and quantification of uptake in tumor. In addition, we investigated the effect of porphyrinHDL-mediated PDT. **RESULTS:** PorphyrinHDL promoted proper intracellular uptake in H460 human lung cancer cell line. When irradiated with a 671 nm PDT laser, porphyrinHDL produced significant therapeutic effectiveness in vitro. After systemically administration in mice with orthotopic lung cancer xenografts, porphyrinHDL demonstrated selective accumulation and photoactivation in tumor with significantly enhanced disease-to-normal tissue contrast. Moreover, porphyrinHDL-PDT significantly induced cell apoptosis in lung tumors (73.2%) with neither toxicity in normal tissues nor damage to adjacent critical structures. **CONCLUSIONS:** SR-BI targeted porphyrinHDL-mediated PDT of lung cancer is selective and effective both in vitro and in vivo. These initial proof-of-principle studies suggest the potential of a "smart" PDT approach for highly selective tumor ablation.

[Metabolism of 4-methylimidazole in fischer 344 rats and B6C3F1 mice.](#) Fennell TR1, Watson SL2, Dhungana S2, Snyder RW2. Food Chem Toxicol. 2018 Oct 11. pii: S0278-6915(18)30761-0. doi: 10.1016/j.fct.2018.10.032. [Epub ahead of print]

4-Methylimidazole (4-MeI) is a widely used chemical, also identified as a by-product of heating foods. In cancer bioassays, 4-MeI induced lung tumors in mice, but not in rats. To establish if metabolic differences could explain species difference in carcinogenicity, this study investigated metabolism of 4-MeI in rat and mouse lung and liver microsomes and S-9 fractions, and in vivo in rats and mice. No metabolites were detected in rat or mouse lung and liver microsomes, or lung S-9 fractions. Male and female F-344 rats and B6C3F1 mice were administered 50 and 150 mg/kg [14C] 4-MeI by gavage. Excreta, exhaled $CO_2$ and volatiles were collected for 48 h. Elimination was mainly via urine, with 79-89% of the radioactivity in urine in rats and 41-70% in mice. Most of the radioactivity (71-88%) in urine was unchanged 4-MeI. Additional radioactive peaks (the largest metabolite was 8-18%) were characterized by LC-MS/MS as 4-hydroxymethylimidazole, its glucuronide, and other oxidized products, including methylhydantoin. 4-MeI was largely excreted unchanged in rats and mice with limited oxidative metabolism and conjugation. 4-MeI was not oxidized in subcellular fractions from rat and mouse lung and liver. Overall, the metabolism of 4-MeI appeared similar between rats and mice.

**Reducing DNA damage by formaldehyde in liquid-based cytology preservation solutions to enable the molecular testing of lung cancer specimens.** Matsuo Y1, Yoshida T2,3, Yamashita K3, Satoh Y1. Cancer Cytopathol. 2018 Oct 21. doi: 10.1002/cncy.22069. [Epub ahead of print]

**BACKGROUND:** Liquid-based cytology (LBC) is a useful cytopathological method, and LBC lung adenocarcinoma specimens may be used for genetic analysis in the near future. In the current study, the authors determined whether LBC specimens can be used for epidermal growth factor receptor (EGFR) mutation analysis in human lung adenocarcinoma cell lines. **METHODS:** Genomic DNA was extracted from 3 lung adenocarcinoma cell lines that were fixed in LBC preservation solution using 2 protocols (one for cultured cells and one for tissues) of a DNA extraction kit. Different fixation times were tested for each protocol: 30 minutes, 1 hour, and 1 to 9 days. As controls, cells also were fixed in 10% formalin or 95% ethanol. The authors investigated the effect of fixation time on DNA fragmentation, polymerase chain reaction (PCR) amplification, and EGFR mutation detection. **RESULTS: T**he DNA yield of LBC specimens tended to decrease depending on fixation time. When using the DNA extraction protocol for tissues, PCR amplification was successful after 9 days of fixation, although extracted genomic DNA that was fixed for >1 hour demonstrated fragmentation. Mutation analyses using the Cycleave PCR method were successful after 7 days of fixation. The DNA extraction protocol for tissues was appropriate for lung adenocarcinoma cell lines that were stored for >1 day in a preservative solution. The results of the current study demonstrated that EGFR mutations can be detected on day 7 using lung adenocarcinoma cell lines fixed in CytoRich Red preservative. **CONCLUSIONS:** When LBC specimens are used for targeted molecular genetic testing, the appropriate preservative solution and extraction protocol first should be determined.

**Evaluating Shared Decision Making for Lung Cancer Screening.** Brenner AT1,2, Malo TL2, Margolis M3, Elston Lafata J2,4, James S3, Vu MB3,5, Reuland DS1,2. JAMA Intern Med. 2018 Oct 1;178(10):1311-1316. doi: 10.1001/jamainternmed.2018.3054.

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

(range, 3:48-27:09 minutes). The mean time spent discussing LCS was 0:59 minute (range, 0:16-2:19 minutes), or 8% of the total visit time (range, 1%-18%). There was no evidence that decision aids or other patient education materials for LCS were used. **CONCLUSIONS AND RELEVANCE:** In this small sample of recorded encounters about initiating LCS, the observed quality of SDM was poor and explanation of potential harms of screening was virtually nonexistent. Time spent discussing LCS was minimal, and there was no evidence that decision aids were used. Although these findings are preliminary, they raise concerns that SDM for LCS in practice may be far from what is intended by guidelines.
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## Adequacy of Samples Obtained by Endobronchial Ultrasound with Transbronchial Needle Aspiration for Molecular Analysis in Patients with Non-Small Cell Lung Cancer. Systematic Review and Meta-Analysis.

Labarca G1,2,3, Folch E3,4, Jantz M3,5, Mehta HJ3,5, Majid A3,6, Fernandez-Bussy S3,7. Ann Am Thorac Soc. 2018 Oct;15(10):1205-1216. doi: 10.1513/AnnalsATS.201801-045OC.

**RATIONALE:** Endobronchial ultrasound and transbronchial needle aspiration (EBUS-TBNA) are commonly used for the diagnosis and mediastinal staging of lung cancer. Molecular markers are becoming increasingly important in patients with lung cancer to define targetable mutations suitable for personalized therapy, such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), reactive oxygen species proto-oncogene (ROS1), and programmed death-ligand 1 (PD-L1). **OBJECTIVES:** To evaluate the adequacy of EBUS-TBNA-derived tissue for molecular analysis. **METHODS:** We searched the MEDLINE, LILACS, www.clinicaltrials.gov , and Epistemonikos databases through January 2018. **DATA EXTRACTION:** Two independent reviewers performed the data search, quality assessment, and data extraction. We included both prospective and retrospective studies; risk of bias was evaluated using the ROBINS-I tool. The primary outcome was the proportion of adequate samples obtained by EBUS-TBNA for molecular analysis. Data were pooled by using a binary random effects model. Finally, evidence was rated by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. **RESULTS:** A total of 33 studies including 2,698 participants were analyzed. In 28 studies that evaluated EBUS-TBNA for the identification of EGFR mutations, the pooled probability of obtaining a sufficient sample was 94.5% (95% confidence interval CI], 93.2-96.4%). For identification of ALK mutations, the pooled probability was 94.9% (95% CI, 89.4-98.8%). Finally, the prevalence of EGFR mutation was 15.8% (95% CI, 12.1-19.4%), and the prevalence of ALK mutation was 2.77% (95% CI, 1.0-4.8%). Data for ROS1 and PD-L1 mutations were not suitable for meta-analysis. **CONCLUSIONS:** EBUS-TBNA has a high yield for molecular analysis of both EGFR and ALK mutations. However, the suitability of TBNA samples for next-generation sequencing is uncertain and should be explored in further studies. Clinical trial registered with PROSPERO (CRD42017080008).


## Accuracy of a novel histoplasmosis enzyme immunoassay to evaluate suspicious lung nodules.

Deppen SA1, Massion PP2, Blume J3, Walker RC4, Antic S2, Chen H5, Durkin MM6, Wheat LJ6, Grogan EL7. Cancer Epidemiol Biomarkers Prev. 2018 Oct 19. pii: cebp.0169.2018. doi: 10.1158/1055-9965.EPI-18-0169. [Epub ahead of print]

**BACKGROUND:** Granulomas caused by infectious lung diseases present as indeterminate pulmonary nodules (IPNs) on radiography. Newly available serum enzyme immunoassay (EIA) for histoplasmosis has not been studied for the evaluation of IPNs. We investigated serum biomarkers of histoplasmosis antibodies as an indication of benign disease in IPNs from a highly endemic region. **METHODS:** 152 serum samples from patients presenting with pulmonary nodules ≤30mm in maximum diameter were analyzed for histoplasmosis antibodies by immunodiffusion and EIA IgG and IgM tests. Serology and FDG-PET/CT scan diagnostic test characteristics were estimated and compared. **RESULTS:** Cancer prevalence was 55% (n=83). Thirty-nine (26%) individuals were positive for IgG histoplasmosis

antibodies. Twelve samples were IgM antibody positive. Immunodiffusion serology was similar to IgM antibody results with thirteen positive tests. Diagnostic likelihood ratios for benign disease were 0.62, 0.33 to 0.28 for FDG-PET/CT, IgG and IgM antibodies, respectively. When both IgG and IgM were positive (n=8), no nodules were cancerous and six were FDG-PET/CT avid. **CONCLUSIONS:** A positive EIA test for both IgM and IgG strongly suggested histoplasmosis etiology and benign granuloma for 12% of benign nodules arising from a highly endemic region. Presence of either IgG or IgM histoplasma antibodies was associated with benign disease. The EIA test was more sensitive in assessing histoplasma exposure than immunodiffusion serology. **IMPACT:** A new CLIA-certified histoplasmosis antibody EIA test measures histoplasmosis exposure, offers a possible alternative clinical diagnosis for benign IPNs and may improve IPN evaluation while avoiding harmful invasive biopsies.

**Identification of Incidental Germline Mutations in Patients With Advanced Solid Tumors Who Underwent Cell-Free Circulating Tumor DNA Sequencing.** Slavin TP1, Banks KC1, Chudova D1, et al. J Clin Oncol. 2018 Oct 19:JCO1800328. doi: 10.1200/JCO.18.00328. [Epub ahead of print]
**PURPOSE:** To determine the potential for detection of incidental germline cancer predisposition mutations through cell-free DNA (cfDNA) analyses in patients who underwent solid tumor somatic mutation evaluation. **PATIENTS AND METHODS:** Data were evaluated from 10,888 unselected patients with advanced (stage III/IV) cancer who underwent Guardant360 testing between November 2015 and December 2016. The main outcome was prevalence of putative germline mutations identified among 16 actionable hereditary cancer predisposition genes. **RESULTS:** More than 50 cancer types were studied, including lung (41%), breast (19%), colorectal (8%), prostate (6%), pancreatic (3%), and ovarian (2%). Average patient age was 63.5 years (range, 18 to 95 years); 43% were male. One hundred and fifty-six individuals (1.4%) had suspected hereditary cancer mutations in 11 genes. Putative germline mutations were more frequent in individuals younger than 50 years versus those 50 years and older (3.0% v 1.2%, respectively; P < .001). Highest yields of putative germline findings were in patients with ovarian (8.13%), prostate (3.46%), pancreatic (3.34%), and breast (2.2%) cancer. Putative germline mutation identification was consistent among 12 individuals with multiple samples. Patients with circulating tumor DNA copy number variation and/or reversion mutations suggestive of functional loss of the wild-type allele in the tumor DNA also are described. **CONCLUSION:** Detection of putative germline mutations from cfDNA is feasible across multiple genes and cancer types without prior mutation knowledge. Many mutations were found in cancers without clear guidelines for hereditary cancer genetic counseling/testing. Given the clinical significance of identifying hereditary cancer predisposition for patients and their families as well as targetable germline alterations such as in BRCA1 or BRCA2, research on the best way to validate and return potential germline results from cfDNA analysis to clinicians and patients is needed.

**CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES**

**NSCLC - SURGERY**

**Factors Associated with New Persistent Opioid Usage After Lung Resection.** Brescia AA1, Harrington CA2, Mazurek A1, et al. Ann Thorac Surg. 2018 Oct 11. pii: S0003-4975(18)31466-8. doi: 10.1016/j.athoracsur.2018.08.057. [Epub ahead of print]
**BACKGROUND:** Opioid dependence, misuse, and abuse in the United States continue to rise. Prior studies indicate an important risk factor for persistent opioid use includes elective surgical procedures, though the probability following thoracic procedures remains unknown. We analyzed the incidence and factors associated with new persistent opioid use after lung resection. **METHODS:** We evaluated data from opioid-naïve cancer patients undergoing lung resection between 2010 and 2014 using insurance

claims from the Truven Health MarketScan Databases. New persistent opioid usage was defined as continued opioid prescription fills between 90 and 180 days following surgery. Variables with p<0.10 by univariate analysis were included in a multivariable logistic regression performed for risk adjustment. Multivariable results were each reported with odds ratio (OR) and confidence interval (CI). **RESULTS:** 3,026 patients (44.8% male; 55.2% female) were identified as opioid-naïve undergoing lung resection. Mean age was 64 + 11 years and mean postoperative length of stay (LOS) was 5.2+3.3 days. 6.5% underwent neoadjuvant therapy, while 21.7% underwent adjuvant therapy. Among opioid-naïve patients, 14% continued to fill opioid prescriptions following lung resection. Multivariable analysis showed that age < 64 (OR 1.28 [CI 1.03-1.59], p=0.028), male sex (1.40 [1.13-1.73], p=0.002), postoperative LOS (1.32 [1.05-1.65], p=0.016), thoracotomy (1.58 [1.24-2.02], p<0.001), and adjuvant therapy (2.19 [1.75-2.75], p<0.001) were independent risk factors for persistent opioid usage. **CONCLUSIONS:** The greatest risk factors for persistent opioid use (14%) following lung resection were adjuvant therapy and thoracotomy. Future studies should focus on reducing excess prescribing, perioperative patient education, and safe opioid disposal.

[**Preoperative albumin-to-globulin ratio predicts survival in patients with non-small-cell lung cancer after surgery.**](#) Zhang H1,2,3,4, Zhang B1,2,3,4, Zhu K5, et al. J Cell Physiol. 2018 Oct 14. doi: 10.1002/jcp.26766. [Epub ahead of print]
The prognostic value of the preoperative albumin-to-globulin ratio (AGR) has not been investigated in non-small-cell lung cancer (NSCLC). Therefore, we aimed to assess the clinical applicability of the preoperative AGR to predict the prognosis in patients with NSCLC. We retrospectively enrolled 545 patients with stage I/II/III NSCLC who underwent surgery at our institution. The cutoff value for preoperative AGR was calculated by using a receiver operating characteristic curve analysis. A low AGR was associated with several clinicopathological variables related to tumor progression. In the multivariate analyses, the preoperative AGR was identified as an independent prognostic factor for disease-free survival (DFS; P = 0.003) and overall survival (OS; P = 0.005). For patients with stage II and III with a preoperative AGR ≤ 1.43, the surgery plus chemotherapy group had a significantly longer DFS and OS than the surgery alone group (P = 0.002 and P = 0.001, respectively); however, a significant difference in DFS and OS between these two groups was not observed in patients with stage II and III with an AGR > 1.43 (P = 0.808 and P = 0.842, respectively). The preoperative AGR is an independent, significant predictor of DFS and OS in patients with NSCLC. Our results also demonstrate that the preoperative AGR might be a predictive marker of the therapeutic effect of postoperative chemotherapy in patients with stage II and III NSCLC.

[**Preoperative thoracic muscle area on computed tomography predicts long-term survival following pneumonectomy for lung cancer.**](#) Troschel FM1, Kuklinski MW1, Knoll SJ2, et al. Interact Cardiovasc Thorac Surg. 2018 Oct 10. doi: 10.1093/icvts/ivy280. [Epub ahead of print]
**OBJECTIVES:** To assess the prognostic role of thoracic muscle as quantified on preoperative computed tomography (CT) for the estimation of overall survival (OS) following pneumonectomy. **METHODS:** Muscle cross-sectional area (CSA) at the level of the fifth (T5) and eighth (T8) thoracic vertebra was measured on CT scans of consecutive patients with lung cancer prior to pneumonectomy. We stratified patients into high and low muscle groups using the gender-specific median of muscle CSA as separator and estimated associations of muscle CSA and OS using the Kaplan-Meier analysis. Multivariable logistic regression adjusted for body mass index, Charlson comorbidity index (includes age), forced expiratory volume in the first second as a % of predicted, sex, race, smoking status, tumour stage and prior lung cancer treatment was performed. **RESULTS:** A total of 128 patients were included (61.0 ± 10.6 years of age, mean body mass index of 26.9 kg/m2, 55.5% men). The T8 level showed fewer artefacts and strong correlation with the T5 level (Pearson's rho = 0.904). T8 CSA was therefore used for subsequent analyses.

Mean T8 CSA was 118.5 cm2 (median 115.3 cm2) in men and 75.2 cm2 (median 74.0 cm2) in women. During a median follow-up of 23.6 months (interquartile range 39.3), 65 patients (50.8%) died, of whom 41 were in the low muscle group. The Kaplan-Meier analysis showed significantly longer OS in the high muscle group (log-rank P = 0.02). Multivariable analysis showed an independent association of muscle CSA and OS (P = 0.02) with a hazard ratio of 0.80 (confidence interval 0.67-0.98) per 10-cm2 increment. **CONCLUSIONS:** Thoracic muscle is independently associated with long-term overall survival following pneumonectomy for lung cancer and may contribute to refined survival estimates in this population.

[**Outcomes following resection of non-small cell lung cancer in octogenarians.**](#) Vazirani J1, Moraes J1, Barnett S2,3,4,5, et al. ANZ J Surg. 2018 Oct 2. doi: 10.1111/ans.14861. [Epub ahead of print]
**BACKGROUND:** The treatment of choice for early stage non-small cell lung cancer (NSCLC) is surgical resection. Little is known about the short- and long-term outcomes among very elderly patients. We sought to determine predictors of short- and long-term survival among octogenarians undergoing curative-intent resection for NSCLC in Victoria, Australia. **METHODS:** We retrospectively reviewed data from all patients aged ≥80 years who underwent curative-intent resection for NSCLC over 12 years (January 2005-December 2016) across five tertiary centres. We examined effect of age, stage of disease, extent of surgery and lung function on short- and long-term survival. **RESULTS:** Two hundred patients aged ≥80 years underwent curative-intent resections. Mortality at 30 and 120 days was 2.9% and 5.9%, respectively. Increased early mortality was observed among those ≥83 years, at 30 days (6.8% versus 0.8%, P = 0.044) and 120 days (12.2% versus 2.3%, P = 0.0096). Early mortality was highest among patients ≥83 years requiring lobectomy, compared to sub-lobar resection at 120 days (17% versus 3.8%, P = 0.019). Long-term survival was predicted by age and stage of disease. Among patients with Stage I disease aged <83 years, lobectomy was associated with superior 5-year survival, compared to sub-lobar resection (83% versus 61%, P = 0.02). **CONCLUSION:** In carefully selected elderly patients undergoing curative-intent resection of early stage NSCLC, both short- and long-term outcomes appear consistent with younger historical cohorts. Early mortality was associated with lobectomy in those with advanced age. Older patients undergoing lobectomy appeared to be at highest risk for early mortality, while younger patients with Stage I disease undergoing at least lobectomy appear to have the best long-term survival.

[**Long-term results of robotic anatomical segmentectomy for early-stage non-small-cell lung cancer.**](#)
Nguyen D1, Gharagozloo F2, Tempesta B2, Meyer M1, Gruessner A3. Eur J Cardiothorac Surg. 2018 Oct 15. doi: 10.1093/ejcts/ezy332. [Epub ahead of print]
**OBJECTIVES:** Anatomical segmentectomy is advocated for curative resection in select patients. We investigated the long-term results of robotic anatomical segmentectomy with mediastinal nodal dissection in patients with early-stage lung cancer. **METHODS:** We retrospectively reviewed patients who underwent robotic anatomical segmentectomy for early-stage non-small-cell lung cancer (NSCLC). The follow-up data were obtained to determine survival and statistically significant risk factors in both univariable and multivariable models. **RESULTS:** Seventy-one patients had clinical stage I NSCLC (36 men, 35 women, mean age 70 ± 12 years). All patients underwent R0 resection. The mean operating time was 134 min. Ten of 71 (14%) patients were upstaged. Eight of 71 (11%) patients were upstaged due to the size of tumour in the pathological specimen, and 2 of 71 (3%) patients were upstaged due to microscopic N2 nodal metastasis. Median hospitalization was 4 days (2-31 days). Complication rate was 29%. There were no complications attributable to the surgical robot. No patient died within 90 days. Mean follow-up was 54 months (range 2 months to 9 years). The overall 5-year survival was 43%, whereas lung cancer-specific 5-year survival was 55%. The 5-year lung cancer-specific survival for pathological stage I disease was 73%. Local or mediastinal recurrence occurred in 4 of 71(5%) patients. Pathological upstaging or recurrence resulted in 0% 5-year survival. The univariable and multivariable analyses

showed that advanced age and pathological upstaging were statistically significant risk factors for lung cancer-specific death. **CONCLUSIONS:** Robotic anatomical segmentectomy with mediastinal nodal dissection is a safe and feasible procedure. Accurate preoperative clinical staging is of critical importance for long-term survival.

[**Minimally invasive approaches do not compromise outcomes for pneumonectomy, a comparison utilizing the National Cancer Database.**](#) Hennon MW1, Kumar A2, Devisetty H2, D'Amico T3, Demmy TL1, Groman A4, Yendamuri S5. J Thorac Oncol. 2018 Oct 4. pii: S1556-0864(18)33176-9. doi: 10.1016/j.jtho.2018.09.024. [Epub ahead of print]

**BACKGROUND:** Minimally invasive approaches are increasingly being used for the conduct of complex surgical procedures. Whether the benefits of minimally invasive approaches compared to thoracotomy for sublobar and lobar lung resection for nonsmall cell lung carcinoma are realized for patients undergoing pneumonectomy is not clear. **METHODS:** The National Cancer Database was queried for patients who underwent pneumonectomy for NSCLC from 2010-2014. Those who underwent resection by a minimally invasive approach (MIS) were compared with those who were done by thoracotomy (Open) in an intention-to-treat analysis. Associations between potential covariates and treatment were analyzed using the Pearson Chi-square test for categorical variables and Wilcoxon Rank Sum test for continuous variables. Univariable and multivariable logistic models and proportional hazards model were used to assess the effect of surgical approach on 30 day and 90 day mortality and overall survival. Relative prognosis was summarized using odds ratios (OR) and hazards ratios (HR) estimates and 95% confidence limits. **RESULTS:** A total of 4,938 patients underwent pneumonectomy during the study period, of which 755 (15.3%) were completed by minimally invasive approaches (MIS). No difference was noted in 30 and 90-day mortality rates for MIS compared to Open approaches (6.8% and 12.3% vs 6.7% and 11.9% respectively, p = 0.9 and 0.86). Tumor histology and stage characteristics were similar between the two groups. Mean lymph nodes examined was higher in the MIS group compared to Open ($17.1 \pm 0.4$ vs $16.1 \pm 0.2$, p=0.034). Conversion rate for the minimally invasive cohort was 36.7%. Surgical approach was not associated with any difference in perioperative mortality with univariable or multivariable analysis. MIS was associated with improved overall survival on univariable analysis, but this was not evident with multivariable analysis. **CONCLUSION:** Pneumonectomy performed by minimally invasive approaches does not compromise perioperative mortality or long term outcomes. Further investigation into the impact of minimally invasive approaches on perioperative outcomes for whole lung resection is warranted.

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

[**Canadian Cancer Trials Group (CCTG) IND215: A phase Ib study of Selumetinib in patients with untreated advanced or metastatic NSCLC who are receiving standard chemotherapy regimens.**](#) Goffin JR1, Nicholas G2, Mates M3, et al. Invest New Drugs. 2018 Oct 13. doi: 10.1007/s10637-018-0680-z. [Epub ahead of print]

Introduction Selumetinib (AZD6244, ARRY-142886) is a potent inhibitor of MEK1/2, thereby inhibiting phosphorylation of ERK2. We investigated the toxicity and the recommended phase II dose of the combination of selumetinib with two platinum based first line chemotherapy combinations in non-small cell lung cancer. Methods This was a phase I trial of escalating doses of selumetinib with carboplatin (AUC 6), paclitaxel (200 mg/m2) (cohort 1) or pemetrexed (500 mg/m2) and cisplatin (75 mg/m2) (cohort 2) in patients with chemotherapy naïve, advanced or metastatic NSCLC. Patients enrolled on cohort 2 had non-squamous histology. Dose escalation of selumetinib proceeded using a 3 + 3 design: 50 mg b.i.d. days 2-19 (dose level 1); 75 mg b.i.d. days 2-19 (dose level 2); and 75 mg b.i.d. continuously.

Adverse events were evaluated using CTC AE v4 and response by RECIST 1.1. Results Thirty-nine patients were enrolled (cohort 1 n = 16; cohort 2, n = 23). There were no dose limiting toxicities in either cohort and the recommended phase II dose for both regimens was standard doses of carboplatin, paclitaxel or pemetrexed and cisplatin with continuous selumetinib at a dose of 75 mg b.i.d. Most adverse events were grade 1 or 2 and were predominantly diarrhea, nausea, stomatitis, peripheral edema, neutropenia, and skin rash. Response rate was 37.5% for cohort 1 and 30.4% for cohort 2. Conclusion Selumetinib at a dose of 75 mg b.i.d continuously can be safely combined with paclitaxel and carboplatin or pemetrexed and cisplatin in patients with advanced or metastatic NSCLC. This trial provided the dose for the regimens used in a randomized phase II trial in NSCLC (CCTG IND.219).

## [Comparative efficacy of brigatinib versus ceritinib and alectinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small cell lung cancer.](#)

Reckamp K1, Lin HM2, Huang J2, Proskorovsky I3, Reichmann W2, Krotneva S3, Kerstein D2, Huang H2, Lee J4. Curr Med Res Opin. 2018 Oct 5:1-8. doi: 10.1080/03007995.2018.1520696. [Epub ahead of print]

**OBJECTIVE:** Brigatinib, ceritinib, and alectinib are approved to treat crizotinib-refractory anaplastic lymphoma kinase-positive (ALK+) non-small cell lung cancer (NSCLC), but no trial has compared them head-to-head. A matching-adjusted indirect comparison (MAIC) was conducted to estimate the relative efficacy of these agents in the crizotinib-refractory setting. **METHODS:** MAIC is a propensity score-type method that adjusts for differences in baseline characteristics between trials to estimate relative efficacy. Analyses were based on patient-level data from the ALTA trial for brigatinib and published summary-level trial data from ASCEND-1 and ASCEND-2 for ceritinib and NP28761 and NP28673 for alectinib. Objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) were compared. **RESULTS:** After matching, all key baseline characteristics were balanced between trials. Compared with ceritinib, brigatinib was associated with longer PFS (ASCEND-1: median 15.7 vs 6.9 months, hazard ratio (HR) [95% confidence interval] = 0.38 [0.26-0.57]; ASCEND-2: median = 18.3 vs 7.2 months, HR = 0.33 [0.20-0.56]) and OS (ASCEND-1: not available; ASCEND-2: median 27.6 vs 14.9 months, HR = 0.33 [0.17-0.63]). Versus alectinib, brigatinib was associated with longer PFS (NP28761: median = 17.6 vs 8.2 months, HR = 0.56 [0.36-0.86]; NP28673: median = 17.6 vs 8.9 months, HR = 0.61 [0.40-0.93]); results for OS were inconclusive (NP28761: median = 27.6 vs 22.7 months, HR = 0.70 [0.42-1.16]; NP28673: median = 27.6 vs 26.0 months, HR = 0.66 [0.39-1.09]). ORR was similar. **CONCLUSION:** In crizotinib-refractory ALK + NSCLC patients, relative efficacy estimates suggest brigatinib may have prolonged PFS and OS vs ceritinib and prolonged PFS vs alectinib.

## [Clinical investigation of the efficacy and toxicity of apatinib (YN968D1) in stage III/IV non-small cell lung cancer after second-line chemotherapy treatment: A retrospective study.](#)

Zhang D1,2, Zhang C2, Huang J1,2, Guan Y2, Guo Q2. Thorac Cancer. 2018 Oct 19. doi: 10.1111/1759-7714.12898. [Epub ahead of print]

**BACKGROUND:** This study was designed to assess the clinical efficacy and toxicity of apatinib (YN968D1) as third or subsequent-line treatment for stage III/IV non-small cell lung cancer (NSCLC). **METHODS:** A total of 100 patients with advanced NSCLC who were treated with apatinib at a daily dose of 250/425/500 mg at Shandong Cancer Hospital from January 2016 to June 2018 were enrolled in our study. The objective response, disease control, and median progression-free survival rates were reviewed and evaluated. Univariate and multivariate analyses were performed to determine the prognostic factors. The main adverse events were evaluated per the Common Terminology Criteria for Adverse Events version 4.0. **RESULTS:** All patients were assessable for response. No complete responses were observed, 11 patients achieved a partial response, and 56 showed stable disease. The objective response rate was 11.0%, the disease control rate was 67.0%, and the median progression-free survival was

2.93 months (95% confidence interval 2.07-3.87). In Cox regression analysis, the Eastern Cooperative Oncology Group performance status score (hazard ratio 1.799; P < 0.05) and smoking history (hazard ratio 1.958; P < 0.05) were predictive indicators for apatinib treatment efficacy. Treatment-related adverse events were tolerated, predictable, reversible, and controllable. **CONCLUSION:** Apatinib was found to be both effective and safe in advanced NSCLC patients without a genetic driver mutation who experienced progression after two or more lines of chemotherapy treatment.

[The Superior Antitumor Effect of Self-Assembled Paclitaxel Nano-filaments for Lung Cancer Cells.](#)
He M1, Zhu J1, Yu N2, Kong H1, Zeng X1, Xie W1, Xu H1. Curr Drug Deliv. 2018 Oct 16. doi: 10.2174/1567201815666181017094003. [Epub ahead of print]
**OBJECTIVES:** Paclitaxel (Ptx) has been regarded as one of the most effective chemotherapeutic drugs for lung cancers. Increasing studies focused on the nano-delivery system of Ptx due to its poor solubility and hypersensitivity. The aim of the resent study was to investigate the antitumor effects of self-assembled Ptx nano-filaments for lung cancer cells. **METHODS:** In the present study, we designed and synthesized novel Ptx-loaded nano-filaments through conjugation of Ptx and succinic acid (SA) (Ptx-SA, P-NFs). Non-small cell lung cancer (NSCLC) A549 and H460 cells were used for detecting the antitumor effects of P-NFs, including cytotoxicity, apoptosis, and migration. Western blotting was performed for analyzing mechanism. **RESULTS:** P-NFs nano-filaments exerted superior antitumor effects against NSCLC cells compared with free Ptx using cytotoxicity tests. Furthermore, P-NFs nano-filaments were much more effective in inducing NSCLC cells apoptosis and inhibiting A549 cells migration than free Ptx. To elucidate the underlying mechanisms, the expression of apoptotic and endoplasmic reticulum (ER) stress proteins was detected. The results indicated that P-NFs nano-filaments enhanced the expression of bax/bcl-2, protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1α (IRE1α), phospho-c-Jun N-terminal kinase (p-JNK), and C/EPB homologous protein (CHOP), which suggested that the strong antitumor effect of P-NFs nano-filaments may be partially attributed to the activation ER stress. **CONCLUSION:** The current work demonstrated that P-NFs nano-filaments showed superior cytotoxicity of lung cancer cells, highlighting a novel profile of nano-filaments delivery systems as potential strategies for facilitating the therapeutic efficacy of Ptx in lung cancer treatment.

[Treatment Patterns by EGFR Mutation Status in Non-Small Cell Lung Cancer Patients in the USA: A Retrospective Database Analysis.](#) Aguilar KM1, Winfree KB2, Muehlenbein CE3, Zhu YE2, Wilson T1, Wetmore S2, Nadler ES4. Adv Ther. 2018 Oct 19. doi: 10.1007/s12325-018-0811-0. [Epub ahead of print]
**INTRODUCTION:** Targeted therapies, including tyrosine kinase inhibitors (TKIs) that target the sensitizing epidermal growth factor receptor (EGFR) gene are recommended for patients with non-small cell lung cancer (NSCLC). Most patients with NSCLC who test positive for the EGFR mutation and receive TKIs develop resistance to these drugs. Questions remain regarding which treatment sequence is optimal for patients with EGFR-mutant NSCLC, and few studies have evaluated patterns of TKI treatment use in NSCLC, irrespective of EGFR mutation status, in a real-world setting. This population-based study aimed to evaluate treatment patterns at a national level in the USA. **METHODS:** This retrospective observational study used data from the US Oncology Network's iKnowMed database. Patients with advanced NSCLC who initiated first-line therapy with erlotinib and/or intravenous chemotherapy between January 1, 2012 and June 30, 2015 and met all other study criteria were included. Descriptive analyses assessed demographic and clinical characteristics and treatment patterns among the overall study cohort, as well as for specific erlotinib treatment subgroups, stratified by EGFR status. **RESULTS:** Among the 3108 patients identified, 18.5% were EGFR positive, 49.8% were EGFR negative, and 31.7% were EGFR documented unknown. For the overall cohort, 18.4% received first-line

erlotinib monotherapy, fewer than 1% received first-line combination therapy (erlotinib plus chemotherapy), 4.7% received second-line erlotinib monotherapy, and 3.3% received second-line combination therapy. First-line erlotinib monotherapy was used in 77.8% of all EGFR positive patients. Almost two-thirds of the overall cohort were not observed to have advanced to second-line therapy. **CONCLUSIONS:** As treatment options evolve, this study provides real-world treatment patterns that suggest concordance with NCCN guidelines and confirm the remaining need to understand sequencing of therapies and related outcomes. **FUNDING:** Eli Lilly and Company.

[Low Baseline Serum Sodium Concentration Is Associated with Poor Clinical Outcomes in Metastatic Non-Small Cell Lung Cancer Patients Treated with Immunotherapy.](#) Fucà G1, Galli G2, Poggi M2, et al. Target Oncol. 2018 Oct 10. doi: 10.1007/s11523-018-0599-5. [Epub ahead of print]
**BACKGROUND:** A consistent percentage of patients with metastatic non-small cell lung cancer (NSCLC) derives no or only marginal benefit from immunotherapy (IO). **OBJECTIVE:** Since serum sodium has been linked to both prognosis in NSCLC and modulation of immune cells activity, we aimed to assess the association between low baseline serum sodium concentration ($\leq 135$ mEq/L) and clinical outcomes of patients with metastatic NSCLC treated with IO. **PATIENTS AND METHODS:** We included metastatic NSCLC patients treated with checkpoint inhibitors in our department from April 2013 to April 2018 with available baseline serum sodium concentration. Demographics, clinical and pathological characteristics were collected. Survival analyses were performed using the Kaplan-Meier method and the Cox proportional-hazards model. **RESULTS:** Of 197 patients included, 26 (13%) presented low baseline serum sodium concentration. Patients in the low sodium cohort experienced a poorer disease control rate (OR 0.36; 95% CI, 0.15-0.86; Wald test P = .02), median overall survival (OS) (2.8 vs. 11.6 months; HR 3.00; 95% CI, 1.80-4.80; P < .001) and progression-free survival (PFS) (1.8 vs. 3.3 months; HR 2.60; 95% CI, 1.70-3.90; P < .001) compared to patients in the control cohort. At multivariate analyses, low baseline serum sodium concentration was independently associated with disease control and OS, but not with PFS. **CONCLUSIONS:** Our study showed for the first time that low baseline serum sodium concentration is associated with impaired clinical outcomes in patients with metastatic NSCLC treated with IO. The role of serum sodium concentration in this setting warrants further pre-clinical and clinical investigation.

[Severe pneumonitis refractory to steroids following anti-PD-1 immunotherapy.](#) Andruska N1, Mahapatra L1, Hebbard C1, Patel P2, Paul V3. BMJ Case Rep. 2018 Oct 8;2018. pii: bcr-2018-225937. doi: 10.1136/bcr-2018-225937.
Anti-programmed death 1 (PD-1) immune checkpoint inhibitors enhance the antitumour activity of the immune system and have produced durable tumour responses in several solid tumours including non-small cell lung cancer (NSCLC). However, PD-1 inhibitors can lead to immune-related adverse events , including pneumonitis, which is typically mild, but can be severe and potentially fatal. Pneumonitis often resolves with steroids, but some cases are steroid refractory, leading to a relapsing and remitting course in milder cases or the need for salvage therapies in more severe cases. Here, we present two patients with NSCLC who developed severe pneumonitis following therapy with nivolumab and pembrolizumab. While one patient improved with steroids and infliximab, the other patient failed to respond to steroids and subsequently died. These cases demonstrate the highly variable presentation and therapeutic responses seen in patients with pneumonitis following anti-PD-1 therapy and illustrate that severe cases can often present refractory to steroid therapy.

[Clinical investigation of the efficacy and toxicity of apatinib (YN968D1) in stage III/IV non-small cell lung cancer after second-line chemotherapy treatment: A retrospective study.](#) Zhang D1,2,

Zhang C2, Huang J1,2, Guan Y2, Guo Q2. Thorac Cancer. 2018 Oct 19. doi: 10.1111/1759-7714.12898. [Epub ahead of print]
**BACKGROUND:** This study was designed to assess the clinical efficacy and toxicity of apatinib (YN968D1) as third or subsequent-line treatment for stage III/IV non-small cell lung cancer (NSCLC). **METHODS:** A total of 100 patients with advanced NSCLC who were treated with apatinib at a daily dose of 250/425/500 mg at Shandong Cancer Hospital from January 2016 to June 2018 were enrolled in our study. The objective response, disease control, and median progression-free survival rates were reviewed and evaluated. Univariate and multivariate analyses were performed to determine the prognostic factors. The main adverse events were evaluated per the Common Terminology Criteria for Adverse Events version 4.0. **RESULTS:** All patients were assessable for response. No complete responses were observed, 11 patients achieved a partial response, and 56 showed stable disease. The objective response rate was 11.0%, the disease control rate was 67.0%, and the median progression-free survival was 2.93 months (95% confidence interval 2.07-3.87). In Cox regression analysis, the Eastern Cooperative Oncology Group performance status score (hazard ratio 1.799; $P < 0.05$) and smoking history (hazard ratio 1.958; $P < 0.05$) were predictive indicators for apatinib treatment efficacy. Treatment-related adverse events were tolerated, predictable, reversible, and controllable. **CONCLUSION:** Apatinib was found to be both effective and safe in advanced NSCLC patients without a genetic driver mutation who experienced progression after two or more lines of chemotherapy treatment.


**Sequential treatment with afatinib and osimertinib in patients with EGFR mutation-positive non-small-cell lung cancer: an observational study.** Hochmair MJ1, Morabito A2, Hao D3, et al. Future Oncol. 2018 Oct 19. doi: 10.2217/fon-2018-0711. [Epub ahead of print]
**AIM:** To assess outcomes in patients with EGFR mutation-positive (Del19, L858R) non-small-cell lung cancer receiving sequential afatinib and osimertinib in a real-world clinical setting. Materials & methods: In this retrospective, observational, multicenter study, patients (n = 204) had T790M-positive disease following first-line afatinib and started osimertinib treatment ≥10 months prior to data entry. Primary outcome was time on treatment. **RESULTS:** Overall median time on treatment was 27.6 months (90% CI: 25.9-31.3), 30.3 months (90% CI: 27.6-44.5) in Del19-positive patients and 46.7 months (90% CI: 26.8-not reached) in Asians. The 2-year overall survival was 78.9%. **CONCLUSION:** In real-world clinical practice, sequential afatinib and osimertinib facilitates prolonged, chemotherapy-free treatment in patients with T790M acquired resistance, and is a potentially attractive strategy, especially for Del19-positive tumors.


**PD-L2 Expression as a Potential Predictive Biomarker for the Response to Anti-PD-1 Drugs in Patients with Non-small Cell Lung Cancer.** Takamori S1, Takada K2, Toyokawa G1, et al. Anticancer Res. 2018 Oct;38(10):5897-5901. doi: 10.21873/anticanres.12933.
**BACKGROUND/AIM:** To investigate the role of programmed cell death-ligand 2 (PD-L2) expression as a predictive biomarker for response to anti-programmed cell death-1 (PD-1) drugs in patients with non-small cell lung cancer (NSCLC). **PATIENTS AND METHODS:** Ten patients who had undergone curative lung resection and received the anti-PD-1 drugs for the recurrence were enrolled. The cut-off value for PD-L2 (antibody clone 176611) expression on tumor cells was set at 50%. Tumor response was evaluated according to immune-related response criteria. **RESULTS:** Seven patients (70.0%) were positive for PD-L2. The response rates were 28.6% (2/7) and 33.3% (1/3) in patients with PD-L2-positive and PD-L2-negative NSCLC, respectively. Disease control was obtained in 2 patients despite the programmed cell death-ligand 1 (PD-L1)-negativity (antibody clone 22C3: 0%, antibody clone SP142: 0%), and these tumors expressed PD-L2 (≥1%). **CONCLUSION:** PD-L2 expression may be a target of immunotherapy in patients with PD-L1-negative NSCLC.

[**A real-world, comparative study of FDA-approved diagnostic assays PD-L1 IHC 28-8 and 22C3 in lung cancer and other malignancies.**](#) Batenchuk C1, Albitar M2, Zerba K1, Sudarsanam S2, Chizhevsky V2, Jin C1, Burns V3. J Clin Pathol. 2018 Oct 1. pii: jclinpath-2018-205362. doi: 10.1136/jclinpath-2018-205362. [Epub ahead of print]

**AIMS:** At the time of analysis, two widely used, drug-specific, tumour-cell programmed death ligand 1 (PD-L1) assays were approved by the US Food and Drug Administration for anti-PD-1 therapies: the Dako PD-L1 immunohistochemistry (IHC) 28-8 pharmDx assay and the Dako PD-L1 IHC 22C3 pharmDx assay. Given that the majority of current PD-L1 testing in US clinical practice is performed at commercial reference laboratories, we aimed to evaluate the concordance of the 28-8 and 22C3 assays in a real-world setting. **METHODS:** Matched PD-L1 IHC 28-8 and 22C3 results from routine assessment were obtained from 1930 patients, including 412 confirmed to have lung cancer, submitted from hospitals in over 38 US states/territories. Biopsies were stained, reviewed and scored by trained/certified pathologists at a single cancer reference laboratory between 2015 and 2017. Rate of concordance between assay findings was assessed by Bland-Altman analysis; overall per cent agreement (OPA), positive per cent agreement and negative per cent agreement; and Cohen's kappa. **RESULTS:** PD-L1 IHC 28-8 and 22C3 displayed strong correlation across all samples and in samples with a confirmed lung cancer diagnosis irrespective of biopsy site. The OPA was 97%-98% for all samples, depending on the expression level defining PD-L1 positivity. In the Bland-Altman analysis, the mean difference in percentage of tumour cells positively stained for PD-L1 between the paired assay findings was -0.80% for all samples and -0.93% in samples with a confirmed lung cancer diagnosis. **CONCLUSIONS:** These data, in conjunction with recent findings, support the analytical concordance of the PD-L1 IHC 28-8 and 22C3 assays for assessing per cent tumour-cell membrane PD-L1 expression.

[**The Fast Real-time Assessment of Combination Therapies in Immuno-ONcology (FRACTION) program: innovative, high-throughput clinical screening of immunotherapies.**](#) Simonsen KL1, Fracasso PM2, Bernstein SH3, Wind-Rotolo M4, Gupta M5, Comprelli A6, Reilly TP7, Cassidy J8. Eur J Cancer. 2018 Nov;103:259-266. doi: 10.1016/j.ejca.2018.07.127. Epub 2018 Oct 3.

**BACKGROUND:** The unprecedented success of immuno-oncology (I-O) agents targeting the cytotoxic T lymphocyte-associated antigen 4 and programmed death-1/programmed death-ligand 1 pathways has stimulated the rapid development of other I-O agents against novel immune targets. Bristol-Myers Squibb has designed a novel phase II platform trial, the Fast Real-time Assessment of Combination Therapies in Immuno-ONcology (FRACTION) Program, to efficiently identify promising combinations for patients with specific malignancies. The concept and study design of the FRACTION Program-currently ongoing in patients with advanced non-small-cell lung cancer (FRACTION-Lung), gastric cancer (FRACTION-Gastric Cancer) and renal cell carcinoma (FRACTION-RCC)-are described. **METHODS:** The FRACTION Program comprises open-label, phase II studies that use adaptive randomisation designs with rolling combination regimens. Master Protocols provide the overall study design framework, whereas Sub-Protocols introduced over time provide details on specific I-O combination therapies to which patients may be randomised. In a Master Protocol, patients are enrolled into different Study Tracks based on characteristics such as prior I-O therapy experience. Patients who progress may be rerandomised to other combination regimens from any ongoing Sub-Protocol. Primary objectives are to assess objective response rate, median duration of response and progression-free survival rate at 24 weeks; the secondary objective is to investigate safety and tolerability. Biomarker collection before and on treatment will facilitate identification of patient subsets who benefit most from each therapy. **CONCLUSIONS:** The FRACTION Program allows for the evaluation of multiple I-O combinations through individual studies for specific tumours using an adaptive trial design and continuous enrolment.

**[PD-L1 Expression in Non-Small-Cell Lung Cancer Including Various Adenocarcinoma Subtypes.](#)**
Miyazawa T1, Marushima H1, Saji H1, Kojima K2, Hoshikawa M3, Takagi M3, Nakamura H1. Ann Thoracic Cardiovasc Surg. 2018 Oct 3. doi: 10.5761/atcs.oa.18-00163. [Epub ahead of print]
**PURPOSE:** Knowledge regarding programmed death-ligand 1 (PD-L1) expression in lung cancer is limited. We aim to clarify PD-L1-positive expression in non-small-cell lung cancer (NSCLC), including adenocarcinoma subtypes. **METHODS:** In all, 90 NSCLC specimens containing various adenocarcinoma subtypes, in addition to squamous cell carcinoma and large-cell carcinoma were selected. PD-L1 was immunohistochemically stained by murine monoclonal antibody clone 22C3. **RESULTS:** When PD-L1-positive expression was defined by tumor proportion score (TPS) $\geq$1%, the positive cases were 0/11 in adenocarcinoma in situ, 0/12 in minimally invasive adenocarcinoma, 1/10 in lepidic predominant adenocarcinoma, 1/13 in papillary predominant adenocarcinoma, 8/14 in acinar predominant adenocarcinoma, 6/11 in solid predominant adenocarcinoma, 0/3 in micropapillary predominant adenocarcinoma, 0/4 in invasive mucinous adenocarcinoma, 4/9 in squamous cell carcinoma, and 2/3 in large-cell carcinoma. PD-L1 positivity was higher in males, smokers, advanced pathologic stages, positive vessel invasion, and positive lymphatic invasion. Postoperative survival analysis revealed that PD-L1-positive expression was a significantly worse prognostic factor in univariate analysis for recurrence-free survival (RFS). **CONCLUSION:** PD-L1-positive tumors were frequent in acinar predominant adenocarcinoma and solid predominant adenocarcinoma than other adenocarcinoma subtypes. PD-L1 expression seemed to increase according to pathologic tumor progression, suggesting a worse postoperative prognosis in NSCLC patients.

## NSCLC - RADIOTHERAPY

**[A Contemporary Update on the Role of Stereotactic Body Radiation Therapy (SBRT) for Liver Metastases in the Evolving Landscape of Oligometastatic Disease Management.](#)** Robin TP1, Raben D1, Schefter TE2. Semin Radiat Oncol. 2018 Oct;28(4):288-294. doi: 10.1016/j.semradonc.2018.06.009. Metastases to the liver are common, and stereotactic body radiation therapy (SBRT) is a recognized tool for ablation of liver metastases. Colorectal cancers commonly metastasize to the liver, and long-term survival is possible after metastasectomy. However, many patients are not candidates for surgical resection, which opened the door to early studies investigating noninvasive techniques such as liver SBRT. Multiple prospective trials have demonstrated excellent local control with this approach coupled with an excellent safety record. The oligometastatic disease state is now appreciated across many histologies, and treatment of liver metastases as a component of oligometastatic disease management has emerged as a rational and relevant strategy. To this end, recent randomized studies in oligometastatic non-small-cell lung cancer demonstrated improved progression-free survival with consolidative local therapy, and this approach is the topic of ongoing cooperative group studies inclusive of patients with an array of primary histologies. Further, there is a push to explore the role of radiation as a means to enhance the efficacy of immune enabling drugs. Recent prospective data evaluating the safety and response of SBRT with anti-CTLA-4 therapy for patients with lung or liver metastasis demonstrated clinical benefit (out of field immune-related partial response or immune-related stable disease $\geq$6 months) in about a quarter of enrolled patients. Interestingly, SBRT to liver metastases was found to elicit a greater systemic immune response than SBRT to lung metastases. Classic management paradigms for metastatic disease are rapidly being supplanted by approaches that are improving outcomes for patients previously offered best supportive care or palliation alone. In this article, we will review the established and emerging potential indications for liver SBRT in this new era of oncologic care.

**Identifying patterns of care for elderly patients with non-surgically treated stage III non-small cell lung cancer: an analysis of the national cancer database.** Miller ED1, Fisher JL2, Haglund KE1, et al. Radiat Oncol. 2018 Oct 5;13(1):196. doi: 10.1186/s13014-018-1142-7.

**BACKGROUND:** To compare patterns of care for elderly patients versus non-elderly patients with non-surgically treated stage III non-small cell lung cancer (NSCLC) using the National Cancer Database (NCDB). We hypothesize that elderly patients are less likely to receive curative treatments, including concurrent chemoradiation (CCRT), compared to non-elderly patients. **METHODS:** We identified patients from the NCDB between 2003 and 2014 with non-surgically treated stage III NSCLC. We defined elderly as ≥70 years old and non-elderly <70 years old. Treatment categories included: no treatment, palliative treatment (chemotherapy alone, radiation (RT) alone <59.4 Gy or chemoradiation (CRT) <59.4 Gy), or definitive treatment (RT alone ≥59.4 Gy or CRT ≥59.4 Gy). Differences in treatment between elderly and non-elderly were tested using the χ2 test. **RESULTS:** We identified 57,602 elderly and 55,928 non-elderly patients. More elderly patients received no treatment (24.5% vs. 13.2%, P < 0.0001) and the elderly were less likely to receive definitive treatment (48.5% vs. 56.3%, P < 0.0001). CCRT was delivered in a significantly smaller proportion of elderly vs. non-elderly patients (66.0% vs. 78.9%, P < 0.0001 in patients treated with definitive intent; 32.0% vs. 44.5%, P < 0.0001 in patients receiving any treatment; and 24.2% vs. 38.6%, P < 0.0001 amongst all patients). **CONCLUSIONS:** In this large study of patients with non-surgically treated stage III NSCLC, elderly patients were less likely to receive any treatment or treatment with definitive intent compared to the non-elderly. The lack of use of concurrent or sequential chemotherapy in the elderly with stage III NSCLC suggests that the optimal treatment approach for this vulnerable population remains undefined.

**Assessment of tumour response after stereotactic ablative radiation therapy for lung cancer: A prospective quantitative hybrid 18 F-fluorodeoxyglucose-positron emission tomography and CT perfusion study.** Yang DM1,2,3, Palma D4,5, Louie A4,5, et al. J Med Imaging Radiat Oncol. 2018 Oct 3. doi: 10.1111/1754-9485.12807. [Epub ahead of print]

**INTRODUCTION:** Stereotactic ablative radiotherapy (SABR) is a guideline-recommended treatment for inoperable stage I non-small cell lung cancer (NSCLC), but imaging assessment of response after SABR is difficult. The goal of this study was to evaluate imaging-based biomarkers of tumour response using dynamic 18 F-FDG-PET and CT perfusion (CTP). **METHODS:** Thirty-one patients with early-stage NSCLC participated in this prospective correlative study. Each underwent dynamic 18 F-FDG-PET/CTP studies on a PET/CT scanner pre- and 8 weeks post-SABR. The dynamic 18 F-FDG-PET measured the tumour SUVmax , SUVmean and the following parameters: K1 , k2 , k3 , k4 and Ki , all using the Johnson-Wilson-Lee kinetic model. CTP quantitatively mapped BF, BV, MTT and PS in tumours and measured largest tumour diameter. Since free-breathing was allowed during CTP scanning, non-rigid image registration of CT images was applied to minimize misregistration before generating the CTP functional maps. Differences between pre- and post-SABR imaging-based parameters were compared. **RESULTS:** Tumour size changed only slightly after SABR (median 26 mm pre-SABR vs. 23 mm post-SABR; P = 0.01). However, dynamic 18 F-FDG-PET and CTP study showed substantial and significant changes in SUVmax , SUVmean , k3 , k4 and Ki . Significant decreases were evident in SUVmax (median 6.1 vs. 2.6; P < 0.001), SUVmean (median 2.5 vs. 1.5; P < 0.001), k3 (relative decrease of 52%; P = 0.002), Ki (relative decrease of 27%; P = 0.03), whereas there was an increase in k4 (+367%; P < 0.001). **CONCLUSIONS:** Hybrid 18 F-FDG-PET/CTP allowed the response of NSCLC to SABR to be assessed regarding metabolic and functional parameters. Future studies are needed, with correlation with long-term outcomes, to evaluate these findings as potential imaging biomarkers of response.

**Radiation Dose Escalation in Accelerated Hyperfractionated Radiotherapy for Stage III Non-small-cell Lung Cancer.** Wada K1, Kishi N2, Kanayama N2, Hirata T2, Morimoto M2, Konishi K2, Imamura

F3, Teshima T2, Ogawa K4. Anticancer Res. 2018 Oct;38(10):5951-5958. doi: 10.21873/
anticanres.12941.
**AIM:** To identify clinical benefits of dose escalation in accelerated hyperfractionated radiotherapy (AH-RT) for stage III non-small-cell lung cancer (NSCLC) using propensity score-matched (PSM) analysis.
**MATERIALS AND METHODS:** ur study retrospectively examined 294 patients undergoing definitive radiotherapy [131 patients, conventional once-daily radiotherapy (OD-RT); and 163, AH-RT] who were followed-up for a median of 40.4 months. The impact of overall survival (OS), progression-free survival (PFS), and locoregional control (LRC) was investigated. **RESULTS:** Pre-PSM, the median OS, PFS, and LRC durations were 23.1 vs. 39.9 (p=0.03), 8.9 vs. 13.5 (p<0.01), and 12.9 vs. 50.3 (p<0.01) months in the OD-RT and AH-RT groups, respectively. After-PSM (two matched groups of 144 patients), AH-RT was associated with better LRC [adjusted hazard ratio (aHR)=0.59, 95% confidence interval (CI)=0.33-0.99, p=0.04] and marginally better PFS (aHR=0.65, 95% CI=0.41-1.03; p=0.06), but not OS (aHR=0.75, 95% CI=0.46-1.24; p=0.26). **CONCLUSION:** After PSM analysis, dose escalation using AH-RT improved LRC and PFS in patients with locally advanced NSCLC. AH-RT can be a promising option for patients with advanced NSCLC.

[**A matched-pair analysis of stereotactic body radiotherapy (SBRT) for oligometastatic lung tumors from colorectal cancer versus early stage non-small cell lung cancer.**](#) Wang X1,2, Zamdborg L3, Ye H3, Grills IS3,4, Yan D3,4. BMC Cancer. 2018 Oct 10;18(1):962. doi: 10.1186/s12885-018-4865-9.
**BACKGROUND:** The use of stereotactic body radiotherapy (SBRT) for early-stage primary non-small cell lung cancer (NSCLC) reported excellent local control rates. But the optimal SBRT dose for oligometastatic lung tumors (OLTs) from colorectal cancer (CRC) has not yet been determined. This study aimed to evaluate whether SBRT to a dose of 48-60 Gy in 4-5 fractions could result in similar local outcomes for OLTs from CRC as compared to early-stage NSCLC, and to examine potential dose-response relationships for OLTs from CRC. **METHODS:** OLTs from CRC and primary NSCLCs treated with SBRT to 48-60 Gy in 4-5 fractions at a single institution were evaluated, and a matched-pair analysis was performed. Local recurrence-free survival (LRFS) was estimated by the Kaplan-Meier method. Univariate Cox regression was performed to identify significant predictors. **RESULTS:** There were 72 lung lesions in 61 patients (24 OLTs from CRC in 15 patients and 48 NSCLCs in 46 patients) were analyzed with a median follow-up of 30 months. LRFS for OLTs from CRC was significantly worse than that of NSCLC when treated with 48-60 Gy/4-5 fx (p = 0.006). The 1, 3 and 5-year LRFS of OLTs from CRC vs NSCLC were 80.6% vs. 100%, 68.6% vs. 97.2%, and 68.6% vs. 81.0%, respectively. On univariate analysis, OLTs from CRC treated with higher dose (BED10 = 132 Gy) exhibited significantly better local recurrence-free survival than those treated to lower doses (BED10 ≤ 105.6 Gy) (p = 0.0022). The 1 and 3-year LRFS rates for OLTs treated to a higher dose (BED10 = 132 Gy) were 88.9% and 81.5%, vs 33.3%, and not achieved for lower doses (BED10 ≤ 105.6 Gy). **CONCLUSION:** The LRFS of OLTs from CRC after SBRT of 48-60 Gy/4-5 fx was significantly worse than that of primary NSCLC. Lower dose SBRT appeared to have inferior control for OLTs of CRC in this cohort. Further studies with larger sample sizes are needed.

[**A method for optimizing planning target volume margins for patients receiving lung stereotactic body radiotherapy.**](#) Wierzbicki M1, Mathew L, Swaminath A. Phys Med Biol. 2018 Oct 2;63(19):195015. doi: 10.1088/1361-6560/aadf26.
Lung stereotactic-body radiotherapy (SBRT) places additional requirements on targeting accuracy over standard approaches. In treatment planning, a tumour volume is geometrically expanded and the resulting planning target volume (PTV) is covered with the prescribed dose. This ensures full dose delivery despite various uncertainties encountered during treatment. We developed a retrospective technique for optimizing the PTV expansion for a patient population. The method relies on deformable image

registration (DIR) of the planning CT to a treatment cone-beam CT (CBCT). The resulting transformation is used to map the planned target onto the treatment geometry, allowing the computation of the achieved target/PTV overlap. Basic validation of the method was performed using an anthropomorphic respiratory motion phantom. A self-validation technique was also implemented to allow estimation of the DIR error for the data being analyzed. Our workflow was used to retrospectively optimize PTV margin for 25 patients treated over 93 fractions. Targets for these patients were contoured on 4D CT images. SBRT delivery followed CBCT acquisition and a couch correction. A post-treatment CBCT was also acquired in some cases. Our basic validation demonstrated that the DIR-based technique is capable of transforming target volumes from planning CTs to treatment CBCTs with sub-mm accuracy. Our clinical analysis showed that the minimum percentages of target volumes covered for 3, 4, and 5 mm PTV margins were 92.1, 97.6, and 99.2, respectively. Analyzing data acquired before and just after treatment demonstrated that margins exceeding 5 mm did not significantly improve coverage. Finally, a 5 mm PTV margin achieved ⩾95% target volume coverage with ⩾95% probability. Our technique is accurate, automated, self-validating, and incorporates complex ITV shapes/deformations to allow PTV margin optimization. The analysis of clinical data indicates a 5 mm PTV margin is optimal for our process. This approach is generalizable to other disease sites and treatment strategies.

[Toxicity Related to Radiotherapy Dose and Targeting Strategy: A Pooled Analysis of Cooperative Group Trials of Combined Modality Therapy for Locally Advanced Non-Small Cell Lung Cancer.](#) Schild SE1, Fan W2, Stinchcombe TE3, et al. J Thorac Oncol. 2018 Oct 4. pii: S1556-0864(18)33173-3. doi: 10.1016/j.jtho.2018.09.021. [Epub ahead of print]
**PURPOSE:** Concurrent chemoradiotherapy(CRT) is the standard treatment for locally-advanced non-small-cell lung cancer(LA-NSCLC). This study was performed to examine thoracic radiotherapy(TRT) parameters and their impact on adverse events(AE's). **PATIENTS AND MATERIALS:** We collected Individual patient data(IPD) from 3600 LA-NSCLC patients participating in 16 cooperative group trials of concurrent CRT. The TRT parameters examined included field design strategy(elective nodal irradiation(ENI) vs. involved field TRT(IF-TRT)) and TRT dose(60Gy vs >60Gy). The primary endpoint of this analysis was the occurrence of AE's. Odd ratios(ORs) for AE's were calculated with univariable and multivariable logistic models. **RESULTS:** TRT doses ranged from 60 to 74Gy. ENI wasn't associated with more grade 3+(>3)AE's than IF-TRT(multivariable OR:0.77(95%CI:0.543-1.102,p=0.1545). Doses >60Gy(high dose) were associated with significantly more grade 3+AE's(multivariable OR:1.82(95%CI1.501-2.203,P<0.0001). In contrast, ENI was associated with significantly more grade 4+(>4)AE's(multivariable OR:1.33(95%CI:1.035-1.709,P=0.0258). Doses>60Gy were also associated with more grade 4+AE's(multivariate OR1.42(95%CI:1.191-1.700,P=0.0001). Grade 5 AE's plus treatment related deaths were more frequent with higher dose TRT(p=0.0012) but not ENI(p=0.099). **CONCLUSIONS:** For LA-NSCLC patients treated with concurrent CRT, IF-TRT wasn't associated with the overall risk of grade 3+AE's but was associated with significantly less grade 4+AE's than ENI-TRT. This is likely the result of irradiating less adjacent critical normal tissue. Higher TRT doses were associated significantly with grade 3+ and 4+AE's. Based on these findings and our prior report on survival, CRT employing IF-TRT and 60Gy(conventionally fractionated) were associated with more favorable patient survival and less toxicity than the use of ENI or higher RT doses.

## SMALL CELL LUNG CANCER - SCLC

[Third-Line Nivolumab Monotherapy in Recurrent Small Cell Lung Cancer: CheckMate 032.](#) Ready N1, Farago AF2, de Braud F3, et al. J Thorac Oncol. 2018 Oct 10. pii: S1556-0864(18)33181-2. doi: 10.1016/j.jtho.2018.10.003. [Epub ahead of print]

**INTRODUCTION:** For patients with recurrent small cell lung cancer (SCLC), topotecan remains the only FDA-approved or EMA-approved second-line treatment, and outcomes are poor. CheckMate 032 is a phase 1/2, multicenter, open-label study of nivolumab or nivolumab plus ipilimumab in SCLC or other advanced/metastatic solid tumors previously treated with ≥1 platinum-based chemotherapies. We report results of third- or later-line (3L+) nivolumab monotherapy treatment in SCLC. **METHODS:** In this analysis, patients with limited-stage or extensive-stage SCLC and disease progression after ≥2 chemotherapy regimens received nivolumab monotherapy 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. The primary end point was objective response rate (ORR). Secondary end points included duration of response (DOR), progression-free survival, overall survival, and safety. **RESULTS:** Between December 4, 2013 and November 30, 2016, 109 patients initiated 3L+ nivolumab monotherapy. At a median follow-up of 28.3 months (from first dose to database lock), ORR was 11.9% (95% confidence interval: 6.5-19.5) with a median DOR of 17.9 months (range, 3.0 to 42.1). At 6 months, 17.2% of patients were progression-free. The 12-month and 18-month overall survival rates were 28.3% and 20.0%, respectively. Grade 3-4 treatment-related adverse events (TRAEs) occurred in 11.9% of patients. Three patients (2.8%) discontinued due to TRAEs. **CONCLUSIONS:** Nivolumab monotherapy provided durable responses and was well tolerated as a 3L+ treatment for recurrent SCLC. These results suggest that nivolumab monotherapy is an effective 3L+ treatment for this patient population.

[Topotecan monotherapy for the treatment of relapsed small cell lung cancer in elderly patients: A retrospective analysis.](#) Imai H1, Yamada Y2, Minemura H3, et al. Thorac Cancer. 2018 Oct 3. doi: 10.1111/1759-7714.12884. [Epub ahead of print]
**BACKGROUND:** Topotecan is one of the most active chemotherapeutic drugs for small cell lung cancer (SCLC). However, its efficacy in elderly patients with SCLC has not been validated. This study evaluated the feasibility and efficacy of topotecan monotherapy in elderly patients with relapsed SCLC.
**METHODS:** Between January 2000 and March 2017, 43 patients aged ≥ 70 years received topotecan monotherapy for relapsed SCLC at four institutions. The clinical outcomes and adverse events of treatment were retrospectively analyzed. **RESULTS:** Twenty-nine patients (median age 75 years; range: 70-83 years) had sensitive-type relapse, while 14 (median age 78 years; range: 71-82 years) had refractory relapse. The median number of treatment cycles was two (range: 1-6). The response rate was 7.0% (10.3% and 0% in sensitive and refractory patients, respectively), while the disease control rate was 23.2% (20.6% and 42.8% in sensitive and refractory patients, respectively). Median progression-free survival was 1.9 months in sensitive patients and 1.4 months in refractory patients (P = 0.87). The median survival time from the start of topotecan therapy was 5.5 months in sensitive patients and 4.0 months in refractory patients (P = 0.64). Grade ≥ 3 hematological toxicities were as follows: leukopenia, 37.2%; neutropenia, 51.1%; anemia, 0%; thrombocytopenia, 32.5%; and febrile neutropenia, 9.3%. No treatment-related deaths occurred. **CONCLUSION:** Although hematological toxicities (particularly neutropenia) were severe, topotecan showed favorable disease control in both sensitive and refractory patients. Topotecan may thus be a preferred treatment for elderly patients with relapsed SCLC.

[Final report of survival and late toxicities in the Phase I study of stereotactic body radiation therapy for peripheral T2N0M0 non-small cell lung cancer (JCOG0702).](#) Onimaru R1, Onishi H2, Ogawa G3, et al. Jpn J Clin Oncol. 2018 Oct 1. doi: 10.1093/jjco/hyy141. [Epub ahead of print]
**PURPOSE:** A dose escalation study to determine the recommended dose with stereotactic body radiation therapy (SBRT) for peripheral T2N0M0 non-small cell carcinomas (JCOG0702) was conducted. The purpose of this paper is to report the survival and the late toxicities of JCOG0702. **MATERIALS AND METHODS:** The continual reassessment method was used to determine the dose level that patients hould be assigned to and to estimate the maximum tolerated dose. The starting dose was 40 Gy in four fractions

at D95 of PTV. **RESULTS:** Twenty-eight patients were enrolled. Ten patients were treated with 40 Gy at D95 of PTV, four patients with 45 Gy, eight patients with 50 Gy, one patient with 55 Gy and five patients with 60 Gy. Ten patients were alive at the last follow-up. Overall survival (OS) for all patients was 67.9% (95% CI 47.3-81.8%) at 3 years and 40.8% (95% CI 22.4-58.5%) at 5 years. No Grade 3 or higher toxicity was observed after 181 days from the beginning of the SBRT. Compared to the toxicities up to 180 days, chest wall related toxicities were more frequent after 181 days.
**CONCLUSIONS:** The 5-year OS of 40.8% indicates the possibility that SBRT for peripheral T2N0M0 non-small cell lung cancer is superior to conventional radiotherapy. The effect of the SBRT dose escalation on OS is unclear and further studies are warranted.

**Prophylactic cranial irradiation for limited-stage small-cell lung cancer patients: secondary findings from the prospective randomized phase 3 CONVERT trial.**
Levy A1, Le Péchoux C2, Mistry H3, Martel-Lafay I4, Bezjak A5, Lerouge D6, Padovani L7, Taylor P8, Faivre-Finn C9. J Thorac Oncol. 2018 Oct 4. pii: S1556-0864(18)33171-X. doi: 10.1016/j.jtho.2018.09.019. [Epub ahead of print]
**INTRODUCTION:** The impact of the dose and fractionation of thoracic radiotherapy on the risk of developing brain metastasis (BM) has not been evaluated prospectively in LS-SCLC patients receiving prophylactic cerebral irradiation (PCI). **METHODS:** Data in patients treated with PCI from the CONVERT trial was analysed. **RESULTS:** 449/547 (82%) received PCI after completion of chemoradiotherapy. Baseline brain imaging consisted of CT-scan in 356/449 patients (79%) and MRI in 83/449 (18%) patients. PCI was delivered to 220/273 participants (81%) in the twice-daily (BD) group and 229/270 in the once-daily (OD) group (85%; p=0.49). Total median PCI dose was 25Gy in both BD and OD groups (p=0.74). In patients who received PCI, 75 (17%) developed BM (35 [8%] in OD and 40 [9%] in BD) and 173 (39%) other extracranial progression. In the univariate analysis, GTV was associated with an increased risk of BM (p=0.007) or other radiological progression events (p=0.006), whereas in a multivariate analysis both thoracic GTV (tGTV) and PS were associated with either progression type. The median OS of patients treated with PCI was 29 months. In the univariate analysis of OS, PCI timing from end of chemotherapy, weight loss >10%, and tGTV were prognostic factors associated with OS. In the multivariate analysis, only tGTV was associated with OS. Delay between end of chemotherapy and PCI was not associated with OS. **CONCLUSION:** Patients receiving OD or BD thoracic RT have the same risk of developing BM. Larger tumours are associated with a higher risk of BM.

**Is prophylactic cranial irradiation necessary in individuals suffering from surgically resected pT1-2N0M0 small cell lung cancer?** Lu H1, Jiang Z2, Li C2. Ir J Med Sci. 2018 Oct 17. doi: 10.1007/s11845-018-1912-0. [Epub ahead of print]
Adjuvant chemotherapeutics and prophylactic cranial irradiation (PCI) are both recommended in the National Comprehensive Cancer Network (NCCN) guidelines for treating individuals suffering from surgically resected pT1-2N0M0 small cell lung cancer (SCLC). Whether adjuvant chemotherapy combined with PCI is superior to adjuvant chemotherapy alone in these patients is largely unknown. PCI may therefore be with uncertain effects in surgically resected pT1-2N0M0 SCLC.

**A pooled analysis of individual patient data from National Clinical Trials Network clinical trials of concurrent chemoradiotherapy for limited-stage small cell lung cancer in elderly patients versus younger patients.** Stinchcombe TE1, Fan W2, Schild SE3, Cancer. 2018 Oct 21. doi: 10.1002/cncr.31813. [Epub ahead of print]
 **BACKGROUND:** Platinum and etoposide with thoracic radiation followed by prophylactic cranial irradiation constitute the standard treatment for limited-stage small cell lung cancer (LS-SCLC). Many

patients with LS-SCLC are elderly with comorbidities. **METHODS:** Individual patient data were collected from 11 phase 2 or 3 trials for LS-SCLC conducted by the National Clinical Trials Network and activated from 1990 to 2010. The primary endpoint was overall survival (OS); the secondary endpoints were progression-free survival (PFS), the rate of severe adverse events, and off-treatment reasons. The outcomes were compared for patients 70 years old or older (elderly patients) and patients younger than 70 years (younger patients). **RESULTS:** Individual patient data from 1049 younger patients (81%) and 254 elderly patients (19%) were analyzed. In the multivariate model, elderly patients, in comparison with younger patients, had worse OS (hazard ratio [HR], 1.38; 95% confidence interval [CI], 1.18-1.63; median OS for elderly patients, 17.8 months; OS for younger patients, 23.5 months) and worse PFS (HR, 1.19; 95% CI, 1.03-1.39; median PFS for elderly patients, 10.6 months; median PFS for younger patients, 12.3 months). Elderly patients, in comparison with younger patients, experienced more grade 5 adverse events (8% vs 3%; $P < .01$) and more grade 3 or higher dyspnea (11% vs 7%; $P = .03$) but less grade 3 or higher esophagitis/dysphagia (14% vs 19%; $P = .04$) and less grade 3 or higher vomiting (11% vs 17%; $P = .01$). Elderly patients completed treatment less often, discontinued treatment because of adverse events and patient refusal more frequently, and died during treatment more frequently. **CONCLUSIONS:** Elderly patients with LS-SCLC have worse PFS and OS and more difficulty in tolerating therapy. Future trials should incorporate assessments of elderly patients, novel monitoring of adverse events, and more tolerable radiation and systemic therapies.

**Apatinib as maintenance therapy in extensive-stage small-cell lung cancer: results from a single-center retrospective study.** Yan X1, Wang Q1, Wang H1, Li P1, Zhang G1, Zhang M1, Zheng X1, Yang J1, Zhang X1, Ma Z2. J Cancer Res Clin Oncol. 2018 Oct 6. doi: 10.1007/s00432-018-2764-8. [Epub ahead of print]

**PURPOSE:** To evaluate the efficacy of maintenance apatinib after chemotherapy for extensive-stage (ED) small-cell lung cancer (SCLC). **PATIENTS AND METHODS:** This was a retrospective analysis of 23 cases of extensive-stage SCLC admitted to the Affiliated Cancer Hospital of Zhengzhou University from January 2015 to December 2017. The patients without progression after induction chemotherapy received apatinib 250 mg per day until disease progression or unacceptable toxicity occurred. We analyzed the median progression-free survival (PFS), median overall survival (OS) and safety. **RESULTS:** Of 23 enrolled patients, 1 was lost to follow-up. The median PFS from the time of maintenance therapy was 4.1 months (95% CI 3.63-4.57 months). The median PFS from the time of induction chemotherapy was 8.3 months (95% CI 7.20-9.40 months). The median OS from the time of maintenance therapy was 12.5 months (95% CI 5.51-19.49 months). The median OS from the time of induction chemotherapy was 17.0 months (95% CI 9.86-24.14 months). The most frequent treatment-related adverse events were hand-foot syndrome (43.5%, 10/23) and secondary hypertension (30.4%, 7/23), followed by fatigue, proteinuria, nausea, and oral mucositis (17.4%, 13.0%, 13.0%, and 8.7%, respectively). Hematologic toxicity included thrombocytopenia (30.4%), leucopenia (26.1%), and anemia (17.4%). The main grade 3 or 4 toxicities were hand-foot syndrome (8.7%, 2/23) and hypertension (4.3%, 1/23). **CONCLUSION:** Maintenance apatinib was safe and achieved encouraging PFS and OS in extensive-stage SCLC.

## PALLIATIVE AND SUPPORTIVE CARE

**Factors Affecting Racial Disparities in End-of-Life Care Costs Among Lung Cancer Patients: A SEER-Medicare-based Study.** Karanth S1, Rajan SS1, Revere FL1, Sharma G2. Am J Clin Oncol. 2018 Oct 8. doi: 10.1097/COC.0000000000000485. [Epub ahead of print]

**OBJECTIVES:** Racial disparities exist in end-of-life lung cancer care, which could potentially lead to considerable racial differences in end-of-life care costs. This study for the first time estimates the racial differences in end-of-life care costs among lung cancer patients, and identifies and quantifies factors that contribute the most to these differences using a statistical decomposition method. **METHODS:** This is a retrospective analysis of patients 66 years and older, diagnosed with stage I-IV lung cancer, who died on or before December 31, 2013, using the Surveillance Epidemiology and End Result-Medicare data from 1991 to 2013. Ordinary least square regression of logarithmically transformed cost was used to estimate racial differences in end-of-life care costs among lung cancer patients. Blinder-Oaxaca decomposition was used to identify and quantify factors that contributed the most to these differences. **RESULTS:** Non-Hispanic blacks had 10% to 13% higher end-of-life care costs as compared with non-Hispanic whites. Geographic variations, baseline comorbidity indices and stage at diagnosis contributed the most to explaining the racial differences in costs, with geographic variation explaining most of the differences. However, the observed factors could only explain 25% to 32% of the racial differences in end-of-life care costs. **CONCLUSIONS:** Geographic differences in access to timely and appropriate care, and provider practice patterns, should be examined to understand the reasons behind geographic variations in racial disparity. Provider-level educational interventions to reduce small area practice variations and differential management of patients by race, as well as racially sensitive patient-level educational and navigational interventions might be critical in improving quality of care and reducing costs during end-of-life.


**Postoperative Pneumonia Prevention in Pulmonary Resections: A Feasibility Pilot Study.**
Semenkovich TR1, Frederiksen C2, Hudson JL2, Subramanian M2, Kollef MH3, Patterson GA2, Kreisel D2, Meyers BF2, Kozower BD2, Puri V2. Ann Thorac Surg. 2018 Oct 3. pii: S0003-4975(18)31350-X. doi: 10.1016/j.athoracsur.2018.08.008. [Epub ahead of print]
**BACKGROUND:** Pneumonia after pulmonary resection occurs in 5-12% of patients and causes substantial morbidity. Oral hygiene regimens lower the incidence of ventilator-associated pneumonias, however, the impact in patients undergoing elective pulmonary resection is unknown. We conducted a prospective pilot study to assess the feasibility of an oral hygiene intervention in this patient cohort. **METHODS:** Patients undergoing elective pulmonary resection were prospectively enrolled in a single arm interventional study with time-matched controls. Participants were asked to brush their teeth with 0.12% chlorhexidine three times daily for five days before their operations and five days or until the time of discharge after their operations. Patients were eligible if they had known or suspected lung cancer and were undergoing (1) any anatomic lung resection or (2) a wedge resection with FEV1 or DLCO <50% predicted. **RESULTS:** 62 patients were enrolled in the pilot intervention group and compared to a contemporaneous cohort of 611 patients who met surgical inclusion criteria. Preoperative adherence to the chlorhexidine toothbrushing regimen was high: median 100% (IQR: 87-100%). Postoperatively, 80% of patients continued toothbrushing, while 20% declined further participation. Among those who participated postoperatively, median adherence was 86% (IQR: 53-100%). There was a trend towards reduction in post-operative pneumonia: 1.6% (1/62) in the intervention cohort vs 4.9% (30/611) in the time-matched cohort (p=0.35). The number needed to treat to prevent one pneumonia was 30 patients. **CONCLUSIONS:** This pilot study demonstrated patients can comply with an inexpensive perioperative oral hygiene regimen that may be promising for reducing morbidity.


**Improving the delivery of physical activity services in lung cancer: A qualitative representation of the patient's perspective.** Granger CL1,2, Parry SM1, Edbrooke L1,3, Abo S2, Leggett N1,2, Dwyer M1, Denehy L3,4. Eur J Cancer Care (Engl). 2018 Oct 4:e12946. doi: 10.1111/ecc.12946. [Epub ahead of print]
**OBJECTIVE:** To explore patient experiences of, and preferences for, physical activity after a lung cancer diagnosis. **METHODS:** This was a qualitative study involving seven patients who had been

treated for lung cancer within the previous 2 years. Participants attended a focus group interview. Conventional content analysis methodology was used to analyse the text by two independent researchers. **RESULTS:** Eight major themes emerged from the data. These were as follows: the influence of past lifestyle and chronic disease; the perceived benefits of physical activity; using physical activity to facilitate return to activities of daily living; the impact of symptoms, capacity and motivation; family and peer support; access to services; health professionals; and enjoyment of different types of physical activity. Patients suggested several factors that could improve their healthcare experience. These include access to exercise professionals particularly after cancer treatment; access to information about physical activity in different formats; supervision from health professionals and peer support; and use of behaviour change strategies to achieve sustainable increases in physical activity. **CONCLUSION:** Our results should be considered in the improvement of lung cancer care pathways as we strive to implement physical activity services into routine clinical care.


[Promotion of Behavioral Change and the Impact on Quality of Life in Elderly Patients with Advanced Cancer: A Physical Activity Intervention of the Multimodal Nutrition and Exercise Treatment for Advanced Cancer Program.](#) Mouri T1, Naito T2, Morikawa A3, Tatematsu N4, Miura S5, Okayama T6, Omae K7, Takayama K1. Asia Pac J Oncol Nurs. 2018 Oct-Dec;5(4):383-390. doi: 10.4103/apjon.apjon_21_18.
**OBJECTIVE:** Physical activity (PA) may improve the quality of life (QOL) of cancer survivors. However, the impact on patients with advanced cancer with high cachectic potential is unknown. We analyzed the feasibility of PA intervention using the multimodal program Nutrition and Exercise Treatment for Advanced Cancer (NEXTAC) and the impact on QOL in elderly patients with advanced cancer. **METHODS:** We recruited 30 patients aged ≥70 years who were scheduled to receive the first-line chemotherapy for newly diagnosed advanced pancreatic or non-small-cell lung cancer. The QOL was assessed using the European Organization for Research and Treatment of Cancer QOL Questionnaire version 3.0, while the PA was measured using a pedometer/accelerometer. Instructors counseled patients to increase daily activity in an 8-week educational intervention. We assessed patient attendance, compliance, and intervention efficacy. **RESULTS:** The median patients' age was 75 years (range, 70-84 years). Twelve patients (40%) were cachectic at baseline. Twenty-eight (93%) patients attended all sessions. Six (21%) and 15 (52%) patients increased their indoor and outdoor activity, respectively. There were significant differences in measured PA, global QOL, and role and emotional functioning between the patients who increased outdoor activity and those who did not. **CONCLUSIONS:** The PA intervention of the NEXTAC program was feasible as the elderly patients with advanced cancer in this study were highly compliant. The majority of patients demonstrated behavioral changes that were associated with the improvement in global QOL. We conduct a randomized phase II study to measure the impact of the NEXTAC program on QOL and functional prognosis.


[Trajectory of insomnia symptoms in older adults with lung cancer: using mixed methods.](#)
Dean GE1, Ziegler P2, Chen H3, Steinbrenner LM2,4, Dickerson SS5. Support Care Cancer. 2018 Oct 15. doi: 10.1007/s00520-018-4488-3. [Epub ahead of print]
**CONTEXT:** A knowledge gap exists in our understanding of the illness and insomnia symptom treatment trajectory in adults with inoperable non-small cell lung cancer (NSCLC). **OBJECTIVES:** Compare valid and reliable sleep-wake measures for insomnia to interpretations of narrative descriptions of sleep to improve our comprehension of sleep-wake disturbances in adults with NSCLC. **METHODS:** This study employed mixed methods (quantitative and qualitative) in a longitudinal design to study adults (n = 26) from ambulatory thoracic clinics. Valid and reliable surveys (Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale), 7-day sleep diary, and actigraphy were obtained with interview narrative interpretations of sleep experiences in the context of lung cancer. Data collection occurred at four-time

points: baseline (before chemotherapy), pre-second chemotherapy, pre-third chemotherapy, and 6 months from baseline. Sleep measures were compared to interpretations from interview narratives to understand context of survey measures. **RESULTS:** Objective quantitative results were congruent with interview narrative interpretations that reflected participants' sleep-wake experiences. Objective sleep-wake measures for insomnia over-time described increasing sleep latency and decreasing sleep duration. The interview narratives provided context and insight into participants' subjective insomnia experiences. While participants' insomnia symptoms were present, they were resigned to endure insomnia, and the subjective measures reflected a more positive perception of sleep outcomes. **CONCLUSION:** A mixed methods approach provides a deeper understanding of sleep-wake disturbances and the differing quantitative objective and subjective results of sleep measures in the context of the participants' experience of the trajectory of insomnia symptoms before, during, and after lung cancer treatment.

[Impact of Cancer Cachexia on Hospitalization-associated Physical Inactivity in Elderly Patients with Advanced Non-small-cell Lung Cancer.](#) Morikawa A1, Naito T2, Sugiyama M1, Okayama T3, Aoyama T4, Tanuma A3, Omae K5, Takahashi T2. Asia Pac J Oncol Nurs. 2018 Oct-Dec;5(4):377-382. doi: 10.4103/apjon.apjon_20_18.
**OBJECTIVE:** New or worsening disability can develop in elderly patients in just 1 week of hospitalization for acute illness. Elderly patients with cancer, particularly those with cancer cachexia, are vulnerable to disability. This study aimed to explore the impact of hospitalization and cachexia on physical activity (PA) in elderly patients during chemotherapy. **METHODS:** We prospectively enrolled 18 patients aged ≥70 years with newly-diagnosed, advanced non-small-cell lung cancer scheduled to initiate first-line chemotherapy. PA was measured using an accelerometer (Lifecorder®, Suzuken Co., Ltd., Japan). Mean daily steps at baseline, during hospitalization, and subsequent weeks (1st, 2nd, and 3rd week after discharge) were compared. **RESULTS:** A total of 30 hospitalizations for chemotherapy were evaluated in 18 patients with a median age of 74.5 years. The median number of baseline daily steps was 3756. Fifteen cases (50%) showed fewer daily steps during hospitalization and no recovery to baseline level during the 1st week after discharge. Long hospitalizations (≥8 days) and the presence of cachexia were associated with persistent physical inactivity. One patient developed disability within 30 days after hospitalization. **CONCLUSIONS:** Physical inactivity was frequently seen after hospitalization for chemotherapy in elderly patients with advanced lung cancer. Longer in-hospital days and the presence of cancer cachexia caused slow recovery from physical inactivity. Individualized hospitalization planning based on careful consideration of patient age and the presence of cancer cachexia may be needed to prevent physical inactivity and disability.

[Psychosocial Support in Cancer Cachexia Syndrome: The Evidence for Supported Self-Management of Eating Problems during Radiotherapy or Chemotherapy Treatment.](#)
Hopkinson J1. Asia Pac J Oncol Nurs. 2018 Oct-Dec;5(4):358-368. doi: 10.4103/apjon.apjon_12_18.
People receiving cancer treatment are at nutritional risk. Their eating problems can lead to malnutrition and weight loss. Involuntary weight loss is also a defining characteristic of tumor-induced cachexia. Weight loss is associated with poor tolerance of treatment, poor treatment outcomes, morbidity, and mortality. Support for self-management of nutritional risk may protect against malnutrition and be important in multimodal therapies to arrest the progression of cachexia. Nurses can help patients by supporting self-management of eating problems. This scoping review is about eating problems during cancer treatment. It considers patient experience and self-management of eating problems during cancer treatment for the proactive management of malnutrition and cachexia. It draws on a systematic search of Medline, CINAHL, PsycINFO, and the Cochrane Library for publications about people with cancer who have eating problems during treatment. Limits were English language; January 2000 to December 2017; adults. The search found studies about eating problems in patients treated with chemotherapy or

radiotherapy for head-and-neck cancer, lung cancer, gastrointestinal cancer, breast cancer, testicular cancer, and ovarian cancer. Nutritional counseling can improve nutritional intake, quality of life, and weight. However, the patient perspective on self-management and how to motivate engagement in nutritional care is unexplored. There is a potential for reducing nutritional risk during cancer treatment using psychoeducation to support behavioral change, thus empower self-management of eating problems. Benefits are likely in subgroups of people receiving cancer treatment, such as those with head and neck, gastrointestinal, and lung cancers.

## COMPLEMENTARY & ALTERNATIVE THERAPY

**Chemical composition and biological activity of extracts from fruiting bodies and mycelial cultures of Fomitopsis betulina.** Sułkowska-Ziaja K1, Szewczyk A2, Galanty A3, Gdula-Argasińska J4, Muszyńska B2. Mol Biol Rep. 2018 Oct 13. doi: 10.1007/s11033-018-4420-4. [Epub ahead of print] Fomitopsis betulina (Bull.) B.K. Cui, M.L. Han & Y.C. Dai has been used for medicinal purposes for over 5000 years. Numerous studies have confirmed the biological activity of compounds found in this species. The purpose of this study was a comparative analysis of selected groups of metabolites in the extracts from fruiting bodies and mycelial cultures. Phenolic acids (syringic, gallic, p-hydroxybenzoic, 3,4-dihydrophenylacetic), indole compounds (L-tryptophan, 5-hydroxy-L-tryptophan, 5-methyltryptamine), sterols (ergosterol, ergosterol peroxide, hexestrol, cholecalciferol), and triterpenes (betulinic acid, betulin) were determined quantitatively by high performance liquid chromatography with UV-Vis/DAD detection, while fatty acids were assessed with the gas chromatography method. Cytotoxic activity against selected human cancer cell lines was determined using the lactate dehydrogenase test. Anti-inflammatory activity was evaluated on lipopolysaccharide activated A549 cells. Those extracts with anti-inflammatory activity were evaluated for their inhibition of pro-inflammatory enzymes. The mycelium extract exhibited significant cytotoxic activity against prostate cancer cells, while the fruiting body extract indicated a moderate effect on the viability of melanoma and prostate cancer. Incubation of lung epithelial cells with biomass extract significantly decreased cyclooxygenase-2 levels compared to LPS activated A549 cells. This paper is the first report of a comparative quantitative analysis of the metabolites in mycelial cultures and fruiting bodies. In addition, a novel element of this study is its comparison of the cytotoxic and anti-inflammatory activity of the obtained extracts. The results of comparing the composition and activity of mycelium and fruiting bodies shows that the cultures could be proposed as a potential biotechnological source for selected biologically active compounds.

**Complementary Medicine, Refusal of Conventional Cancer Therapy, and Survival Among Patients With Curable Cancers.** Johnson SB1, Park HS1, Gross CP2, Yu JB1,2. AMA Oncol. 2018 Oct 1;4(10):1375-1381. doi: 10.1001/jamaoncol.2018.2487.
**IMPORTANCE:** There is limited information on the association among complementary medicine (CM), adherence to conventional cancer treatment (CCT), and overall survival of patients with cancer who receive CM compared with those who do not receive CM. **OBJECTIVES:** To compare overall survival between patients with cancer receiving CCT with or without CM and to compare adherence to treatment and characteristics of patients receiving CCT with or without CM. **DESIGN, SETTING, AND PARTICIPANTS:** This retrospective observational study used data from the National Cancer Database on 1 901 815 patients from 1500 Commission on Cancer-accredited centers across the United States who were diagnosed with nonmetastatic breast, prostate, lung, or colorectal cancer between January 1, 2004, and December 31, 2013. Patients were matched on age, clinical group stage, Charlson-Deyo comorbidity score, insurance type, race/ethnicity, year of diagnosis, and cancer type. Statistical analysis was conducted from November 8, 2017, to April 9, 2018. **EXPOSURES:** Use of CM was defined as "Other-Unproven:

Cancer treatments administered by nonmedical personnel" in addition to at least 1 CCT modality, defined as surgery, radiotherapy, chemotherapy, and/or hormone therapy. **MAIN OUTCOMES AND MEASURES:** Overall survival, adherence to treatment, and patient characteristics. **RESULTS:** The entire cohort comprised 1 901 815 patients with cancer (258 patients in the CM group and 1 901 557 patients in the control group). In the main analyses following matching, 258 patients (199 women and 59 men; mean age, 56 years [interquartile range, 48-64 years]) were in the CM group, and 1032 patients (798 women and 234 men; mean age, 56 years [interquartile range, 48-64 years]) were in the control group. Patients who chose CM did not have a longer delay to initiation of CCT but had higher refusal rates of surgery (7.0% [18 of 258] vs 0.1% [1 of 1031]; P < .001), chemotherapy (34.1% [88 of 258] vs 3.2% [33 of 1032]; P < .001), radiotherapy (53.0% [106 of 200] vs 2.3% [16 of 711]; P < .001), and hormone therapy (33.7% [87 of 258] vs 2.8% [29 of 1032]; P < .001). Use of CM was associated with poorer 5-year overall survival compared with no CM (82.2% [95% CI, 76.0%-87.0%] vs 86.6% [95% CI, 84.0%-88.9%]; P = .001) and was independently associated with greater risk of death (hazard ratio, 2.08; 95% CI, 1.50-2.90) in a multivariate model that did not include treatment delay or refusal. However, there was no significant association between CM and survival once treatment delay or refusal was included in the model (hazard ratio, 1.39; 95% CI, 0.83-2.33). **CONCLUSIONS AND RELEVANCE:** In this study, patients who received CM were more likely to refuse additional CCT, and had a higher risk of death. The results suggest that mortality risk associated with CM was mediated by the refusal of CCT.

[**Bioactivity-guided isolation of ginsenosides from Korean Red Ginseng with cytotoxic activity against human lung adenocarcinoma cells.**](#) Yu JS1, Roh HS2, Baek KH2, et al. J Ginseng Res. 2018 Oct;42(4):562-570. doi: 10.1016/j.jgr.2018.02.004. Epub 2018 Feb 16.
**BACKGROUND:** Lung cancer is the leading cause of cancer-related death worldwide. In this study, we used a bioactivity-guided isolation technique to identify constituents of Korean Red Ginseng (KRG) with antiproliferative activity against human lung adenocarcinoma cells. **METHODS:** Bioactivity-guided fractionation and preparative/semipreparative HPLC purification were used with LC/MS analysis to separate the bioactive constituents. Cell viability and apoptosis in human lung cancer cell lines (A549, H1264, H1299, and Calu-6) after treatment with KRG extract fractions and constituents thereof were assessed using the water-soluble tetrazolium salt (WST-1) assay and terminal deoxyribonucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining, respectively. Caspase activation was assessed by detecting its surrogate marker, cleaved poly adenosine diphosphate (ADP-ribose) polymerase, using an immunoblot assay. The expression and subcellular localization of apoptosis-inducing factor were assessed using immunoblotting and immunofluorescence, respectively. **RESULTS AND CONCLUSION:** Bioactivity-guided fractionation of the KRG extract revealed that its ethyl acetate-soluble fraction exerts significant cytotoxic activity against all human lung cancer cell lines tested by inducing apoptosis. Chemical investigation of the ethyl acetatesoluble fraction led to the isolation of six ginsenosides, including ginsenoside Rb1 (1), ginsenoside Rb2 (2), ginsenoside Rc (3), ginsenoside Rd (4), ginsenoside Rg1 (5), and ginsenoside Rg3 (6). Among the isolated ginsenosides, ginsenoside Rg3 exhibited the most cytotoxic activity against all human lung cancer cell lines examined, with IC50 values ranging from 161.1 μM to 264.6 μM. The cytotoxicity of ginsenoside Rg3 was found to be mediated by induction of apoptosis in a caspase-independent manner. These findings provide experimental evidence for a novel biological activity of ginsenoside Rg3 against human lung cancer cells.

**Smoking and Lung Cancer Mortality in the United States From 2015 to 2065: A Comparative Modeling Approach.** Jeon J1, Holford TR2, Levy DT3, Feuer EJ4, Cao P1, Tam J1, Clarke L5, Clarke J5, Kong CY6, Meza R1. Ann Intern Med. 2018 Oct 9. doi: 10.7326/M18-1250. [Epub ahead of print] **BACKGROUND:** Tobacco control efforts implemented in the United States since the 1960s have led to considerable reductions in smoking and smoking-related diseases, including lung cancer. **OBJECTIVE:** To project reductions in tobacco use and lung cancer mortality from 2015 to 2065 due to existing tobacco control efforts. **DESIGN:** Comparative modeling approach using 4 simulation models of the natural history of lung cancer that explicitly relate temporal smoking patterns to lung cancer rates. **SETTING:** U.S. population, 1964 to 2065. **PARTICIPANTS:** Adults aged 30 to 84 years. **MEASUREMENTS:** Models were developed using U.S. data on smoking (1964 to 2015) and lung cancer mortality (1969 to 2010). Each model projected lung cancer mortality by smoking status under the assumption that current decreases in smoking would continue into the future (status quo trends). Sensitivity analyses examined optimistic and pessimistic scenarios. **RESULTS:** Under the assumption of continued decreases in smoking, age-adjusted lung cancer mortality was projected to decrease by 79% between 2015 and 2065. Concomitantly, and despite the expected growth, aging, and longer life expectancy of the U.S. population, the annual number of lung cancer deaths was projected to decrease from 135 000 to 50 000 (63% reduction). However, 4.4 million deaths from lung cancer are still projected to occur in the United States from 2015 to 2065, with about 20 million adults aged 30 to 84 years continuing to smoke in 2065. **LIMITATION:** Projections assumed no changes to tobacco control efforts in the future and did not explicitly consider the potential effect of lung cancer screening. **CONCLUSION:** Tobacco control efforts implemented since the 1960s will continue to reduce lung cancer rates well into the next half-century. Additional prevention and cessation efforts will be required to sustain and expand these gains to further reduce the lung cancer burden in the United States.

**Pilot Randomized Trial of a Pharmacy Intervention for Older Adults with Cancer.** Nipp RD1, Ruddy M2, Fuh CX2, et al. Oncologist. 2018 Oct 19. pii: theoncologist.2018-0408. doi: 10.1634/theoncologist.2018-0408. [Epub ahead of print] **BACKGROUND:** Oncology clinicians often struggle with managing medications and vaccinations in older adults with cancer. We sought to demonstrate the feasibility and preliminary efficacy of integrating pharmacists into the care of older adults with cancer to enhance medication management and vaccination administration. **METHODS:** We randomly assigned patients aged ≥65 years with breast, gastrointestinal, or lung cancer receiving first-line chemotherapy to the pharmacy intervention or usual care. Patients assigned to the intervention met with a pharmacist once during their second or third chemotherapy infusion. We obtained information about patients' medications and vaccinations via patient report and from the electronic health record (EHR) at baseline and week 4. We determined the number of discrepant (difference between patient report and EHR) and potentially inappropriate (Beers Criteria assessed by nonintervention pharmacists blinded to group assignment) medications. We defined the intervention as feasible if >75% of patients enrolled in the study and received the pharmacist visit. **RESULTS:** From January 17, 2017, to October 27, 2017, we enrolled and randomized 60 patients (80.1% of patients approached). Among those assigned to the intervention, 96.6% received the pharmacist visit. At week 4, intervention patients had higher rates of acquiring vaccinations for pneumonia (27.6% vs. 0.0%, p = .002) and influenza (27.6% vs. 0.0%, p = .002) compared with usual care. Intervention patients had fewer discrepant (5.82 vs. 8.07, p = .094) and potentially inappropriate (3.46 vs. 4.80, p = .069) medications at week 4, although differences were not significant. **CONCLUSION:** Integrating pharmacists into the care of older adults with cancer is feasible with encouraging preliminary efficacy for enhancing medication

management and improving vaccination rates. **IMPLICATIONS FOR PRACTICE:** Results of this study showed the feasibility, acceptability, and preliminary efficacy of an intervention integrating pharmacists into the care of older adults with cancer. Notably, patients assigned to the intervention had fewer discrepant medications and were more likely to acquire vaccinations for pneumonia and influenza. Importantly, this work represents the first randomized controlled trial involving the integration of pharmacists into the outpatient oncologic care of older adults with cancer. In the future, a larger randomized trial is needed to demonstrate the efficacy of this care model to enhance medication management and improve vaccination outcomes for older patients with cancer.


[The unintended impact of smoking-risk information on concerns about radon: A randomized controlled trial.](#) Gold JM1, Stuart JO1, Thiem KC1, Field RW2, Fernandez-Baca J3, Windschitl PD1. Health Psychol. 2018 Oct 18. doi: 10.1037/hea0000681. [Epub ahead of print]
**OBJECTIVE:** Health communications are often viewed by people with varying levels of risk. This project examined, in the context of radon risk messages, whether information relevant to high-risk individuals can have an unintended influence on lower-risk individuals. Two studies assessed whether information about lung cancer risk from smoking reduced concerns about lung cancer risk from radon among nonsmokers. **METHOD:** American nonsmokers viewed radon messages that varied in what they communicated about smoking's effect on lung cancer risk. Study 1 used a 4-arm factorial, randomized, controlled design in which smoking information was included or excluded from messages assembled from 2 existing radon pamphlets. Study 2 used a 3-arm parallel, randomized, controlled design in which a new radon message excluded smoking information, described smoking as a lung cancer risk, or also described smoking's synergistic effect with radon. **RESULTS:** In Study 1, the inclusion of smoking information reduced nonsmokers' (n = 462) concern-related reactions to possible radon exposure. In Study 2, nonsmokers' (n = 583) concern-related reactions were reduced in both smoking-information conditions; intentions to test their home for radon and perceived importance of testing were reduced in the synergistic condition. **CONCLUSION:** People reading health-risk information contextualize their risk relative to the risk of others. For people at midlevel risk, concern and related reactions prompted by a health message may be dampened when the message includes information about others who are more at risk. In the case of radon and smoking risks, the inclusion of smoking information can reduce the impact that radon messages have on nonsmokers. (PsycINFO Database Record (c) 2018 APA, all rights reserved).


[Impact Of The Affordable Care Act (Aca) Medicaid Expansion On Cancer Admissions and Surgeries.](#) Eguia E1,2, Cobb AN1,2, Kothari AN2, Molefe A3, Afshar M4, Aranha GV5, Kuo PC6. Ann Surg. 2018 Oct;268(4):584-590. doi: 10.1097/SLA.0000000000002952.
**OBJECTIVE:** This study aims to evaluate the trends in cancer (CA) admissions and surgeries after the Affordable Care Act (ACA) Medicaid expansion. **METHODS:** This is a retrospective study using HCUP-SID analyzing inpatient CA (pancreas, esophagus, lung, bladder, breast, colorectal, prostate, and gastric) admissions and surgeries pre- (2010-2013) and post- (2014) Medicaid expansion. Surgery was defined as observed resection rate per 100 cancer admissions. Nonexpansion (FL) and expansion states (IA, MD, and NY) were compared. A generalized linear model with a Poisson distribution and logistic regression was used with incidence rate ratios (IRR) and difference-in-differences (DID). **RESULTS:** There were 317,858 patients in our sample which included those with private insurance, Medicaid, or no insurance. Pancreas, breast, colorectal, prostate, and gastric CA admissions significantly increased in expansion states but decreased in nonexpansion states. (IRR 1.12, 1.14, 1.11, 1.34, 1.23; P<.05) Lung and colorectal CA surgeries (IRR 1.30, 1.25; P<.05) increased, while breast CA surgeries (IRR 1.25; P<.05) decreased less in expansion states. Government subsidized, or self-pay patients had greater odds of undergoing lung, bladder, and colorectal CA surgery (OR 0.45 vs 0.33; 0.60 vs 0.48; 0.47 vs 0.39; P<.05) in expansion states after reform. **CONCLUSIONS:** In states that expanded Medicaid coverage under the

ACA, the rate of surgeries for colorectal and lung CA increased significantly, while breast CA surgeries decreased less. Parenthetically, these cancers are subject to population screening programs. We conclude that expanding insurance coverage results in enhanced access to cancer surgery.

### [Reductions in Cigarettes per Day and Mortality Among Older Adults in The United States.](#)
Inoue-Choi M1, Hartge P1, Park Y2, Abnet CC1, Freedman ND1. Am J Epidemiol. 2018 Oct 9. doi: 10.1093/aje/kwy227. [Epub ahead of print]
Many smokers do not quit but instead reduce the number of cigarettes that they smoke per day (CPD) over their lifetime, yet the associations of such changes in CPD with health risks are unclear. We examined the association of changes in CPD with subsequent mortality (2004-2011) among 253,947 participants of the NIH-AARP Diet and Health Study. We identified cigarette smokers who quit, decreased, maintained, or increased their CPD between ages 25-29 and 50-59 using a questionnaire assessing smoking history in 2004-2005. Hazard ratios (HR) and 95% confidence intervals (CI) were from multivariable-adjusted Cox proportional hazards regression. Relative to never smokers, smokers who maintained a consistent CPD had 2.93 times (95%CI: 2.82, 3.05) higher all-cause mortality risk, with still higher risks observed in participants who increased their CPD (HR: 3.37, 95%CI: 3.23, 3.52). Risks were lower among participants who decreased their CPD (HR: 2.38, 95%CI: 2.25, 2.52) or quit smoking (HR for quitting between 30-39 years: 1.32, 95%CI: 1.25, 1.39). Similar patterns were observed for smoking-related causes of death, with particularly strong associations for lung cancer and respiratory disease. Reductions in CPD over the lifetime meaningfully decrease mortality risk. But cessation provides a larger benefit than even large declines in CPD.

### [A qualitative study of Realtor knowledge, attitudes, and practices related to radon health effects: implications for comprehensive cancer control.](#) Momin B1, McNaughton C2, Galanek JD3, Neri A4, Gallaway MS5, Puckett M5. Cancer Causes Control. 2018 Oct 3. doi: 10.1007/s10552-018-1086-0. [Epub ahead of print]
**BACKGROUND:** Lung cancer is the leading cause of cancer-related deaths in the United States, and radon exposure is the second leading risk factor. Fewer than 25% of existing U.S. homes have been tested for radon, and only 5-10% of new homes use some form of radon prevention. **OBJECTIVE:** This qualitative study sought to determine radon-related knowledge, attitudes, and practices among Realtors to inform cancer control activities at local and state levels. **METHODS:** We conducted focus groups with Realtors in four states to collect information about knowledge, attitudes, and practices regarding radon. **RESULTS:** Realtors reported obtaining information on radon in similar ways, being aware of radon and its characteristics, and dealing with radon issues as a normal part of home sales. Differences in attitudes toward testing varied across states. Realtors in states with radon policies generally expressed more positive attitudes toward testing than those in states without policies. Radon mitigation was identified as an added expense to buyers and sellers. Realtors cited concerns about the reliability and credibility of mitigation systems and installers. **CONCLUSIONS:** These findings suggest that attitudes and practices vary among Realtors and that additional educational resources about radon as a cancer risk factor may be beneficial. When comprehensive cancer control programs update their plans, they may want to add objectives, strategies, or activities to reduce radon exposure and prevent lung cancer. These activities could include partnering with Realtors to improve their knowledge, attitudes, and practices about radon, as well as developing and distributing radon educational resources.