



## Caring Ambassadors Lung Cancer Program Literature Review, June 2019

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### BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

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[Apoptosis induction and AKT/NF- \$\kappa\$ B inactivation are associated with regorafenib-inhibited tumor progression in non-small cell lung cancer in vitro and in vivo.](#) Weng MC1, Li MH2, Chung JG3, Liu YC4, Wu JY5, Hsu FT6, Wang HE7. *Biomed Pharmacother.* 2019 Aug;116:109032. doi: 10.1016/j.biopha.2019.109032. Epub 2019 Jun 1.

Non-small cell lung cancer (NSCLC) is a malignant lung cancer type with poor prognosis. NF- $\kappa$ B, the oncogenic transcription factor, has been recognized as an important mediator in progression of NSCLC. Regorafenib, a multikinase inhibitor, was demonstrated to inhibit tumor progression through suppression of ERK/NF- $\kappa$ B signaling in hepatocellular carcinoma cells in vitro and in vivo. However, whether regorafenib inhibit progression of NSCLC is ambiguous. Thus, the major purpose of present study was to evaluate anticancer efficacy and underlying mechanism of regorafenib on tumor progression in NSCLC in vitro and in vivo. CL-1-5-F4 cells were treated with regorafenib, NF- $\kappa$ B (QNZ) or AKT (LY294002) inhibitor for 24 or 48 h. Then, we performed cell viability assay, NF- $\kappa$ B reporter gene assay, transwell invasion assay and apoptosis related flow cytometry assay on cellular level to verify anti-cancer effect and mechanism of regorafenib. CL-1-5-F4 bearing animal model was treated with vehicle or regorafenib for 28 days. The therapeutic efficacy and mechanism of regorafenib in CL-1-5-F4 bearing animal model were investigated by tumor size evaluation, whole body computer tomography (CT) scan, Haemotoxylin and Eosin (H&E) stain and immunohistochemistry (IHC) stain. Our results demonstrated regorafenib significantly inhibited tumor growth and induced apoptosis through extrinsic/intrinsic pathways in NSCLC in vitro and in vivo. Furthermore, we also found the suppression of AKT/NF- $\kappa$ B signaling was required for regorafenib inhibited expression of progression-related and invasion-related proteins. Our finding indicated apoptosis induction and suppression of AKT/NF- $\kappa$ B signaling were associated with regorafenib-inhibited progression of NSCLC in vitro and in vivo.

[Glutathione reductase \(GSR\) gene deletion and chromosome 8 aneuploidy in primary lung cancers detected by fluorescence in situ hybridization.](#) Baity M1, Wang L2, Correa AM2, et al. *Am J Cancer Res.* 2019 Jun 1;9(6):1201-1211. eCollection 2019.

Our recent study demonstrated that cancer cells with compromised glutathione homeostasis, including reduced expression of the glutathione reductase (GSR) gene, were selectively killed by inhibition of thioredoxin reductase. The human GSR gene is located on chromosome 8p, a region often lost in lung and other cancers. However, whether GSR is altered in primary lung cancer remains unknown. To analyze alterations of GSR in lung cancer, we performed fluorescence in situ hybridization with probes for GSR and the chromosome 8 centromere (CEP8) in 45 surgical specimens of primary lung cancer, including 24 lung adenocarcinomas, 10 squamous cell carcinomas, 8 neuroendocrine cancers, and 3 small cell lung cancers. Twenty-five surgically resected normal lung tissue specimens from these lung cancer patients were used as a control. The signal ratio of GSR to CEP8 per cell was used to identify gain or loss of GSR. GSR loss was detected in 6 of 24 (25%) adenocarcinoma specimens and 5 of 10 (50%) squamous cell carcinoma specimens, but not in neuroendocrine cancer or small cell lung cancer specimens. We also found that 19 of 45 (42%) specimens had chromosome 8 aneuploidy (more or less than 2 signals for CEP8), including 8 with both aneuploidy and GSR deletion. Chromosome 8 aneuploidy was detected in all types of lung cancer analyzed. Univariate and multivariable logistic regression analyses indicated that male patients had an increased risk of GSR deletion (hazard ratio [HR] = 4.77, 95% confidence interval [CI] = 1.00-22.86, P = 0.051), and patients who had undergone preoperative radiation therapy or had a self-reported history of cigarette smoking had an increased risk of chromosome 8 aneuploidy (preoperative radiation: HR = 18.63, 95% CI = 0.90-384.17, P = 0.058; smoking: HR = 7.59, 95% CI = 0.86-66.75, P = 0.068), although the p values did not reach significance. Because GSR deficiency and chromosome 8 aneuploidy have implications in targeted therapy and/or immunotherapy for cancer, they might serve as predictive biomarkers for precision therapy of lung cancers.

**[Interleukin-17 Promotes Migration and Invasion of Human Cancer Cells Through Upregulation of MTA1 Expression.](#)** Guo N1,2, Shen G1, Zhang Y3, Moustafa AA1, Ge D1, You Z1,4,5,6,7,8. *Front Oncol.* 2019 Jun 20;9:546. doi: 10.3389/fonc.2019.00546. eCollection 2019.

Interleukin-17 (IL-17) has been shown to promote development of prostate, colon, skin, lung, breast, and pancreatic cancer. The purpose of this study was to determine if IL-17 regulates MTA1 expression and its biological consequences. Human cervical cancer HeLa and human prostate cancer DU-145 cell lines were used to test if IL-17 regulates metastasis associated 1 (MTA1) mRNA and protein expression using quantitative reverse transcription-polymerase chain reaction and Western blot analysis, respectively. Cell migration and invasion were studied using wound healing assays and invasion chamber assays. Thirty-four human cervical tissues were stained for IL-17 and MTA1 using immunohistochemical staining. We found that IL-17 increased MTA1 mRNA and protein expression in both cell lines. Cell migration was accelerated by IL-17, which was abolished by knockdown of MTA1 expression with small interference RNA (siRNA). Further, cell invasion was enhanced by IL-17, which was eliminated by MTA1 knockdown. Human cervical intra-epithelial neoplasia (CIN) and cervical cancer tissues had increased number of IL-17-positive cells and MTA1 expression compared to normal cervical tissues. The number of IL-17-positive cells was positively correlated with MTA1 expression. These findings demonstrate that IL-17 upregulates MTA1 mRNA and protein expression to promote HeLa and DU-145 cell migration and invasion.

**[Nicotine promotes the development of non-small cell lung cancer through activating LINC00460 and PI3K/Akt signaling.](#)** Zhao H1, Wang Y2, Ren X3. *Biosci Rep.* 2019 Jun 7;39(6). pii: BSR20182443. doi: 10.1042/BSR20182443. Print 2019 Jun 28.

**OBJECTIVE:** Nicotine, the main ingredient in tobacco, is identified to facilitate tumorigenesis and accelerate metastasis in tumor. Studies in recent years have reported that long intergenic non-protein coding RNA 460 (LINC00460) is strongly associated with lung cancer poor prognosis and nicotine dependence. Nonetheless, it is unclear whether nicotine promotes the development of lung cancer through

activation of LINC00460. **METHODS:** We determined that LINC00460 expression in lung cancer tissues and the prognosis in patients with non-small cell lung carcinoma (NSCLC) using Gene Expression Profiling Interactive Analysis (GEPIA) website and The Cancer Genome Atlas (TCGA) database. Through in vitro experiments, we studied the effects of nicotine on LINC00460 in NSCLC cell lines using Cell Counting Kit-8 (CCK-8), transwell test, flow cytometry, quantitative reverse-transcription polymerase chain reaction (qRT-PCR) and Western blot assays. **RESULTS:** We identified the significant up-regulated expression level of LINC00460 in NSCLC tissues and cell lines, especially, the negative correlation of LINC00460 expression level with overall survival (OS). In in vitro experiments, LINC00460 was overexpressed in NSCLC cell lines under nicotine stimulation. Nicotine could relieve the effect of LINC00460 knockdown on NSCLC cell proliferation, migration and apoptosis. The same influence was observed on PI3K/Akt signaling pathway. **CONCLUSIONS:** In summary, this is the first time to examine the potential roles of LINC00460 in lung cancer cell proliferation, migration and apoptosis induced by nicotine. This may help to develop novel therapeutic strategies for the prevention and treatment of metastatic tumors from cigarette smoke-caused lung cancer by blocking the nicotine-activated LINC00460 pathway.

**Surgery after chemoradiotherapy in patients with stage III (N2 or N3, excluding T4) non-small-cell lung cancer: a systematic review.** Swaminath A1, Vella ET2, Ramchandar K3, Robinson A4, Simone C5, Sun A6, Ung YC7, Yasufuku K8, Ellis PM9. *Curr Oncol.* 2019 Jun;26(3):e398-e404. doi: 10.3747/co.26.4549. Epub 2019 Jun 1.

**BACKGROUND:** Chemoradiation with curative intent is considered the standard of care in patients with locally advanced, stage iii non-small-cell lung cancer (nslc). However, some patients with stage iii (N2 or N3, excluding T4) nslc might be eligible for surgery. The objective of the present systematic review was to investigate the efficacy of surgery after chemoradiotherapy compared with chemoradiotherapy alone in patients with potentially resectable locally advanced nslc. **METHODS:** A search of the medline, embase, and PubMed databases sought randomized controlled trials (rcts) comparing surgery after chemoradiotherapy with chemoradiotherapy alone in patients with stage iii (N2 or N3, excluding T4) nslc. **RESULTS:** Three included rcts consistently found no statistically significant difference in overall survival between patients with locally advanced nslc who received surgery and chemoradiotherapy or chemoradiotherapy alone. Only one rct found that progression-free survival was significantly longer in patients treated with chemoradiation and surgery (hazard ratio: 0.77; 95% confidence interval: 0.62 to 0.96). In a post hoc analysis of the same trial, the overall survival rate was higher in the surgical group than in matched patients in a chemoradiation-only group if a lobectomy was performed ( $p = 0.002$ ), but not if a pneumonectomy was performed. Furthermore, fewer treatment-related deaths occurred in patients who underwent lobectomy than in those who underwent pneumonectomy. **CONCLUSIONS:** For patients with locally advanced nslc, the benefits of surgery after chemoradiation are uncertain. Surgery after chemoradiation for patients who do not require a pneumonectomy might be an option.

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## SCREENING, BIOMARKER TESTING, DIAGNOSIS AND STAGING

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**Small Lung Tumor Biopsy Samples Are Feasible for High Quality Targeted Next Generation Sequencing.** Kage H1, Kohsaka S2, Shinozaki-Ushiku A3, et al. *Cancer Sci.* 2019 Jun 21. doi: 10.1111/cas.14112. [Epub ahead of print]

Next generation sequencing (NGS) has been implemented in clinical oncology to analyze multiple genes and guide therapy. In patients with advanced lung cancer, small biopsies such as CT-guided needle biopsy (CTNB), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), or transbronchial biopsy (TBB) are less invasive and are preferable to resection to make a pathological diagnosis. However, quality of DNA/RNA and NGS from small lung tumor biopsy samples are unknown.

One hundred and seven consecutive samples were obtained from thoracic tumors or metastatic sites for targeted NGS analysis between April 2017 and March 2018. Fifteen samples were through CTNB, 11 through EBUS-TBNA, 11 through TBB, and 70 through surgical resection. All samples were formalin-fixed and paraffin-embedded. DNA and RNA quality were measured by the ddCq method and the percentage of RNA fragments above 200 nucleotides (DV200), respectively. Our custom-made probes were designed to capture exon sequences of 464 cancer-related genes and transcripts of 463 genes. DNA and RNA yield from the three biopsy methods were similar, and less than the yield obtained from resected samples. Quality of DNA and RNA was similar across all methods. Overall, 12 of 15 CTNB samples (80%), all 11 EBUS-TBNA samples, and 9 of 11 TBB samples (82%) underwent fully adequate NGS assays from DNA. NGS analysis from RNA was successful in all 12 CTNB samples, 9 of 11 EBUS-TBNA samples (82%), and 8 of 11 TBB samples (73%). CTNB, EBUS-TBNA, and TBB mostly resulted in adequate DNA and RNA quality and enabled high-quality targeted NGS analysis. This article is protected by copyright. All rights reserved.

[Accuracy of Canine Scent Detection of Non-Small Cell Lung Cancer in Blood Serum.](#) Junqueira H, Quinn TA, Biringer R, Hussein M, Smeriglio C, Barrueto L, Finizio J, Huang XYM. J Am Osteopath Assoc. 2019 Jun 17. doi: 10.7556/jaoa.2019.077. [Epub ahead of print]

Early detection provides the best opportunity for lung cancer survival; however, lung cancer is difficult to detect early because symptoms do not often appear until later stages. Current screening methods such as x-ray and computed tomographic imaging lack the sensitivity and specificity needed for effective early diagnosis. Dogs have highly developed olfactory systems and may be able to detect cancer in its primary stages. Their scent detection could be used to identify biomarkers associated with various types of lung cancer. **OBJECTIVE:** To determine the accuracy of trained beagles' ability to use their olfactory system to differentiate the odor of the blood serum of patients with lung cancer from the blood serum of healthy controls. **METHODS:** Over the course of 8 weeks, operant conditioning via clicker training was used to train dogs to use their olfactory system to distinguish blood serum from patients with malignant lung cancer from blood serum from healthy controls in a double-blind study. After training, non-small cell lung cancer and healthy control blood serum samples were presented to the dogs, and the sensitivity and specificity of each dog were analyzed. **RESULTS:** Four dogs were trained for the study, but 1 was unmotivated by training and removed from the study. Three dogs were able to correctly identify the cancer samples with a sensitivity of 96.7%, specificity of 97.5%, positive predictive value of 90.6%, and negative predictive value of 99.2%. **CONCLUSION:** Trained dogs were able to identify non-small cell lung cancer samples from healthy controls. The findings of this study provide a starting point for a larger-scale research project designed to explore the use of canine scent detection as a tool for cancer biomarkers.

[5-year overall survival in patients with lung cancer eligible or ineligible for screening according to US Preventive Services Task Force criteria: a prospective, observational cohort study.](#) Luo YH1, Luo L2, Wampfler JA3, Wang Y4, Liu D5, Chen YM6, Adjei AA7, Midthun DE8, Yang P9. Lancet Oncol. 2019 Jun 26. pii: S1470-2045(19)30329-8. doi: 10.1016/S1470-2045(19)30329-8. [Epub ahead of print]

**BACKGROUND:** The US Preventive Services Task Force (USPSTF) recommends lung cancer screening among individuals aged 55-80 years with a 30 pack-year cigarette smoking history and, if they are former smokers, those who quit within the past 15 years. Our previous report found that two-thirds of newly diagnosed patients with lung cancer do not meet these criteria; they are reported to be either long-term quitters ( $\geq 15$  years since quitting) or from a younger age group (age 50-54 years). We aimed to assess survival outcomes in these two subgroups. **METHODS:** For this prospective, observational cohort study we identified and followed up patients aged 50-80 years with lung cancer, with a smoking history of 30

pack-years or more, and included both current smokers and former smokers who quit within the past 30 years. We identified patients from two cohorts in the USA: a hospital cohort (Mayo Clinic, Rochester, MN) and a community cohort (Olmsted County, MN). Patients were divided into those meeting USPSTF criteria (USPSTF group) versus those not meeting USPSTF criteria (long-term quitters or the younger age group). The main outcome was overall survival at 5 years after diagnosis. 5-year overall survival was analysed with and without matching age and pack-years smoked for long-term quitters. The USPSTF group was subdivided into two age subgroups (55-69 years and 70-80 years) for multivariable regression analysis. **FINDINGS:** Between Jan 1, 1997, and Dec 31, 2017, 8739 patients with lung cancer were identified and followed up. Median follow-up was 6.5 (IQR 3.8-10.0) years, and median overall survival was 16.9 months (95% CI 16.2-17.5). 5-year overall survival was 27% (95% CI 25-30) in long-term quitters, 22% (19-25) in the younger age group, and 23% (22-24) in the USPSTF group. In both cohorts, 5-year overall survival did not differ significantly between long-term quitters and the USPSTF group (hospital cohort: hazard ratio [HR] 1.02 [95% CI 0.94-1.10]; p=0.72; community cohort: 0.97 [0.75-1.26]; p=0.82); matched analysis showed similar results in both cohorts. 5-year overall survival also did not differ significantly between the younger age group and the USPSTF group in both cohorts (hospital cohort: HR 1.16 [95% CI 0.98-1.38], p=0.08; community cohort: 1.16 [0.74-1.82]; p=0.52); multivariable regression analyses stratified by age group yielded similar findings. **INTERPRETATION:** Patients with lung cancer who quit 15 or more years before diagnosis and those who are up to 5 years younger than the age cutoff recommended for screening, but otherwise meet USPSTF criteria, have a similar risk of death to those individuals who meet all USPSTF criteria. Individuals in both subgroups could benefit from screening, as expansion of USPSTF screening criteria to include these subgroups could enable earlier detection of lung cancer and improved survival outcomes. **FUNDING:** National Institutes of Health and the Mayo Clinic Foundation.

[Feasibility of liquid biopsy using plasma and platelets for detection of anaplastic lymphoma kinase rearrangements in non-small cell lung cancer.](#) Park CK<sup>1,2</sup>, Kim JE<sup>1,2</sup>, Kim MS<sup>1,2</sup>, et al. *J Cancer Res Clin Oncol.* 2019 Jun 1. doi: 10.1007/s00432-019-02944-w. [Epub ahead of print]

**PURPOSE:** Fluorescence in situ hybridization (FISH) using tumor tissue is the gold standard for detection of anaplastic lymphoma kinase (ALK) rearrangement in non-small cell lung cancer (NSCLC). However, this method often is not repeatable due to difficulties in the acquisition of tumor tissues. Blood-based liquid biopsy using reverse transcription polymerase chain reaction (RT-PCR) is expected to be useful to overcome this limitation. Here, we investigated the feasibility of liquid biopsy using plasma and platelets for detection of ALK rearrangement and prediction of ALK inhibitor treatment outcomes.

**METHODS:** ALK-FISH assays were performed in 1128 tumor specimens of NSCLC between January 2015 and June 2018. We retrospectively analyzed formalin-fixed paraffin-embedded (FFPE) tissues from previously confirmed FISH-positive (n = 199) and -negative (n = 920) cases. We recruited patients who had available tissue specimens and agreed to venous sampling. RNA was extracted from FFPE blocks, plasma, and platelets. Fusion RNA of echinoderm microtubule-associated protein-like 4 (EML4)-ALK was detected by quantitative PCR. **RESULTS:** Thirty-three FISH-positive and 28 FISH-negative patients were enrolled. In validation, data compared with FISH, RT-PCR using FFPE tissues showed 54.5% sensitivity, 78.6% specificity, and 75.5% accuracy. Liquid biopsy had higher sensitivity (78.8%), specificity (89.3%) and accuracy (83.6%). Higher positivity for liquid biopsy was shown in subgroups with delayed ( $\geq 6$  months from diagnosis) blood sampling (plasma, 85.7%; platelets, 87.0%). In 26 patients treated with crizotinib, the platelet-positive subgroup showed longer median duration of treatment (7.2 versus 1.5 months), longer median progression-free survival (5.7 months versus 1.7 months), a higher overall response rate (70.6% versus 11.1%), and a higher disease control rate (88.2% versus 44.4%) than the platelet-negative subgroup. **CONCLUSION:** Liquid biopsy could have applications in the diagnosis

of ALK-positive NSCLC, even when using RT-PCR, and platelets can be useful for predicting treatment outcomes of ALK inhibitors.

[Targeting SLMAP-ALK-a novel gene fusion in lung adenocarcinoma.](#) Pagan C1, Barua S1, Hsiao SJ1, Mansukhani M1, Saqi A1, Murty V1, Fernandes H1. Cold Spring Harb Mol Case Stud. 2019 Jun 3;5(3). pii: a003939. doi: 10.1101/mcs.a003939. Print 2019 Jun.

Assessment of ALK gene rearrangements is strongly recommended by the Molecular Testing Guideline for Selection of Lung Cancer Patients proposed by IASLC, AMP, and CAP at the time of diagnosis for patients with advanced stage disease. Non-small-cell lung cancer (NSCLC) with ALK gene rearrangements or the resulting fusion proteins have been, for the most part, successfully targeted with ALK tyrosine kinase inhibitors (TKIs). The most frequent rearrangement, the EML4-ALK oncogenic fusion, has more than 10 distinct variants, each with a discrete breakpoint in EML4. Recent studies have suggested that EML4-ALK variants may have differential responses to TKIs. Additionally, non-EML4-ALK fusions that result from ALK rearrangements with diverse 5' partners could possibly have varied biologic and clinical implications in their therapeutic responses and outcomes of patients with NSCLC. Existing literature documents at least 20 non-EML4 fusion partners for ALK, and the clinical responsiveness to crizotinib ranges from increased sensitivity to resistance. This underscores the importance of identifying the precise 5' fusion partner to ALK before initiation of therapy. Herein we report the identification of a novel SLMAP-ALK fusion in a patient with NSCLC.

[Assessment of non-lobe-specific lymph node metastasis in clinical stage IA non-small cell lung cancer.](#) Zhang Z1, Miao J1, Chen Q1, Fu Y1, Li H1, Hu B1. Thorac Cancer. 2019 Jul;10(7):1597-1604. doi: 10.1111/1759-7714.13121. Epub 2019 Jun 17.

**BACKGROUND:** The rationality of selective mediastinal lymph node dissection based on lobe-specific metastasis is still controversial. The correlation of lymph node metastasis in lobe-specific lymphatic drainage regions (LSDRs) and non-LSDRs has not been widely reported. The purpose of this study was to investigate the variables affecting nodal metastasis in non-LSDRs and to further evaluate the rationality of selective lymphadenectomy in clinical stage IA non-small cell lung cancer (NSCLC) patients.

**METHODS:** The clinicopathological information of 316 patients with clinical stage IA NSCLC who underwent lobectomy with systematic lymph node dissection between June 2014 and June 2018 was retrospectively collected for analysis. **RESULTS:** The overall lymph node metastasis rate was 19.3%. For 35 patients with positive LSDR lymph nodes, the non-LSDR lymph node metastasis rate was 31.4%. Only one patient (0.4%) among 281 patients with negative LSDR lymph nodes had nodal spread in non-LSDRs. Univariate analysis identified that solid consistency, worse differentiation, and positive status in LSDRs were unfavorable predictive variables of lymph node metastasis in non-LSDRs. Multivariate analysis showed that nodal metastasis in LSDRs was the only independent predictor of nodal involvement in non-LSDRs ( $P < 0.001$ ). **CONCLUSION:** For patients with clinical stage IA NSCLC, non-LSDR lymph node metastasis mainly depends on the involvement of the LSDR lymph node. Our observations may indicate the potential implications for the reasonable management of lymphadenectomy in stage IA NSCLC patients.

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NSCLC - SURGERY

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[Surgery or radiotherapy for stage I lung cancer? An intention-to-treat analysis.](#) Spencer KL1,2,3, Kennedy MPT1,3, Lummis KL4, Ellames DAB1, Snee M1, Brunelli A1, Franks K1, Callister MEJ1. *Eur Respir J.* 2019 Jun 20;53(6). pii: 1801568. doi: 10.1183/13993003.01568-2018. Print 2019 Jun.

**INTRODUCTION:** Surgery is the standard of care for early-stage lung cancer, with stereotactic ablative body radiotherapy (SABR) a lower morbidity alternative for patients with limited physiological reserve. Comparisons of outcomes between these treatment options are limited by competing comorbidities and differences in pre-treatment pathological information. This study aims to address these issues by assessing both overall and cancer-specific survival for presumed stage I lung cancer on an intention-to-treat basis.

**METHODS:** This retrospective intention-to-treat analysis identified all patients treated for presumed stage I lung cancer within a single large UK centre. Overall survival, cancer-specific survival, and combined cancer and treatment-related survival were assessed with adjustment for confounding variables using Cox proportional hazards and Fine-Gray competing risks analyses. **RESULTS:** 468 patients (including 316 surgery and 99 SABR) were included in the study population. Compared with surgery, SABR was associated with inferior overall survival on multivariable Cox modelling (SABR HR 1.84 (95% CI 1.32-2.57)), but there was no difference in cancer-specific survival (SABR HR 1.47 (95% CI 0.80-2.69)) or combined cancer and treatment-related survival (SABR HR 1.27 (95% CI 0.74-2.17)). Combined cancer and treatment-related death was no different between SABR and surgery on Fine-Gray competing risks multivariable modelling (subdistribution hazard 1.03 (95% CI 0.59-1.81)). Non-cancer-related death was significantly higher in SABR than surgery (subdistribution hazard 2.16 (95% CI 1.41-3.32)). **CONCLUSION:** In this analysis, no difference in cancer-specific survival was observed between SABR and surgery. Further work is needed to define predictors of outcome and help inform treatment decisions.

[Postoperative Recurrence and Survival After Segmentectomy for Clinical Stage 0 or IA Lung Cancer.](#) Kamigaichi A1, Tsutani Y1, Fujiwara M1, Mimae T1, Miyata Y1, Okada M2. *Clin Lung Cancer.* 2019 Jun 13. pii: S1525-7304(19)30146-9. doi: 10.1016/j.clcc.2019.06.004. [Epub ahead of print]

**BACKGROUND:** Although radical segmentectomy is an accepted treatment option for small-sized lung cancer, the outcomes remain unclear. The present study aimed to elucidate recurrence patterns and to identify predictors of time to recurrence after intentional segmentectomy for early lung cancer.

**PATIENTS AND METHODS:** Prospectively collected data of 166 patients who could tolerate lobectomy and underwent intentional segmentectomy for clinical stage 0 or IA non-small-cell lung cancer between 2007 and 2016 were retrospectively analyzed. Surgical indication for intentional segmentectomy was clinical stage 0 or IA ground glass opacity-dominant tumor  $\leq 3$  cm or solid-dominant tumor  $\leq 2$  cm on high-resolution computed tomography. **RESULTS:** The median follow-up duration was 48.8 months, during which 6 (3.6%) patients developed recurrences. The 5-year recurrence-free survival and 5-year overall survival rates were 93.1% (95% confidence interval [CI], 87.9%-96.1%) and 93.5% (95% CI, 87.7%-96.4%), respectively. Two (1.2%) patients who developed local-only recurrences subsequently underwent completion lobectomy; no cancer-related deaths were seen for these patients. In multivariable analysis, consolidation to maximum tumor diameter (C/T) ratio (hazard ratio, 1.07; 95% CI, 1.01-1.22;  $P = .02$ ) was an independent predictive factor for time to recurrence. All 6 patients with recurrence had a tumor with a C/T ratio of 86% or higher. **CONCLUSIONS:** Based on these findings, favorable survival is expected after intentional segmentectomy for selected patients with clinical stage 0 or IA non-small-cell lung cancer. Patients with a higher C/T ratio tumor appear to be at higher risk of recurrence after intentional segmentectomy.

**Effect of insurance type on perioperative outcomes after robotic-assisted pulmonary lobectomy for lung cancer.** Deol PS1, Sipko J1, Kumar A2, Tsalatsanis A2, Moodie CC3, Garrett JR3, Fontaine JP4,

**BACKGROUND:** Insurance type has been reported to be an independent predictor of overall survival in lung cancer patients. We studied the effect of insurance type on patient outcomes after minimally invasive pulmonary lobectomy for lung cancer. **METHODS:** We retrospectively analyzed 433 consecutive patients who underwent robotic-assisted pulmonary lobectomy by one surgeon during an 80-month period. Perioperative outcomes and intraoperative and postoperative complications were noted. Disposition at discharge after surgery (favorable, eg, transfer to home with self-care or with home health nursing and/or physical therapy, versus unfavorable, eg, long-term acute care or rehabilitation facility, hospice, or death) and 5-year overall survival (5-years OS) were also recorded. We used Pearson  $\chi^2$ , analysis of variance (ANOVA), and Kruskal-Wallis test to compare variables and Cox regression for survival analysis. **RESULTS:** There were 107 patients (mean age 57.5 years) with private insurance, 118 (mean age 70.3 years) with public insurance (Medicare or Medicaid), 196 (mean age 71.8 year;  $P < .001$ ) with combination insurance plans (Medicare plus a privately supplied supplemental), and 12 patients with no insurance (excluded owing to low sample size). There were more current smokers in the public insurance group, more former smokers in the combination insurance group, and more nonsmokers in the private insurance group ( $P = .03$ ). There were more comorbidities in the public and combination insurance groups versus the private insurance group, including gastroesophageal reflux disease ( $P = .003$ ), hypertension ( $P = .01$ ), and hyperlipidemia ( $P < .001$ ). The groups had no differences in tumor size or pathologic stage. There were higher numbers of intraoperative conversions to open lobectomy in the private and public insurance groups versus the combination insurance group ( $P = .001$ ). Also, the private and combination insurance groups had more cases of favorable disposition at discharge after surgery compared with the public insurance group ( $P < .001$ ). Multivariable regression analyses identified private insurance type as an independent predictor of favorable disposition at discharge (public versus private plan; odds ratio, 0.43; 95% confidence interval [CI], 0.22-0.85,  $P = .02$ ) and 5-year OS (combination versus private plan; hazard ratio, 2.68; 95% CI, 1.26-5.67,  $P = .01$ ; public versus private plan; HR, 2.84; 95% CI, 1.37-5.89;  $P = .01$ ). **CONCLUSION:** Although public or combination insurance type was associated with greater risk of all-cause mortality, and public insurance type was associated with less favorable disposition at discharge after surgery and overall conversion to open lobectomy, insurance type was not associated with increased intraoperative complications, hospital duration of stay, or in-hospital mortality after minimally invasive robotic-assisted pulmonary lobectomy.

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

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**Salvage treatment with anlotinib for advanced non-small cell lung cancer.** Wu D1, Nie J1, Dai L1, et al. Thorac Cancer. 2019 Jul;10(7):1590-1596. doi: 10.1111/1759-7714.13120. Epub 2019 Jun 10.

**BACKGROUND:** This real-world study assessed the efficacy and toxicity of anlotinib as salvage treatment in Chinese patients with advanced non-small cell lung cancer (NSCLC). **METHODS:** The medical records of 81 patients with advanced NSCLC who had failed at least two lines of chemotherapy were retrospectively collected. All patients were administered anlotinib treatment until disease progression or intolerance as a result of adverse events. Survival curves were created using the Kaplan-Meier method. The log-rank test was used for univariate analysis of progression-free survival (PFS) between groups. Cox regression was used to estimate the statistically significant factors based on univariate analysis. **RESULTS:** The median PFS was five months (95% confidence interval [CI] 3.5-6.5). The objective response rate (ORR) was 7% and the disease control rate (DCR) was 84%. The following subgroups of patients had longer PFS ( $P < 0.05$ ): squamous cell carcinoma, no brain or liver metastases, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1, and no previous VEGF-



tyrosine kinase inhibitor treatment. The results of Cox regression indicated that an ECOG PS of 0-1 (hazard ratio 0.152, 95% CI 0.057-0.403; P = 0.00) and patients without brain metastases (hazard ratio 0.421, 95% CI 0.195-0.911; P = 0.028) had longer PFS following anlotinib treatment. **CONCLUSION:** Anlotinib, which is well tolerated, plays a significant role in the salvage treatment of advanced NSCLC. Patients with advanced NSCLC with an ECOG PS of 0-1 and no brain metastases achieved longer PFS following anlotinib salvage treatment.

**Cardiotoxicity with immune system targeting drugs: a meta-analysis of anti-PD/PD-L1 immunotherapy randomized clinical trials.** Rahouma M1, Karim NA2, Baudo M3, et al.

Immunotherapy. 2019 Jun;11(8):725-735. doi: 10.2217/imt-2018-0118.

**BACKGROUND:** With antiprogrammed death receptor-1 (anti-PD-L1) therapy, a recent meta-analysis reported higher incidence of cutaneous, endocrine and gastrointestinal complications especially with dual anti-PD-L1 immunotherapy (IMM). **METHODS:** Our primary outcome was assessment of all cardiotoxicity grades in IMM compared with different treatments, thus a systemic review and a meta-analysis on randomized clinical trials (RCTs) were done. **RESULTS:** We included 11 RCTs with 6574 patients (3234 patients in IMM arm vs 3340 patients in the other arm). Three non-small-cell lung cancer RCTs, seven melanoma RCTs and only one prostatic cancer RCT met the inclusion criteria. There were five RCTs that compared monoimmunotherapy to chemotherapy "(n = 2631 patients)". No difference exists in all cardiotoxicity grades or high-grade cardiotoxicity (p > 0.05). Lung cancer exhibited a higher response rate and lower mortality in IMM. **CONCLUSION:** There was no reported statistically significant cardiotoxicity associated with anti-PD/PD-L1 use. Lung cancer subgroups showed better response and survival rates.

**Nivolumab plus ipilimumab versus chemotherapy as first-line treatment in advanced non-small-cell lung cancer with high tumour mutational burden: patient-reported outcomes results from the randomised, open-label, phase III CheckMate 227 trial.** Reck M1, Schenker M2, Lee KH3, et al. Eur J

Cancer. 2019 Jul;116:137-147. doi: 10.1016/j.ejca.2019.05.008. Epub 2019 Jun 11.

**BACKGROUND:** In the phase III CheckMate 227 study, first-line nivolumab + ipilimumab significantly prolonged progression-free survival (co-primary end-point) versus chemotherapy in patients with advanced non-small-cell lung cancer (NSCLC) and high tumour mutational burden (TMB;  $\geq 10$  mutations/megabase). **AIM:** To evaluate patient-reported outcomes (PROs) in this population.

**METHODS:** Disease-related symptoms and general health status were assessed using the validated PRO questionnaires Lung Cancer Symptom Scale (LCSS) and EQ-5D, respectively. LCSS average symptom burden index (ASBI) and three-item global index (3-IGI) and EQ-5D visual analogue scale (VAS) and utility index (UI) scores and changes from baseline were analysed descriptively. Longitudinal changes were assessed by mixed-effect model repeated measures (MMRMs) and time to first deterioration/improvement analyses. **RESULTS:** In the high TMB population, PRO questionnaire completion rates were ~90% at baseline and >80% for most on-treatment assessments. During treatment, mean changes from baseline with nivolumab + ipilimumab showed early, clinically meaningful improvements in LCSS ASBI/3-IGI and EQ-5D VAS/UI; with chemotherapy, symptoms and health-related quality of life remained stable (LCSS ASBI/3-IGI, EQ-5D UI) or improved following induction (EQ-5D VAS).

MMRM-assessed changes in symptom burden were improved with nivolumab + ipilimumab versus chemotherapy. Symptom deterioration by week 12 was lower with nivolumab + ipilimumab versus chemotherapy (22.3% versus 35.0%; absolute risk reduction: 12.7% [95% confidence interval 2.4-22.5]), irrespective of discontinuation. Time to first deterioration was delayed with nivolumab + ipilimumab versus chemotherapy across LCSS and EQ-5D summary measures. **CONCLUSION:** First-line nivolumab + ipilimumab demonstrated early, sustained improvements in PROs versus chemotherapy in patients with advanced NSCLC and high TMB. **CLINICAL TRIAL REGISTRATION:** NCT02477826.

[Nivolumab for advanced non-small cell lung cancer patients with mild idiopathic interstitial pneumonia: A multicenter, open-label single-arm phase II trial.](#) Fujimoto D1, Yomota M2, Sekine A3, Morita M4, Morimoto T5, Hosomi Y2, Ogura T3, Tomioka H4, Tomii K6. Lung Cancer. 2019 Jun 3. pii: S0169-5002(19)30494-5. doi: 10.1016/j.lungcan.2019.06.001. [Epub ahead of print]

**OBJECTIVES:** The efficacy of nivolumab against metastatic non-small cell lung cancer (NSCLC) has been demonstrated; however, pneumonitis is relatively common and is a potentially life-threatening immune-related adverse event. Patients with idiopathic interstitial pneumonia (IIP) have a higher risk of pneumonitis and are generally excluded from clinical trials. Additionally, to date, a multicenter prospective trial for previously-treated NSCLC patients with IIP has not been performed. To fulfill this unmet medical need, we conducted a multicenter, open-label single-arm phase II trial to evaluate the efficacy and safety of nivolumab in NSCLC patients with mild IIP. **MATERIALS AND METHODS:** Eligible patients had previously-treated, inoperable NSCLC with mild IIPs. Mild IIP was defined as a predicted vital capacity of at least 80% and possible usual interstitial pneumonia (UIP) or inconsistent with UIP pattern by chest high-resolution computed tomography. Primary end point was the 6 months PFS rate and secondary end point was the safety of this therapy. **RESULTS:** Eighteen patients were enrolled in this trial. Six months PFS rate was 56%, response rate was 39%, and disease control rate was 72%. There were no treatment-related deaths. One drug-related grade 3/4 nonhematologic event (grade 3 neurotoxicity) was observed. Two patients had grade 2 pneumonitis which improved by corticosteroid therapy. **CONCLUSIONS:** Nivolumab could be an effective therapy for NSCLC patients with mild IIPs.

[Dacomitinib in the Management of Advanced Non-Small-Cell Lung Cancer.](#) Lau SCM1, Batra U2, Mok TSK3,4, Loong HH5,6,7. Drugs. 2019 Jun;79(8):823-831. doi: 10.1007/s40265-019-01115-y. The use of targeted therapy in the management of epidermal growth factor receptor (EGFR)-mutated non-small-cell lung cancer is an important milestone in the management of advanced lung cancer. There are several generations of EGFR tyrosine kinase inhibitors available for clinical use. Dacomitinib is a second-generation irreversible EGFR tyrosine kinase inhibitor with early-phase clinical studies showing efficacy in non-small-cell lung cancer. In the recently published ARCHER 1050 phase III study, dacomitinib given at 45 mg/day orally was superior to gefitinib, a first-generation reversible EGFR tyrosine kinase inhibitor, in improving both progression-free survival and overall survival when given as first-line therapy. There is no prospective evidence to support the use of dacomitinib as subsequent therapy in patients previously treated with chemotherapy or a first-generation EGFR tyrosine kinase inhibitor such as gefitinib and erlotinib. Dacomitinib has not demonstrated any benefit in unselected patients with non-small-cell lung cancer, and its use should be limited to those with known EGFR-sensitizing mutations. Dacomitinib is associated with increased toxicities of diarrhea, rash, stomatitis, and paronychia compared with first-generation EGFR inhibitors. Global quality of life was maintained when assessed in phase III studies. Overall, dacomitinib is an important first-line agent in EGFR-mutated non-small-cell lung cancer in otherwise fit patients whose toxicities can be well managed.

[PD-L1 for selecting non-small-cell lung cancer patients for first-line immuno-chemotherapy combination: a systematic review and meta-analysis.](#) Rossi A1, Noia VD2, Gkountakos A3, et al. Immunotherapy. 2019 Jul;11(10):921-930. doi: 10.2217/imt-2018-0198. Epub 2019 Jun 3. **AIM:** With the final aim to explore the first-line treatment options for non-small-cell lung cancer (NSCLC) patients, we performed a systematic review and literature-based meta-analysis of available clinical trials exploring immunotherapy in combination versus standard histology-based chemotherapy. **MATERIALS & METHODS:** We evaluated interactions according to type of treatment-add-on strategy: immunotherapy in combination versus standard chemotherapy-based regimens. Hazard ratio (HR) for overall survival (OS) and progression-free survival (PFS) were extracted and cumulated. **RESULTS:**

Seven trials (4278 patients) were included. The addition of immunotherapy to standard chemotherapy-based regimens significantly increased OS (HR 0.74;  $p = 0.001$ ) and PFS (HR 0.61;  $p < 0.0001$ ) compared with standard-of-care in NSCLC patients in first-line setting. **CONCLUSION:** Immunotherapy-based regimens constantly improved OS and PFS compared with chemotherapy in first-line treatment of nononcogene-addicted NSCLC.

**Five-Year Overall Survival for Patients With Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study.** Garon EB1, Hellmann MD2, Rizvi NA3, et al. *J Clin Oncol.* 2019 Jun 2;JCO1900934. doi: 10.1200/JCO.19.00934. [Epub ahead of print]

**PURPOSE:** Pembrolizumab monotherapy has demonstrated durable antitumor activity in advanced programmed death ligand 1 (PD-L1) -expressing non–small-cell lung cancer (NSCLC). We report 5-year outcomes from the phase Ib KEYNOTE-001 study. These data provide the longest efficacy and safety follow-up for patients with NSCLC treated with pembrolizumab monotherapy. **PATIENTS AND METHODS:** Eligible patients had confirmed locally advanced/metastatic NSCLC and provided a contemporaneous tumor sample for PD-L1 evaluation by immunohistochemistry using the 22C3 antibody. Patients received intravenous pembrolizumab 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks. Investigators assessed response per immune-related response criteria. The primary efficacy end point was objective response rate. Overall survival (OS) and duration of response were secondary end points. **RESULTS:** We enrolled 101 treatment-naïve and 449 previously treated patients. Median follow-up was 60.6 months (range, 51.8 to 77.9 months). At data cutoff–November 5, 2018–450 patients (82%) had died. Median OS was 22.3 months (95% CI, 17.1 to 32.3 months) in treatment-naïve patients and 10.5 months (95% CI, 8.6 to 13.2 months) in previously treated patients. Estimated 5-year OS was 23.2% for treatment-naïve patients and 15.5% for previously treated patients. In patients with a PD-L1 tumor proportion score of 50% or greater, 5-year OS was 29.6% and 25.0% in treatment-naïve and previously treated patients, respectively. Compared with analysis at 3 years, only three new-onset treatment-related grade 3 adverse events occurred (hypertension, glucose intolerance, and hypersensitivity reaction, all resolved). No late-onset grade 4 or 5 treatment-related adverse events occurred. **CONCLUSION:** Pembrolizumab monotherapy provided durable antitumor activity and high 5-year OS rates in patients with treatment-naïve or previously treated advanced NSCLC. Of note, the 5-year OS rate exceeded 25% among patients with a PD-L1 tumor proportion score of 50% or greater. Pembrolizumab had a tolerable long-term safety profile with little evidence of late-onset or new toxicity.

**Clinical Modality of Resistance and Subsequent Management of Patients with Advanced Non-small Cell Lung Cancer Failing Treatment with Osimertinib.** Mu Y1, Hao X1, Yang K2, Ma D1, Wang S1, Xu Z1, Li J3, Xing P4. *Target Oncol.* 2019 Jun;14(3):335-342. doi: 10.1007/s11523-019-00644-6.

**BACKGROUND:** The third-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) osimertinib has become the standard treatment for patients with pretreated EGFR-mutated non-small cell lung cancer (NSCLC) who acquire the T790M resistance mutation. However, no standard treatment after osimertinib failure has been established. **OBJECTIVE:** This study was undertaken to explore the clinical resistance modality upon failure of osimertinib therapy and to assess post-progression treatments in a real-world setting. **PATIENTS AND METHODS:** Medical data were retrospectively collected in our cancer center of patients with advanced NSCLC treated between 1 March 2017 and 1 July 2018, and who developed resistance to osimertinib. **RESULTS:** A total of 65 patients were analyzed. Clinical resistance modality varied among patients: 15 (23.1%) with local progression, 29 (44.6%) with gradual progression, and 21 (32.3%) with dramatic progression. Most patients experienced intrathoracic progression only (40/65, 61.5%), while ten (15.4%) cases presented intracranial failure only. Upon progressive disease, 20 patients (30.8%) received subsequent chemotherapy, and showed a trend for

longer median overall survival (OS) than in those receiving a non-chemotherapy regimen (25.0 vs. 11.8 months,  $p = 0.106$ ). Thirty-nine patients (60.0%) continued osimertinib beyond progression with a median post-progression treatment duration of 4.1 months. No significant difference in median OS was seen between patients who continued osimertinib and those who discontinued osimertinib (18.9 vs. 15.1 months,  $p = 0.802$ ). In subgroup analyses, OS was improved in patients who experienced dramatic progression and were treated with chemotherapy, but data were immature for patients with local or gradual progression. **CONCLUSIONS:** Chemotherapy could be an effective option after osimertinib failure in unselected patients.

[Effectiveness of first-line treatments in metastatic squamous non-small-cell lung cancer.](#) Levy BP1, Signorovitch JE2, Yang H2, Patterson-Lomba O2, Xiang CQ2, Parisi M3. *Curr Oncol.* 2019 Jun;26(3):e300-e308. doi: 10.3747/co.26.4485. Epub 2019 Jun 1.

**BACKGROUND:** Commonly used first-line (1L) chemotherapies for patients with advanced squamous-cell lung cancer (scc) include gemcitabine-platinum (gp), nab-paclitaxel-carboplatin (nabpc), and sb-paclitaxel-carboplatin (sbpc) regimens. However, no head-to-head trials have compared those treatments. In the present study, we compared the efficacy of 1L gp, nabpc, and sbpc in patients with scc and in patients with scc who subsequently received second-line (2L) immunotherapy. **METHODS:** Medical records of patients who initiated the 1L treatments of interest between June 2014 and October 2015 were reviewed by 132 participating physicians. Kaplan-Meier curves were used to evaluate overall survival (os), progression-free survival (pfs), and treatment discontinuation (td), and then Cox proportional hazards regression was used to compare the results between the cohorts. **RESULTS:** Medical records of 458 patients with scc receiving gp ( $n = 139$ ), nabpc ( $n = 159$ ), or sbpc ( $n = 160$ ) as 1L therapy were reviewed. Median os was longer with nabpc (23.9 months) than with gp (16.9 months; adjusted hazard ratio vs. nabpc: 1.55;  $p < 0.05$ ) and with sbpc (18.3 months; adjusted hazard ratio: 1.42;  $p = 0.10$ ). No differences were observed in pfs (median pfs: 8.8, 8.0, and 7.6 months for gp, nabpc, and sbpc respectively; log-rank  $p = 0.76$ ) or in td (median td: 5.5, 5.7, and 4.6 months respectively;  $p = 0.65$ ). For patients who subsequently received 2L immunotherapy, no differences in os were observed (median os: 27.3, 25.0, and 23.0 months respectively;  $p = 0.59$ ). **CONCLUSIONS:** In a nationwide sample of scc patients, longer median os was associated with 1L nabpc than with gp and sbpc. Median os for all 1L agents considered was similar in the subgroup of patients who sequenced to a 2L immunotherapy.

[Adjuvant Chemotherapy Increases Programmed Death-Ligand 1 \(PD-L1\) Expression in Non-small Cell Lung Cancer Recurrence.](#) Lacour M1, Hiltbrunner S2, Lee SY2, Soltermann A3, Rushing EJ4, Soldini D3, Weder W1, Curioni-Fontecedro A5. *Clin Lung Cancer.* 2019 Jun 5. pii: S1525-7304(19)30140-8. doi: 10.1016/j.clc.2019.05.013. [Epub ahead of print]

**BACKGROUND:** Despite recent studies, the effect of chemotherapy on programmed death-ligand 1 (PD-L1) expression remains controversial. In this study, we investigated whether PD-L1 expression is affected by platinum-based chemotherapy. Furthermore, we evaluated correlation of PD-L1 expression with oncogenic driver alterations. **MATERIALS AND METHODS:** We retrospectively evaluated changes in PD-L1 expression by immunohistochemical (IHC) analysis in resected specimens and in biopsies at non-small cell lung cancer recurrence in patients receiving or not adjuvant chemotherapy after surgical resection. Four IHC score groups were defined: TC0  $< 1\%$ , T  $\geq 1\%$  and  $< 5\%$ , TC2  $\geq 5\%$  and  $< 50\%$ , and TC3  $\geq 50\%$ . **RESULTS:** Thirty-six patients with adenocarcinoma were included. Twenty (56%) patients underwent adjuvant chemotherapy, and 16 (44%) patients did not receive adjuvant chemotherapy. PD-L1 expression was present in 10 (28%) of 36 initial tumor specimens. From patients receiving adjuvant chemotherapy, 7 (35%) of 20 tumor biopsies showed significant upregulation in PD-L1 expression at recurrence. In contrast, from patients with no adjuvant therapy, only 2 (12.5%) of 16 showed a change in PD-L1 expression. Six (17%) of 36 patients were PD-L1-negative in the primary

tumor and turned positive at recurrence. KRAS mutation was present in 70% of patients expressing PD-L1. **CONCLUSION:** PD-L1 expression in non-small cell lung cancer can change from primary to recurrence, implicating the need for re-biopsy at recurrence. Moreover, chemotherapy might increase expression of PD-L1, supporting a combinatorial therapy with chemotherapy and anti-PD(L)1 treatment.

[Adjuvant Chemotherapy Increases Programmed Death-Ligand 1 \(PD-L1\) Expression in Non-small Cell Lung Cancer Recurrence.](#) Lacour M1, Hiltbrunner S2, Lee SY2, Soltermann A3, Rushing EJ4, Soldini D3, Weder W1, Curioni-Fontecedro A5. Clin Lung Cancer. 2019 Jun 5. pii: S1525-7304(19)30140-8. doi: 10.1016/j.clcc.2019.05.013. [Epub ahead of print]

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## NSCLC - RADIOTHERAPY

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[Epidermal growth factor receptor mutations: association with favorable local tumor control following Gamma Knife radiosurgery in patients with non-small cell lung cancer and brain metastases.](#) Lee CC1,2,3, Hsu SPC1,2, et al. J Neurosurg. 2019 Jun 21:1-8. doi: 10.3171/2019.4.JNS19446. [Epub ahead of print]

**OBJECTIVE:** The presence of epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer (NSCLC) has been associated with elevated radiosensitivity in vitro. However, results from clinical studies on radiosensitivity in cases of NSCLC with EGFR mutations are inconclusive. This paper presents a retrospective analysis of patients with NSCLC who underwent regular follow-up imaging after radiotherapy for brain metastases (BMs). The authors also investigated the influence of EGFR mutations on the efficacy of Gamma Knife radiosurgery (GKRS). **METHODS:** This study included 264 patients (1069 BMs) who underwent GKRS treatment and for whom EGFR mutation status, demographics, performance status, and tumor characteristics were available. Radiological images were obtained at 3 months after GKRS and at 3-month intervals thereafter. Kaplan-Meier plots and Cox regression analysis were used to correlate EGFR mutation status and other clinical features with tumor control and overall survival. **RESULTS:** The tumor control rates and overall 12-month survival rates were 87.8% and 65.5%, respectively. Tumor control rates in the EGFR mutant group versus the EGFR wild-type group were 90.5% versus 79.4% at 12 months and 75.0% versus 24.5% at 24 months. During the 2-year follow-up period after SRS, the intracranial response rate in the EGFR mutant group was approximately 3-fold higher than that in the wild-type group ( $p < 0.001$ ). Cox regression multivariate analysis identified EGFR

mutation status, extracranial metastasis, primary tumor control, and prescribed margin dose as predictors of tumor control ( $p = 0.004$ ,  $p < 0.001$ ,  $p = 0.004$ , and  $p = 0.026$ , respectively). Treatment with a combination of GKRS and tyrosine kinase inhibitors (TKIs) was the most important predictor of overall survival ( $p < 0.001$ ). **CONCLUSIONS:** The current study demonstrated that, among patients with NSCLC-BMs, EGFR mutations were independent prognostic factors of tumor control. It was also determined that a combination of GKRS and TKI had the most pronounced effect on prolonging survival after SRS. In select patient groups, treatment with SRS in conjunction with EGFR-TKIs provided effective tumor control for NSCLC-BMs.

### [Timing of adjuvant radiation therapy and survival outcomes after surgical resection of intracranial non-small cell lung cancer metastases.](#)

Sheppard JP1, Prashant GN1, Chen CHJ1, et al. Clin Neurol Neurosurg. 2019 Jun 15;183:105389. doi: 10.1016/j.clineuro.2019.105389. [Epub ahead of print]

**OBJECTIVE:** To investigate if delay of adjuvant radiotherapy (ART) beyond 6 post-operative weeks affects survival outcomes in patients undergoing craniotomy or craniectomy for resection of non-small cell lung cancer (NSCLC) intracranial metastases. **PATIENTS AND METHODS:** We performed a retrospective analysis of 28 patients undergoing resection of intracranial metastases and ART at our institution from 2001 to 2016. We assessed survival outcomes for patients who received delayed versus non-delayed ART, as well as associated risk factors. **RESULTS:** Among 28 patients, 8 (29%) had delayed ART beyond 6 post-operative weeks. Fifteen received stereotactic radiotherapy (SRT), 8 (29%) received whole brain radiotherapy (WBRT), and 5 (18%) received combination WBRT + SRT. There were no significant differences in ART modality or dosing, age, sex, number of intracranial metastases, primary metastasis volume, rates of chemotherapy, extracranial metastases, or post-operative functional scores between groups. Expected post-operative survival was shorter with delayed ART (7 months versus 28 months,  $P = 0.01$ ). The most common reason for delayed ART was complicated post-operative course ( $n = 3.38\%$ ). Significant risk factors for delayed ART included non-routine discharge ( $P = 0.01$ ) and additional invasive procedures between surgery and ART start date ( $P = 0.02$ ). **CONCLUSIONS:** Our results suggest delayed ART in patients undergoing surgical resection of intracranial NSCLC metastases is associated with shorter overall survival. However, risk factors for delayed ART, including non-routine discharge and the need for additional invasive procedures, may have in themselves reflected poorer clinical courses that may have also contributed to the observed survival differences.

### [Quantification of global lung inflammation using volumetric 18F-FDG PET/CT parameters in locally advanced non-small-cell lung cancer patients treated with concurrent chemoradiotherapy: a comparison of photon and proton radiation therapy.](#)

Rice SR1, Saboury B2, Houshmand S2, et al. Nucl Med Commun. 2019 Jun;40(6):618-625. doi: 10.1097/MNM.0000000000000997.

**INTRODUCTION:** Radiation pneumonitis is a major dose-limiting complication in thoracic radiation therapy (RT) and presents clinically in the first few months after RT. We evaluated the feasibility of quantifying pulmonary parenchymal glycolysis (PG) as a surrogate of global lung inflammation and radiation-induced pulmonary toxicity using a novel semiautomatic lung segmentation technique in non-small-cell lung cancer (NSCLC) patients and compared PG in patients treated with photon or proton RT. **PATIENTS AND METHODS:** We evaluated 18 consecutive locally advanced NSCLC patients who underwent pretreatment and post-treatment F-FDG PET/CT treated with definitive (median: 66.6 Gy; 1.8 Gy fractions) photon or proton RT between 2010 and 2014. Lung volume segmentation was conducted using 3D Slicer by performing simple thresholding. Pulmonary PG was calculated by summing F-FDG uptake in the whole lung. **RESULTS:** In nine patients treated with photon RT, significant increases in PG in both ipsilateral (mean difference:  $1400 \pm 510$ ;  $P = 0.02$ ) and contralateral (mean difference:  $1200 \pm 450$ ;  $P = 0.03$ ) lungs were noted. In nine patients treated with proton therapy, no increase in pulmonary PG was observed in either the ipsilateral ( $P = 0.30$ ) or contralateral lung ( $P = 0.98$ ).

**CONCLUSION:** We observed a significant increase in global lung inflammation bilaterally as measured by quantification of PG. However, no significant change in global lung inflammation was noted after proton therapy. Future larger studies are needed to determine whether this difference correlates with lower risks of radiation pneumonitis in NSCLC patients treated with proton therapy.

**[Comparison Between Stereotactic and Conventional Radiotherapy for Solitary Lung Tumor After Resection of Lung Cancer.](#)** Takahashi S1, Go T2, Anada M3, Kinoshita T3, Nishide T3, Yokomise H2, Shibata T3. *Anticancer Res.* 2019 Jun;39(6):2957-2962. doi: 10.21873/anticancer.13426.

**BACKGROUND/AIM:** We retrospectively compared stereotactic body radiotherapy (SBRT) with conventionally fractionated radiotherapy (CFRT) for a solitary lung tumor after resection of a non-small cell lung cancer (NSCLC), due to a lack of data concerning whether SBRT or CFRT is more effective in this setting. **PATIENTS AND METHODS:** SBRT using 48 Gy in 4 fractions was administered to 15 patients with a peripheral tumor (SBRT group). CFRT using 66-70 Gy in 33-35 fractions was administered to 11 patients with a central tumor (CFRT group). **RESULTS:** The median follow-up time was 32 months (range: 9-79 months). The 3-year overall survival rates in SBRT and CFRT groups were 81% and 40%, respectively ( $p=0.008$ ). The 3-year local control rates in SBRT and CFRT groups were 83% and 35%, respectively ( $p=0.035$ ). Regarding toxicities, no significant differences were found between the two groups. **CONCLUSION:** Compared to CFRT, SBRT may be more effective in solitary-lung-tumor patients after the complete resection of an NSCLC as with inoperable-stage I-NSCLC patients.

**[A Prospective Study of Magnetic Resonance Imaging Assessment of Post-radiation Changes Following Stereotactic Body Radiation Therapy for Non-small Cell Lung Cancer.](#)** Munoz-

Schuffenegger P1, Kandel S2, Alibhai Z3, Hope A1, Bezzak A1, Sun A1, Simeonov A1, Cho BCJ1, Giuliani M4. *Clin Oncol (R Coll Radiol).* 2019 Jun 5. pii: S0936-6555(19)30206-7. doi: 10.1016/j.clon.2019.05.014. [Epub ahead of print]

**AIMS:** Follow-up computed tomography scans after lung stereotactic body radiation therapy (SBRT) are difficult to interpret due to the presence of benign fibrosis, which can make the detection of local recurrence difficult. The objective of this study was to determine the feasibility of a novel thoracic magnetic resonance imaging (MRI) protocol incorporating diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) imaging for the assessment of the treated lung parenchyma after SBRT. **MATERIALS AND METHODS:** On a prospective trial, post-treatment MR images were acquired in 30 patients treated with SBRT (divided into three different cohorts according to the likelihood of local recurrence as per an expert panel). These images were assessed by an expert thoracic radiologist blind to clinical data, who indicated local recurrence in a dichotomous manner. Local recurrence was confirmed by biopsy or subsequent growth on follow-up computed tomography scans. **RESULTS:** Thirty patients underwent MRI as part of this study; 27/30 patients were analysable for local recurrence. MRI was conducted at a median of 27.3 months (range 6.5-71 months) from SBRT. No side-effects resulted from either MRI or contrast administration. At a median follow-up time of 45 months after treatment, three local recurrence episodes have occurred. MRI assessment diagnosed seven patients as having a local recurrence, which was later confirmed in three and did not miss any of the true local recurrences. When comparing apparent diffusion coefficient (ADC) values according to local recurrence, the mean ADC value for the local recurrence-free group was  $1770 \times 10^{-3} \text{ mm}^2/\text{s}$  (range  $1038-3105 \times 10^{-3} \text{ mm}^2/\text{s}$ ) versus  $981 \times 10^{-3} \text{ mm}^2/\text{s}$  (range  $926.6-1065 \times 10^{-3} \text{ mm}^2/\text{s}$ ) for the local recurrence group ( $P = 0.0014$ ).

**CONCLUSIONS:** A novel 3.0 T MRI protocol incorporating DWI and DCE was feasible and confirmed the suspicion of local recurrence in patients with highly suspicious computed tomography scans. This imaging tool could potentially aid in selecting patients for salvage treatment after local SBRT failure. Future work should be pursued to validate these findings.

[Incidence of radionecrosis in single-fraction radiosurgery compared with fractionated radiotherapy in the treatment of brain metastasis.](#) Donovan EK1, Parpia S2, Greenspoon JN1. *Curr Oncol.* 2019 Jun;26(3):e328-e333. doi: 10.3747/co.26.4749. Epub 2019 Jun 1.

**INTRODUCTION:** Radiation-induced brain necrosis ["radionecrosis" (rn)] is a relatively uncommon but potentially severe adverse effect of stereotactic radiosurgery (srs) for brain metastasis. Although dose, volume, and hypofractionation have been suggested to affect rn rates, patient and treatment variability in this population make it difficult to clearly delineate the risk. We set out to establish the effect of fractionation on rn rates by reviewing patients receiving simultaneous multi-fraction and single-fraction treatment at our centre. **METHODS:** Patients receiving simultaneous (within 1 month) 1-fraction (ssrs) and 3-fraction (fsrs) radiosurgery treatments during 2012-2015 were identified in our institution's database. Serial post-srs magnetic resonance imaging (mri) was reviewed to determine rn and local recurrence. The effect of maximum dose, volume, whole-brain radiotherapy (wbrt), and fractionation on rn development was assessed using logistic regression for paired data. Results are reported using odds ratios (ors) and corresponding 95% confidence intervals (cis). **RESULTS:** Of 90 patients identified, 22 had at least a 6-month mri follow-up. Median follow-up was 320 days. The most common primary tumour type was non-small-cell lung cancer, followed by breast and rectal cancer. Radionecrosis developed in 16 patients [21 of 62 lesions (34%), with 4 being symptomatic (20%)]. Of the 21 lesions in which rn developed, 11 received 3 fractions, and 10 received 1 fraction. The or for the association between the incidence of rn and maximum dose was 1.0 (95% ci: 0.9 to 1.1); for fractionation it was 1.0 (95% ci: 0.3 to 3.6); for previous wbrt, it was 0.4 (95% ci: 0.2 to 1.2); and for a 10-unit increase in volume, it was 3.1 (95% ci: 1.0 to 9.6). Local recurrence developed in 8 patients (12%), 6 of whom belonged to the ssrs group. **CONCLUSIONS:** Our results indicate that patients receiving srs for multiple brain metastases experience a higher rate of rn than is reported in the literature and poorer survival despite having equivalent local control. Maximum dose did not appear to be associated with rn risk in our cohort, but volume was significantly associated with rn risk. Although fractionated treatment did not directly lower the rate of rn in this population, it might have played a role in reducing the magnitude of the rn risk in large-volume lesions. Further investigation will help to delineate optimal dose and fractionation so as to minimize rn while maintaining local control in this group.

[Long term outcome after 48 Gy stereotactic ablative body radiotherapy for peripheral stage I non-small cell lung cancer.](#) Dubaere E1, Goffaux M2, Wanet M1, et al. *BMC Cancer.* 2019 Jun 28;19(1):639. doi: 10.1186/s12885-019-5863-2.

**BACKGROUND:** To evaluate the outcome of patients treated with stereotactic ablative body radiotherapy (SABR) with curative intent for stage I non-small cell lung cancer (NSCLC) with regard to local, regional and distant tumor control, disease-free survival (DFS), overall survival (OS) and toxicity. **METHODS:** Data of 300 patients treated with SABR for NSCLC cancer for the period of November 2007 to June 2016 were retrospectively analyzed. Of which, 189 patients had single primary lung lesion and were included in the study. The prescribed dose for the tumor was 48 Gy, given in 12 Gy  $\times$  4 fractions for all patients. In 2010, an improved protocol was established in advanced technology for the planning CT, dose calculation and imaging. Cumulative incidence function (CIF) of local, regional, distant or any recurrences were computed using competing risk analysis with death as a competing event. Survivals (DFS and OS) were estimated using the Kaplan-Meier method and Cox proportional regression was used for comparisons. Toxicities were graded according to the common terminology criteria for adverse events version 4.0 (CTCAE v.4). **RESULTS:** Diagnosis was histologically confirmed in 42% of the patients (N = 80). At 1, 2 and 4 years, the cumulative incidence function (CIF) of local relapses were 8% [4-13%], 15% [10-21%] and 18% [12-25%], the CIF of regional relapses were 4% [2-8%], 10% [6-16%] and 12% [8-19%], the CIF of distant relapses were 9% [5-14%], 15% [11-22%] and 20% [15-28%] and the CIF of



any relapses were 14% [10-20%], 28% [22-36%], 34% [27-43%], respectively. After 1, 2 and 4 years, the OS rates were 83% [95% CI: 78-89%] (N = 128), 65% [95% CI: 57-73%] (N = 78) and 37% [95% CI: 29-47%] (N = 53), respectively. The median survival time was 37 months. The DFS after 1, 2 and 4 years reached 75% [95% CI: 68-81%] (N = 114), 49% [95% CI: 42-58%] (N = 60) and 31% [95% CI: 24-41%] (N = 41), respectively. No grade 4 or 5 toxicity was observed. **CONCLUSIONS:** We observed a long-term local control and survival after SABR for peripheral stage I NSCLC in this large series of patients with the expected low toxicity.

### **Cardiac Radiation Dose, Cardiac Disease, and Mortality in Patients With Lung Cancer.**

Atkins KM1, Rawal B2, Chaunzwa TL3, et al. J Am Coll Cardiol. 2019 Jun 18;73(23):2976-2987. doi: 10.1016/j.jacc.2019.03.500.

**BACKGROUND:** Radiotherapy-associated cardiac toxicity studies in patients with locally advanced non-small cell lung cancer (NSCLC) have been limited by small sample size and nonvalidated cardiac endpoints. **OBJECTIVES:** The purpose of this analysis was to ascertain whether cardiac radiation dose is a predictor of major adverse cardiac events (MACE) and all-cause mortality (ACM). **METHODS:** This retrospective analysis included 748 consecutive locally advanced NSCLC patients treated with thoracic radiotherapy. Fine and Gray and Cox regressions were used to identify predictors for MACE and ACM, adjusting for lung cancer and cardiovascular prognostic factors, including pre-existing coronary heart disease (CHD). **RESULTS:** After a median follow-up of 20.4 months, 77 patients developed  $\geq 1$  MACE (2-year cumulative incidence, 5.8%; 95% confidence interval [CI]: 4.3% to 7.7%), and 533 died. Mean radiation dose delivered to the heart (mean heart dose) was associated with a significantly increased risk of MACE (adjusted hazard ratio [HR]: 1.05/Gy; 95% CI: 1.02 to 1.08/Gy;  $p < 0.001$ ) and ACM (adjusted HR: 1.02/Gy; 95% CI: 1.00 to 1.03/Gy;  $p = 0.007$ ). Mean heart dose ( $\geq 10$  Gy vs.  $< 10$  Gy) was associated with a significantly increased risk of ACM in CHD-negative patients (178 vs. 118 deaths; HR: 1.34; 95% CI: 1.06 to 1.69;  $p = 0.014$ ) with 2-year estimates of 52.2% (95% CI: 46.1% to 58.5%) versus 40.0% (95% CI: 33.5% to 47.4%); but not among CHD-positive patients (112 vs. 82 deaths; HR: 0.94; 95% CI: 0.70 to 1.25;  $p = 0.66$ ) with 2-year estimates of 54.6% (95% CI: 46.8% to 62.7%) versus 50.8% (95% CI: 41.5% to 60.9%), respectively ( $p$  for interaction = 0.028). **CONCLUSIONS:** Despite the competing risk of cancer-specific death in locally advanced NSCLC patients, cardiac radiation dose exposure is a modifiable cardiac risk factor for MACE and ACM, supporting the need for early recognition and treatment of cardiovascular events and more stringent avoidance of high cardiac radiotherapy dose.

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## **SMALL CELL LUNG CANCER - SCLC**

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**Role of prophylactic cranial irradiation for elderly patients with limited-disease small-cell lung cancer: inverse probability of treatment weighting using propensity score.** Kim TG1, Pyo H2, Ahn YC2, Noh JM2, Oh D2. J Radiat Res. 2019 Jun 5. pii: rrz040. doi: 10.1093/jrr/rrz040. [Epub ahead of print]

Studies of prophylactic cranial irradiation (PCI) focused on elderly patients with small-cell lung cancer (SCLC) are rarely conducted. We aimed to identify whether there is a survival benefit of prophylactic cranial irradiation (PCI) in elderly patients using a single institution's retrospective data. A total of 234 patients with limited-disease SCLC (LD-SCLC) treated with thoracic chemoradiotherapy were evaluated; of these, 139 patients received PCI. To minimize treatment selection bias, patients were adjusted using the propensity score on factors associated with receipt of PCI. Cox proportional hazard model and Kaplan-Meier analyses were used to identify which subgroup may benefit from PCI. Median follow-up time was 22 months (range 1-150 months). PCI was associated with favorable brain metastasis-free survival, disease-specific survival, and overall survival in the entire population [hazard ratios (HR) 0.588, 95%

confidence interval (CI) 0.338-1.024,  $P = 0.060$ ; HR 0.477, 95% CI 0.331-0.687,  $P < 0.001$ ; HR 0.543, 95% CI 0.383-0.771,  $P = 0.001$ , respectively). However, PCI had no significant relationship with overall survival in patients aged  $\geq 65$  years with cT3-4 disease and/or females gender (HR 0.817, 95% CI 0.098-6.849,  $P = 0.853$ ; HR 1.082, 95% CI 0.114-10.227,  $P = 0.946$ , respectively). The benefits and risks of PCI in elderly patients with LD-SCLC need to be scrutinized, especially in those with high T stage tumors and/or females.

**Improved prognosis and increased tumor infiltrating lymphocytes in small cell lung cancer patients with neurologic paraneoplastic syndromes.** Iams WT1, Shiuan E2, Meador CB2, et al. J Thorac Oncol. 2019 Jun 12. pii: S1556-0864(19)30463-0. doi: 10.1016/j.jtho.2019.05.042. [Epub ahead of print]

**BACKGROUND:** Approximately 10% of patients with small cell lung cancer (SCLC) develop a paraneoplastic syndrome (PNS). Neurologic PNS are thought to improve prognosis, which we hypothesized is related to increased tumor infiltrating lymphocytes and immune recognition.

**METHODS:** We queried 2,512,042 medical records from a single institution to identify SCLC patients with and without PNS and performed manual, retrospective chart review. We then performed multiplexed fluorescence immunohistochemistry and automated quantitative analysis (AQUA® Technology) on tumors to assess CD3, CD4, and CD8 T cell infiltrates and PD-1/PD-L1 interactions. T cell infiltrates and PD-1/PD-L1 interaction scores were compared among patients with neurologic PNS, endocrinologic PNS, and a control group without PNS. Clinical outcomes were analyzed using the Kaplan-Meier method and Cox proportional-hazards models. **RESULTS:** We evaluated 145 SCLC patients: 55 with PNS (25 neurologic and 30 endocrinologic) and 90 controls. Patients with neurologic PNS experienced improved overall survival (OS) compared to patients with endocrinologic PNS and controls (median OS 24mo vs. 12mo vs. 13mo, respectively). Of the 145 patients, we identified tumor tissue from 34 patients that was adequate for AQUA analysis. Among 37 specimens from these 34 patients, patients with neurologic PNS had increased T cell infiltrates ( $p=0.033$ ) and PD-1/PD-L1 interaction ( $p=0.014$ ) compared to tumors from patients with endocrinologic PNS or controls. **CONCLUSION:** Tumor tissue from patients with SCLC with neurologic PNS demonstrated increased tumor infiltrating lymphocytes and PD-1/PD-L1 interaction consistent with an inflamed tumor microenvironment.

**PET Imaging of a [18F]-radiolabeled PARP Inhibitor Monitors the Therapeutic Efficacy of Talazoparib in Small Cell Lung Cancer Patient-Derived Xenografts.** Laird J1, Lok BH2, Carney B3, Kossatz S4, de Stanchina E5, Reiner T6, Poirier JT7, Rudin CM8. J Thorac Oncol. 2019 Jun 10. pii: S1556-0864(19)30453-8. doi: 10.1016/j.jtho.2019.05.032. [Epub ahead of print]

**INTRODUCTION:** Inhibitors of poly-(ADP)-ribose polymerase (PARP) are promising therapeutics for small cell lung cancer (SCLC). We tested whether PARP inhibitor (PARPi) target engagement as measured by a radiolabeled PARP inhibitor ([18F]PARPi) has the potential to predict drug efficacy in vivo. **METHODS:** Tumor growth inhibition during daily talazoparib treatment was evaluated in mice engrafted with SCLC patient-derived xenografts to evaluate talazoparib efficacy at multiple doses. Mice were intravenously injected with [18F]PARPi radiotracer at multiple time points after single doses of oral talazoparib to quantitatively assess the extent to which talazoparib could reduce tumor radiotracer uptake and PET/CT activity. Tumors were harvested and tumor PAR level was measured by ELISA.

**RESULTS:** A dose range of talazoparib with differential therapeutic efficacy was established, with significant delay in time to reach 1000 mm<sup>3</sup> for tumors treated with 0.3 mg/kg ( $p=0.02$ ) but not 0.1 mg/kg talazoparib. On PET/CT with [18F]PARPi, reduction in [18F]PARPi uptake after talazoparib dosing was consistent with talazoparib clearance, with reduction in PET activity attenuating over 24 hours. Talazoparib target engagement, measured by maximum tumor PET uptake, increased in a dose dependent manner (3.9% vs. 2.1% ID/g for 0.1 and 0.3 mg/kg at 3 hours post-talazoparib,  $p=0.003$ ) and correlated with PARP enzymatic activity among individual tumors as measured by total tumor PAR ( $p=0.04$ ,  $R=0.62$ )

at 1 hour post-talazoparib). **CONCLUSIONS:** PET imaging using [18F]PARPi has the potential to be a powerful tool in treatment monitoring by assessing PARP inhibitor target engagement in real-time.

**Initial management of small-cell lung cancer (limited- and extensive-stage) and the role of thoracic radiotherapy and first-line chemotherapy: a systematic review.** Sun A1, Durocher-Allen LD2, Ellis PM3,4, Ung YC5, Goffin JR3, Ramchandrar K6, Darling G7. *Curr Oncol.* 2019 Jun;26(3):e372-e384. doi: 10.3747/co.26.4481. Epub 2019 Jun 1.

**BACKGROUND:** Patients with limited-stage (ls) or extensive-stage (es) small-cell lung cancer (sclc) are commonly given platinum-based chemotherapy as first-line treatment. Standard chemotherapy for patients with ls sclc includes a platinum agent such as cisplatin combined with the non-platinum agent etoposide. The objective of the present systematic review was to investigate the efficacy of adding radiotherapy to chemotherapy in patients with es sclc and to determine the appropriate timing, dose, and schedule of chemotherapy or radiation for patients with sclc. **METHODS:** The medline and embase databases were searched for randomized controlled trials (rcts) comparing treatment with radiotherapy plus chemotherapy against treatment with chemotherapy alone in patients with es sclc. Identified rcts were also included if they compared various timings, doses, and schedules of treatment for patients with es sclc or ls sclc. **RESULTS:** Sixty-four rcts were included. In patients with ls sclc, overall survival was greatest with platinum-etoposide compared with other chemotherapy regimens. In patients with es sclc, overall survival was greatest with chemotherapy containing platinum-irinotecan than with chemotherapy containing platinum-etoposide (hazard ratio: 0.84; 95% confidence interval: 0.74 to 0.95;  $p = 0.006$ ). The addition of radiation to chemotherapy for patients with es sclc showed mixed results. There was no conclusive evidence that the timing, dose, or schedule of thoracic radiation affected treatment outcomes in sclc. **CONCLUSIONS:** In patients with ls sclc, cisplatin-etoposide plus radiotherapy should remain the standard therapy. In patients with es sclc, the evidence is insufficient to recommend the addition of radiotherapy to chemotherapy as standard practice to improve overall survival. However, on a case-by-case basis, radiotherapy might be added to reduce local recurrence. The most commonly used chemotherapy is platinum-etoposide; however, platinum-irinotecan can be considered.

**MYC-driven small cell lung cancer is metabolically distinct and vulnerable to arginine depletion.** Chalishazar MD1, Wait SJ2, Huang F3, et al. *Clin Cancer Res.* 2019 Jun 4. pii: clincanres.4140.2018. doi: 10.1158/1078-0432.CCR-18-4140. [Epub ahead of print]

**PURPOSE:** Small cell lung cancer (SCLC) has been treated clinically as a homogeneous disease, but recent discoveries suggest that SCLC is heterogeneous. Whether metabolic differences exist among SCLC subtypes is largely unexplored. In this study, we aimed to determine whether metabolic vulnerabilities exist between SCLC subtypes that can be therapeutically exploited. **EXPERIMENTAL DESIGN:** We performed steady state metabolomics on tumors isolated from distinct GEMMs representing the MYC and MYCL-driven subtypes of SCLC. Using genetic and pharmacological approaches, we validated our findings in chemo-naive and resistant human SCLC cell lines, multiple GEMMs, four human cell line xenografts, and four newly-derived PDX models. **RESULTS:** We discover that SCLC subtypes driven by different MYC family members have distinct metabolic profiles. MYC-driven SCLC preferentially depends on arginine-regulated pathways including polyamine biosynthesis and mTOR pathway activation. Chemo-resistant SCLC cells exhibit increased MYC expression and similar metabolic liabilities as chemo-naive MYC-driven cells. Arginine depletion with pegylated arginine deiminase (ADI-PEG 20) dramatically suppresses tumor growth and promotes survival of mice specifically with MYC-driven tumors, including in GEMMs, human cell line xenografts, and a PDX from a relapsed patient. Finally, ADI-PEG 20 is significantly more effective than the standard of care chemotherapy. **CONCLUSIONS:** These data identify metabolic heterogeneity within SCLC and suggest arginine deprivation as a subtype-specific therapeutic vulnerability for MYC-driven SCLC.

[Potential immune escape mechanisms underlying the distinct clinical outcome of immune checkpoint blockades in small cell lung cancer.](#)

Tian Y1, Zhai X2,3, Han A3, Zhu H4,5, Yu J6,7. J Hematol Oncol. 2019 Jun 28;12(1):67. doi: 10.1186/s13045-019-0753-2.

Small cell lung cancer (SCLC) is one of the deadliest cancer types in the world. Despite the high response rate to frontline platinum-containing doublets, relapse is inevitable for the majority of patients and the prognosis is poor. Topotecan, which has limited efficacy, has remained the standard second-line therapy for approximately three decades. Although SCLC has a high mutation burden, the clinical efficacy of immune checkpoint blockades (ICBs) in SCLC is far less pronounced than that in non-small cell lung cancer (NSCLC). Only atezolizumab in combination with chemotherapy improved overall survival over chemotherapy alone in the phase III CheckMate 133 trial and has recently received FDA approval as first-line therapy. Most studies concerning ICBs in SCLC are limited to early-phase studies and found that ICBs were not superior to traditional chemotherapy. Why is there such a large difference between SCLC and NSCLC? In this review, comparative analyses of previous studies indicate that SCLC is even more immunodeficient than NSCLC and the potential immune escape mechanisms in SCLC may involve the low expression of PD-L1 and the downregulation of major histocompatibility complex (MHC) molecules and regulatory chemokines. In consideration of these immune dysfunctions, we speculate that chemotherapy and radiotherapy prior to immunotherapy, the combination of ICBs with antiangiogenic treatment, and selecting tumor mutation burden in combination with PD-L1 expression as biomarkers could be promising strategies to improve the clinical efficacy of immunotherapy for SCLC.

[Comprehensive genomic profiling of small cell lung cancer in Chinese patients and the implications for therapeutic potential.](#)

Hu J1,2, Wang Y3, Zhang Y4, Yu Y4, Chen H4, Liu K4, Yao M4, Wang K4,5, Gu W6,7, Shou T1,2. Cancer Med. 2019 Jun 14. doi: 10.1002/cam4.2199. [Epub ahead of print]

**BACKGROUND:** Small cell lung cancer (SCLC) is one of the deadliest malignancies and accounts for nearly 15% of lung cancers. Previous study had revealed the genomic characterization of SCLC in Western patients. However, little is known about that in Chinese SCLC patients. **METHODS:** Formalin-fixed paraffin-embedded tumor tissues and matched blood samples from 122 Chinese SCLC patients were collected for next generation sequencing to detect 450 cancer-related genes. All pathological diagnoses were confirmed by independent pathologists. **RESULTS:** The most frequently altered genes were TP53 (93.4%), RB1 (78.7%), LRP1B (18.9%), KMT2D (15.6%), FAT1 (11.5%), KMT2C (11.5%), SPTA1 (11.5%), STK24 (11.5%), FAM135B (10.7%), and NOTCH1 (10.7%). The gene fusion/rearrangement detection rate was 16.4%, and mostly occurred in chromosomes 7 and 17. The rate of co-occurring mutations of TP53 and RB1 in these Chinese SCLC patients was 74.6%, and lower than the reported Western patients (90.9%,  $P = 0.007$ ). The most common gene mutations (83.6%) were found in cell cycle signaling pathway in Chinese SCLC patients. Mutation of Wnt and Notch signaling pathways in the Chinese cohort were lower than Western cohort ( $P = 0.0013$  and  $0.0068$ ). A significant association was found between high tumor mutation burden and mutations involved in FAT1, TP53, SPTA1, KEAP1, KMT2D, MAGI2, NOTCH2, NOTCH3, FLT1, KDM6A, and FAT4. **CONCLUSIONS:** In this study, we characterized the genomic alterations profile of Chinese SCLC patients. Compared with westerners, the genetic alterations of Chinese SCLC patients presented different patterns. Our data might provide useful information in targeted therapy and drug development for Chinese SCLC patients.

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## PALLIATIVE AND SUPPORTIVE CARE

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[Dispositional mindfulness, self-compassion, and compassion from others as moderators between stress and depression in caregivers of patients with lung cancer.](#)

Hsieh CC1, Yu CJ2, Chen HJ3, Chen

YW4, Chang NT1, Hsiao FH1,5. *Psychooncology*. 2019 Jul;28(7):1498-1505. doi: 10.1002/pon.5106. Epub 2019 Jun 6.

**OBJECTIVE:** The present study aimed to identify the most important protective factors predicting caregivers' depressive symptoms among factors of caregivers' dispositional mindfulness, self-compassion, compassion from others, and patients' dispositional mindfulness and their moderator effects on the relationship between caregiving stress and depressive symptoms. **METHODS:** A total of 72 lung cancer outpatients and their family caregivers participated in this study. Family caregivers completed the Kingston Caregiver Stress Scale, Beck Depression Inventory-II (BDI-II), Five Facet Mindfulness Questionnaire (FFMQ), Self-Compassion Scale, and Compassion from Others Scale. Patients completed the EORTC Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), BDI-II, and FFMQ. **RESULTS:** After controlling for patients' factors (treatment status, symptom distress, and depressive symptoms) and caregivers' health status, caregivers' stress and dispositional mindfulness, the domain of mindful awareness, and self-compassionate action were significantly associated with their depressive symptoms. Further analysis indicated that mindful awareness or self-compassionate action could buffer the effect of caregiving stress on depressive symptoms. When the two moderators, mindful awareness and self-compassionate action, were tested simultaneously, only self-compassionate action remained as a significant moderating effect. **CONCLUSIONS:** Caregivers' mindful awareness and self-compassionate action were protective factors, which mitigate the impact of caregiving stress on their depressive symptoms. Therefore, the future supportive program aims at training the competencies of self-compassionate action with mindful awareness, which may enhance caregivers' coping resources.

[Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer.](#) Cavalheri V1, Burtin C, Formico VR, Nonoyama ML, Jenkins S, Spruit MA, Hill K. *Cochrane Database Syst Rev*. 2019 Jun 17;6:CD009955. doi: 10.1002/14651858.CD009955.pub3.

Update of Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer. [Cochrane Database Syst Rev. 2013]

**BACKGROUND:** Decreased exercise capacity and health-related quality of life (HRQoL) are common in people following lung resection for non-small cell lung cancer (NSCLC). Exercise training has been demonstrated to confer gains in exercise capacity and HRQoL for people with a range of chronic conditions, including chronic obstructive pulmonary disease and heart failure, as well as in people with prostate and breast cancer. A programme of exercise training may also confer gains in these outcomes for people following lung resection for NSCLC. This systematic review updates our 2013 systematic review.

**OBJECTIVES:** The primary aim of this review was to determine the effects of exercise training on exercise capacity and adverse events in people following lung resection (with or without chemotherapy) for NSCLC. The secondary aims were to determine the effects of exercise training on other outcomes such as HRQoL, force-generating capacity of peripheral muscles, pressure-generating capacity of the respiratory muscles, dyspnoea and fatigue, feelings of anxiety and depression, lung function, and mortality. **SEARCH METHODS:** We searched for additional randomised controlled trials (RCTs) in the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library 2019, Issue 2 of 12), MEDLINE (via PubMed) (2013 to February 2019), Embase (via Ovid) (2013 to February 2019), SciELO (The Scientific Electronic Library Online) (2013 to February 2019), and PEDro (Physiotherapy Evidence Database) (2013 to February 2019). **SELECTION CRITERIA:** We included RCTs in which participants with NSCLC who underwent lung resection were allocated to receive either exercise training, which included aerobic exercise, resistance exercise, or a combination of both, or no exercise training.

**DATA COLLECTION AND ANALYSIS:** Two review authors screened the studies and identified those eligible for inclusion. We used either postintervention values (with their respective standard deviation (SD)) or mean changes (with their respective SD) in the meta-analyses that reported results as mean difference (MD). In meta-analyses that reported results as standardised mean difference (SMD), we

placed studies that reported postintervention values and those that reported mean changes in separate subgroups. We assessed the certainty of evidence for each outcome by downgrading or upgrading the evidence according to GRADE criteria. **MAIN RESULTS:** Along with the three RCTs included in the original version of this review (2013), we identified an additional five RCTs in this update, resulting in a total of eight RCTs involving 450 participants (180 (40%) females). The risk of selection bias in the included studies was low and the risk of performance bias high. Six studies explored the effects of combined aerobic and resistance training; one explored the effects of combined aerobic and inspiratory muscle training; and one explored the effects of combined aerobic, resistance, inspiratory muscle training and balance training. On completion of the intervention period, compared to the control group, exercise capacity expressed as the peak rate of oxygen uptake (VO<sub>2</sub>peak) and six-minute walk distance (6MWD) was greater in the intervention group (VO<sub>2</sub>peak: MD 2.97 mL/kg/min, 95% confidence interval (CI) 1.93 to 4.02 mL/kg/min, 4 studies, 135 participants, moderate-certainty evidence; 6MWD: MD 57 m, 95% CI 34 to 80 m, 5 studies, 182 participants, high-certainty evidence). One adverse event (hip fracture) related to the intervention was reported in one of the included studies. The intervention group also achieved greater improvements in the physical component of general HRQoL (MD 5.0 points, 95% CI 2.3 to 7.7 points, 4 studies, 208 participants, low-certainty evidence); improved force-generating capacity of the quadriceps muscle (SMD 0.75, 95% CI 0.4 to 1.1, 4 studies, 133 participants, moderate-certainty evidence); and less dyspnoea (SMD -0.43, 95% CI -0.81 to -0.05, 3 studies, 110 participants, very low-certainty evidence). We observed uncertain effects on the mental component of general HRQoL, disease-specific HRQoL, handgrip force, fatigue, and lung function. There were insufficient data to comment on the effect of exercise training on maximal inspiratory and expiratory pressures and feelings of anxiety and depression. Mortality was not reported in the included studies. **AUTHORS' CONCLUSIONS:** Exercise training increased exercise capacity and quadriceps muscle force of people following lung resection for NSCLC. Our findings also suggest improvements on the physical component score of general HRQoL and decreased dyspnoea. This systematic review emphasises the importance of exercise training as part of the postoperative management of people with NSCLC.

[Immune Checkpoint Inhibitor Outcomes for Patients With Non-Small-Cell Lung Cancer Receiving Baseline Corticosteroids for Palliative Versus Nonpalliative Indications.](#) Ricciuti B1, Dahlberg SE1, Adeni A1, Sholl LM2, Nishino M2, Awad MM1. *J Clin Oncol.* 2019 Jun 17;JCO1900189. doi: 10.1200/JCO.19.00189. [Epub ahead of print]

**PURPOSE:** Baseline use of corticosteroids is associated with poor outcomes in patients with non-small-cell lung cancer (NSCLC) treated with programmed cell death-1 axis inhibition. To approach the question of causation versus correlation for this association, we examined outcomes in patients treated with immunotherapy depending on whether corticosteroids were administered for cancer-related palliative reasons or cancer-unrelated indications. **PATIENTS AND METHODS:** Clinical outcomes in patients with NSCLC treated with immunotherapy who received  $\geq 10$  mg prednisone were compared with outcomes in patients who received 0 to  $< 10$  mg of prednisone. **RESULTS:** Of 650 patients, the 93 patients (14.3%) who received  $\geq 10$  mg of prednisone at the time of immunotherapy initiation had shorter median progression-free survival (mPFS) and median overall survival (mOS) times than patients who received 0 to  $< 10$  mg of prednisone (mPFS, 2.0 v 3.4 months, respectively;  $P = .01$ ; mOS, 4.9 v 11.2 months, respectively;  $P < .001$ ). When analyzed by reason for corticosteroid administration, mPFS and mOS were significantly shorter only among patients who received  $\geq 10$  mg prednisone for palliative indications compared with patients who received  $\geq 10$  mg prednisone for cancer-unrelated reasons and with patients receiving 0 to  $< 10$  mg of prednisone (mPFS, 1.4 v 4.6 v 3.4 months, respectively; log-rank  $P < .001$  across the three groups; mOS, 2.2 v 10.7 v 11.2 months, respectively; log-rank  $P < .001$  across the three groups). There was no significant difference in mPFS or mOS in patients receiving  $\geq 10$  mg of prednisone for cancer-unrelated indications compared with patients receiving 0 to  $< 10$  mg of prednisone.

**CONCLUSION:** Although patients with NSCLC treated with  $\geq 10$  mg of prednisone at the time of immunotherapy initiation have worse outcomes than patients who received 0 to  $< 10$  mg of prednisone, this difference seems to be driven by a poor-prognosis subgroup of patients who receive corticosteroids for palliative indications.

### [Hope-related goal cognitions and daily experiences of fatigue, pain, and functional concern among lung cancer patients.](#)

Steffen LE1, Cheavens JS2, Vowles KE3, Gabbard J4, Nguyen H5, Gan GN6, Edelman MJ7, Smith BW3. Support Care Cancer. 2019 Jun 1. doi: 10.1007/s00520-019-04878-y. [Epub ahead of print]

**PURPOSE:** Cross-sectional research suggests that thinking about multiple ways to reach goals (hope pathways) and the belief that one can reach them (hope agency) may be adaptive for lung cancer patients. We examined the between-person and within-person associations among aspects of hope agency and pathways thinking, daily fatigue, pain, and functional concerns (e.g., sense of independence, usefulness) among lung cancer patients during active treatment. **METHODS:** Data from a daily diary study were used to examine relations among hope agency, hope pathways, fatigue, pain, and functional concern in 50 patients with advanced lung cancer. Participants were accrued from one outpatient cancer center and completed the study between 2014 and 2015. **RESULTS:** Adjusting for covariates and the previous day's symptoms or concern, patients who engaged in higher pathways thinking reported lower daily symptoms, whereas those who engaged in higher agency thinking reported less functional concern. Within-person increases in pathways thinking were associated with less daily fatigue, pain, and functional concern; within-person increases in agency thinking were associated with less daily fatigue and pain. Models examining symptoms and concerns as predictors of hope suggested within-person increases in functional concern and fatigue and pain were related to lower agency and pathways thinking the same day. Patients with higher fatigue and pain did not report lower agency or pathways thinking, but patients with more functional concern did. **CONCLUSIONS:** Increases in hope pathways thinking may be associated with lower symptoms and better functioning in lung cancer patients. This suggests that it is important to determine the efficacy of interventions that emphasize the pathways the component of hope.

### [Manifestations of anxiety and coping strategies in patients with metastatic lung cancer and their family caregivers: a qualitative study.](#)

Hendriksen E1, Rivera A2, Williams E2, Lee E2, Sporn N3, Cases MG1, Palesh O1. Psychol Health. 2019 Jul;34(7):886-899. doi: 10.1080/08870446.2019.1579909. Epub 2019 Jun 3.

**OBJECTIVE:** Advanced non-small cell lung cancer (NSCLC) is common, deadly, and associated with impairing anxiety for patients and caregivers who often co-experience similar symptoms that can vary together over time. We aimed to discover themes as to how NSCLC patients and caregivers express and cope with anxiety. **DESIGN:** Semi-structured interviews of patient-caregiver dyads (N = 21), coded using NVivo Software. Main Outcome Measures: Open-ended questions on anxiety mutuality, giving or receiving care, communication, and the most difficult aspects of having or caring for someone with Stage IV NSCLC. Results: Analyses revealed that patients and caregivers were linked psychologically, co-experiencing symptoms of distress or coping, rising and falling together. Shared patient and caregiver themes emerged of cognitive, behavioural and physiological manifestations of anxiety and coping mechanisms. **CONCLUSIONS:** Patient and caregiver expressions of anxiety and coping methods mapped onto the cognitive-behavioural model, implying potential use of cognitive behavioural therapy (CBT) to address these issues. This expands understanding of symptoms and coping strategies in NSCLC, explores patient-caregiver interaction, and confirms the need for future clinical intervention. Future research should focus on development and dissemination of CBT-based dyadic interventions addressing anxiety in NSCLC patients and caregivers.

**[Acceptance and Commitment Therapy for Symptom Interference in Advanced Lung Cancer and Caregiver Distress: A Pilot Randomized Trial.](#)**

Mosher CE1, Secinti E2, Hirsh AT2, Hanna N3, Einhorn LH3, Jalal SI4, Durm G3, Champion VL5, Johns SA6. *J Pain Symptom Manage.* 2019 Jun 27. pii: S0885-3924(19)30365-3. doi: 10.1016/j.jpainsymman.2019.06.021. [Epub ahead of print]

**CONTEXT:** Advanced lung cancer patients typically have a poor prognosis and many symptoms that interfere with functioning, contributing to high rates of emotional distress in both patients and family caregivers. There remains a need for evidence-based interventions to improve functional outcomes and distress in this population. **OBJECTIVES:** This pilot trial examined the feasibility and preliminary efficacy of telephone-based Acceptance and Commitment Therapy (ACT) for symptomatic, advanced lung cancer patients and their distressed family caregivers. Primary outcomes were patient symptom interference with functioning and patient and caregiver distress. **METHODS:** Symptomatic, advanced lung cancer patients and distressed caregivers (n=50 dyads) were randomly assigned to six sessions of ACT or an education/support condition. Patients completed measures of symptom interference and measures assessing the severity of fatigue, pain, sleep disturbance, and breathlessness. Patients and caregivers completed measures of distress and illness acceptance and struggle. **RESULTS:** The eligibility screening rate (51%) and retention rate (76% at 6 weeks post-intervention) demonstrated feasibility. No group differences were found with respect to patient and caregiver outcomes. Both groups showed a small, significant decrease in struggle with the illness over the study period, but did not show meaningful change in other outcomes. **CONCLUSION:** Findings suggest that telephone-based ACT is feasible for many advanced lung cancer patients and caregivers, but may not substantially reduce symptom interference and distress. Low baseline levels of certain symptoms may have contributed to null findings. Next steps include applying ACT to specific, clinically meaningful symptom interference and varying intervention dose and modality.

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**COMPLEMENTARY & ALTERNATIVE THERAPY**

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**[Cytological effects of honokiol treatment and its potential mechanism of action in non-small cell lung cancer.](#)**

Zhang J1, Zhang Y1, Shen W1, Fu R1, Ding Z1, Zhen Y2, Wan Y3. *Biomed Pharmacother.* 2019 Jun 5;117:109058. doi: 10.1016/j.biopha.2019.109058. [Epub ahead of print]

**PURPOSE:** In this study, we aimed to explore key micro(mi)RNAs and their potential regulatory mechanisms induced by honokiol treatment in non-small cell lung cancer (NSCLC) cells. **METHODS:** NSCLC A549 cells were treated with 0 (control) or 45  $\mu$ M honokiol. Cell proliferation and migration were determined using CCK-8 and transwell assay, respectively, and apoptosis was determined using flow cytometry. RNA-sequencing was performed to detect the transcript expression levels. The differentially expressed miRNAs (DE-miRNAs) between the honokiol group and the control group were screened and analyzed for their functions and pathways. Then, protein-protein interaction (PPI) networks and miRNA-mRNA regulatory networks were constructed. In addition, survival analysis based on the key miRNAs was performed. Finally, the expression of the key miRNAs and their target genes were determined, and their effects on drug sensitivity were validated using their inhibitors. **RESULTS:** Cell proliferation and migration were inhibited ( $P < 0.01$ ), and the apoptosis rate was increased ( $P < 0.01$ ) after honokiol treatment compared to that in the control group. A total of 26 upregulated and 20 downregulated DE-miRNAs were screened. DE-miRNAs were enriched in 10 pathways and 48 biological processes, such as the PI3K/AKT signaling pathway (involving miR-148a-3p). The miRNA-mRNA regulatory networks involved eight upregulated (including miR-148a-3p and let-7c-5p) and seven downregulated miRNAs (including miR-7-5p) and 190 target mRNAs. Survival analysis revealed that let-7c-5p, miR-148a-3p, and miR-148a-5p levels correlated with NSCLC prognosis. The expression of let-7c-5p, miR-148a-3p, and miR-148a-5p was significantly increased and negatively correlated with the expression of their target genes. The cytological effects of honokiol on A549 cells was partly reversed by treatment with



the inhibitors of Let-7c-5p and miR-148a-3p. **CONCLUSION:** Let-7c-5p, miR-148a-3p, miR-148a-5p, and miR-7-5p are favorable indicators of NSCLC patients treated with honokiol.

[Yi-qi-yang-yin-tian-sui-fang enhances cisplatin-induced tumor eradication and inhibits interleukin-7 reduction in non-small cell lung cancer.](#) Ke B1, Wu X1, Yang Q2, Huang Y3, Wang F4, Gong Y5, Liu J5, Shi L6. *Biosci Rep.* 2019 Jun 28;39(6). pii: BSR20190052. doi: 10.1042/BSR20190052. Print 2019 Jun 28.

Traditional Chinese Medicine (TCM) has been recognized to be conducive to enhancing the efficiency and reducing the side effects in the whole course of cancer treatment. The mechanisms of TCM/chemotherapy combination involved with interleukin-7 (IL-7) potentially enhance immune responses against tumor. In the present study, we emphasized on a herbal formulation Yi-qi-yang-yin-tian-sui-fang or TCM for short, and investigated its roles in chemotherapy in non-small cell lung cancer (NSCLC). The mice bared with tumor were treated with cisplatin (DDP) and simultaneously administrated with/without low, medium and high doses of TCMs (effective content: 0.5, 2.0 and 8.0 g/per mice) via oral gavage. The results indicated that combination of TCM further elevated the therapy efficiency of DDP in a dose-dependent manner. The growth of tumor cells was estimated by Ki-67 stain and terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick-end labeling (TUNEL) assay. The addition of TCM to the DDP treatment could significantly decrease the expression of Ki-67 and promote the apoptosis of tumor cells. In addition, the serum IL-7 level was down-regulated by DDP but restored by the treatment of TCM. The expression of IL-7 and its receptor IL-7R in tumor tissues was also recovered by TCM. Furthermore, the side effect from bone marrow suppression (myelosuppression) induced by DDP were assessed. TCM could abrogate DDP-induced apoptosis of bone marrow and also remarkably induced the expressions of IL-7 and hematopoietic growth factors including G-CSF, GM-CSF, SCF, and SDF-1 in bone marrow. These data indicated that this TCM combined with DDP showed superior anti-tumor effects with reduced myelosuppression via up-regulating IL-7.

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## MISCELLANEOUS WORKS

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[Effective stakeholder engagement: design and implementation of a clinical trial \(SWOG S1415CD\) to improve cancer care.](#) Barger S1, Sullivan SD2, Bell-Brown A1, et al. *BMC Med Res Methodol.* 2019 Jun 11;19(1):119. doi: 10.1186/s12874-019-0764-2.

**BACKGROUND:** The Fred Hutchinson Cancer Research Center has engaged an External Stakeholder Advisory Group (ESAG) in the planning and implementation of the TrACER Study (S1415CD), a five-year pragmatic clinical trial assessing the effectiveness of a guideline-based colony stimulating factor standing order intervention. The trial is being conducted by SWOG through the National Cancer Institute Community Oncology Research Program in 45 clinics. The ESAG includes ten patient partners, two payers, two pharmacists, two guideline experts, four providers and one medical ethicist. This manuscript describes the ESAG's role and impact on the trial. **METHODS:** During early trial development, the research team assembled the ESAG to inform plans for each phase of the trial. ESAG members provide feedback and engage in problem solving to improve trial implementation. Each year, members participate in one in-person meeting, web conferences and targeted email discussion. Additionally, they complete a survey that assesses their satisfaction with communication and collaboration. The research team collected and reviewed stakeholder input from 2014 to 2018 for impact on the trial. **RESULTS:** The ESAG has informed trial design, implementation and dissemination planning. The group advised the trial's endpoints, regimen list and development of cohort and usual care arms. Based on ESAG input, the research team enhanced patient surveys and added pharmacy-related questions to the component application to assess order entry systems. ESAG patient partners collaborated with the research team to develop a patient brochure and study summary for clinic staff. In addition to identifying recruitment

strategies and patient-oriented platforms for publicly sharing results, ESAG members participated as co-authors on this manuscript and a conference poster presentation highlighting stakeholder influence on the trial. The annual satisfaction survey results suggest that ESAG members were satisfied with the methods, frequency and target areas of their engagement in the trial during project years 1-3. **CONCLUSIONS:** Diverse stakeholder engagement has been essential in optimizing the design, implementation and planned dissemination of the TrACER Study. The lessons described in the manuscript may assist others to effectively partner with stakeholders on clinical research.

### **Smoking and Smoking Cessation Among Persons with Tobacco- and Non-tobacco-Associated Cancers.**

Gallaway MS1, Huang B2,3, Chen Q3, Tucker TC3,4, McDowell JK3, Durbin E3,5, Stewart SL6, Tai E6. *J Community Health*. 2019 Jun;44(3):552-560. doi: 10.1007/s10900-019-00622-z.

**PURPOSE:** To examine smoking and use of smoking cessation aids among tobacco-associated cancer (TAC) or non-tobacco-associated cancer (nTAC) survivors. Understanding when and if specific types of cessation resources are used can help with planning interventions to more effectively decrease smoking among all cancer survivors, but there is a lack of research on smoking cessation modalities used among cancer survivors. **METHODS:** Kentucky Cancer Registry data on incident lung, colorectal, pancreatic, breast, ovarian, and prostate cancer cases diagnosed 2007-2011, were linked with health administrative claims data (Medicaid, Medicare, private insurers) to examine the prevalence of smoking and use of smoking cessation aids 1 year prior and 1 year following the cancer diagnosis. TACs included colorectal, pancreatic, and lung cancers; nTAC included breast, ovarian, and prostate cancers. **RESULTS:** There were 10,033 TAC and 13,670 nTAC survivors. Smoking before diagnosis was significantly higher among TAC survivors ( $p < 0.0001$ ). Among TAC survivors, smoking before diagnosis was significantly higher among persons who: were males (83%), aged 45-64 (83%), of unknown marital status (84%), had very low education (78%), had public insurance (89%), Medicaid (85%) or were uninsured (84%). Smoking cessation counseling and pharmacotherapy were more common among TAC than nTAC survivors ( $p < 0.01$  and  $p = 0.05$ , respectively). **DISCUSSION:** While smoking cessation counseling and pharmacotherapy were higher among TAC survivors, reducing smoking among all cancer survivors remains a priority, given cancer survivors are at increased risk for subsequent chronic diseases, including cancer. Tobacco cessation among all cancer survivors (not just those with TAC) can help improve prognosis, quality of life and reduce the risk of further disease. Health care providers can recommend for individual, group and telephone counseling and/or pharmacotherapy recommendations. These could also be included in survivorship care plans.

### **Body Mass Index (BMI), BMI Change, and Overall Survival in Patients With SCLC and NSCLC: A Pooled Analysis of the International Lung Cancer Consortium.**

Shepshelovich D1, Xu W2, Lu L3, et al. *J Thorac Oncol*. 2019 Jun 1. pii: S1556-0864(19)30416-2. doi: 10.1016/j.jtho.2019.05.031. [Epub ahead of print]

**INTRODUCTION:** The relationships between morbid obesity, changes in body mass index (BMI) before cancer diagnosis, and lung cancer outcomes by histology (SCLC and NSCLC) have not been well studied. **METHODS:** Individual level data analysis was performed on 25,430 patients with NSCLC and 2787 patients with SCLC from 16 studies of the International Lung Cancer Consortium evaluating the association between various BMI variables and lung cancer overall survival, reported as adjusted hazard ratios (aHRs) from Cox proportional hazards models and adjusted penalized smoothing spline plots. **RESULTS:** Overall survival of NSCLC had putative U-shaped hazard ratio relationships with BMI based on spline plots: being underweight (BMI  $< 18.5$  kg/m<sup>2</sup>; aHR = 1.56; 95% confidence interval [CI]: 1.43-1.70) or morbidly overweight (BMI  $> 40$  kg/m<sup>2</sup>; aHR = 1.09; 95% CI: 0.95-1.26) at the time of diagnosis was associated with worse stage-specific prognosis, whereas being overweight (25 kg/m<sup>2</sup>  $\leq$  BMI  $< 30$  kg/m<sup>2</sup>; aHR = 0.89; 95% CI: 0.85-0.95) or obese (30 kg/m<sup>2</sup>  $\leq$  BMI  $\leq 40$  kg/m<sup>2</sup>; aHR = 0.86; 95% CI:

0.82-0.91) was associated with improved survival. Although not significant, a similar pattern was seen with SCLC. Compared with an increased or stable BMI from the period between young adulthood until date of diagnosis, a decreased BMI was associated with worse outcomes in NSCLC (aHR = 1.24; 95% CI: 1.2-1.3) and SCLC patients (aHR=1.26 (95% CI: 1.0-1.6). Decreased BMI was consistently associated with worse outcome, across clinicodemographic subsets. **CONCLUSIONS:** Both being underweight or morbidly obese at time of diagnosis is associated with lower stage-specific survival in independent assessments of NSCLC and SCLC patients. In addition, a decrease in BMI at lung cancer diagnosis relative to early adulthood is a consistent marker of poor survival.

**Factors Associated With Age Disparities Among Cancer Clinical Trial Participants.** Ludmir EB1, Mainwaring W2, Lin TA1,2, et al. JAMA Oncol. 2019 Jun 3. doi: 10.1001/jamaoncol.2019.2055. [Epub ahead of print]

**IMPORTANCE:** Seminal investigation 2 decades ago alerted the oncology community to age disparities in participation in cooperative group trials; less is known about whether these disparities persist in industry-funded research. **OBJECTIVE:** To characterize the age disparities among trial enrollees on randomized clinical trials (RCTs) of common cancers in clinical oncology and identify factors associated with wider age imbalances. **DATA SOURCES:** Phase 3 clinical oncology RCTs were identified through ClinicalTrials.gov. **STUDY SELECTION:** Multiarm RCTs assessing a therapeutic intervention for patients with breast, prostate, colorectal, or lung cancer (the 4 most common cancer disease sites) were included. **DATA EXTRACTION AND SYNTHESIS:** Trial data were extracted from ClinicalTrials.gov. Trial screening and parameter identification were independently performed by 2 individuals. Data were analyzed in 2018. **MAIN OUTCOMES AND MEASURES:** The difference in median age (DMA) between the trial participant median age and the population-based disease-site-specific median age was determined for each trial. **RESULTS:** Three hundred two trials met inclusion criteria. The trials collectively enrolled 262 354 participants; 249 trials (82.5%) were industry-funded. For all trials, the trial median age of trial participants was a mean of 6.49 years younger than the population median age (95% CI, -7.17 to -5.81 years;  $P < .001$ ). Age disparities were heightened among industry-funded trials compared with non-industry-funded trials (mean DMA, -6.84 vs -4.72 years;  $P = .002$ ). Enrollment criteria restrictions based on performance status or age cutoffs were associated with age disparities; however, industry-funded trials were not more likely to use these enrollment restrictions than non-industry-funded trials. Age disparities were also larger among trials that evaluated a targeted systemic therapy and among lung cancer trials. Linear regression modeling revealed a widening gap between trial and population median ages over time at a rate of -0.19 years annually (95% CI, -0.37 to -0.01 years;  $P = .04$ ). **CONCLUSIONS AND RELEVANCE:** Age disparities between trial participants and the incident disease population are pervasive across trials and appear to be increasing over time. Industry sponsorship of trials is associated with heightened age imbalances among trial participants. With an increasing role of industry funding among cancer trials, efforts to understand and address age disparities are necessary to ensure generalizability of trial results as well as equity in trial access.

**Comparison of Hospitals Affiliated With PPS-Exempt Cancer Centers, Other Hospitals Affiliated With NCI-Designated Cancer Centers, and Other Hospitals That Provide Cancer Care.** Merkow RP1,2, Yang AD1,2, Pavey E1, Song MW3, Chung JW1,2, Bentrem DJ1,2,4, Bilimoria KY1,2. JAMA Intern Med. 2019 Jun 17. doi: 10.1001/jamainternmed.2019.0914. [Epub ahead of print]

**IMPORTANCE:** Congress has exempted 11 specialized cancer centers in the United States from the Prospective Payment System (PPS). These centers are also exempt from reporting many of the process-of-care and outcome measures to the Centers for Medicare & Medicaid Services that are required for hospitals in the PPS. It is not known how hospitals affiliated with PPS-exempt cancer centers differ from other hospitals affiliated with National Cancer Institute cancer centers (NCI-CCs) or other US hospitals

that provide cancer care. **OBJECTIVE:** To examine differences between hospitals affiliated with PPS-exempt cancer centers, other hospitals affiliated with NCI-CCs, and other hospitals that provide cancer care on metrics that could be used in public reporting. **DESIGN, SETTING, AND PARTICIPANTS:** This retrospective cohort study compared hospital characteristics and cancer-related services using data from the American Hospital Association Annual Survey and US News Best Hospitals rankings. With a 100% sample of Medicare beneficiaries who underwent 1 of 9 cancer operations (brain tumor resection, colorectal resection, cystectomy, esophagectomy, gastrectomy, liver resection, lung resection, pancreatic resection, prostatectomy) from January 1, 2011, to May 31, 2015, we used hierarchical logistic regression methods to compare differences in 18 postoperative outcomes. Data analysis was conducted from February 2018 to August 2018. **MAIN OUTCOMES AND MEASURES:** This study evaluated hospital characteristics, including cancer-specific services, patient comorbidity burden, and cancer surgery postoperative outcomes, from PPS-exempt cancer centers, NCI-affiliated cancer centers, and other US hospitals that provide cancer care. **RESULTS:** Hospitals affiliated with PPS-exempt cancer centers (n = 15) and NCI-CCs (n = 54) were similar in hospital characteristics, basic cancer-related services, and patient comorbidity burden. Compared with NCI-CCs, PPS-exempt cancer centers had significantly higher US News reputation scores (mean [SD], 17.5 [24.0] vs 2.6 [4.8]; P < .001) but no differences in oncology patient volume, patient safety ratings, comorbidity burden, nurse staffing, US News total cancer scores, or US News survival scores. Hospitals affiliated with PPS-exempt cancer centers and NCI-CCs had similar adjusted postoperative outcomes for 15 of 18 measures, including mortality, readmission, and surgical site infections. Compared with hospitals affiliated with PPS-exempt cancer centers, patients treated at NCI-CCs were more likely to have postoperative sepsis (3.1% vs 1.7%; P = .002), acute renal failure (6.2% vs 3.9%; P = .01), and urinary tract infection (6.4% vs 4.0%; P = .002). Compared with the other hospitals that provide cancer care (n = 3578), PPS-exempt cancer center status was associated with improved outcomes for 7 of 18 measures, including mortality, sepsis, acute renal failure, pulmonary failure, and failure to rescue. **CONCLUSIONS AND RELEVANCE:** Hospitals affiliated with PPS-exempt cancer centers and NCI-CCs had generally similar hospital characteristics, patient comorbidity burden, and cancer surgery outcomes. These findings raise questions about why some cancer centers are designated as PPS-exempt and why most hospitals are not required to publicly report cancer-specific quality metrics.

#### [County-level radon exposure and all-cause mortality risk among Medicare beneficiaries.](#)

Yitshak-Sade M1, Blomberg AJ2, Zanobetti A2, Schwartz JD3, Coull BA4, Kloog I5, Dominici F4, Koutrakis P2. *Environ Int.* 2019 Jun 11;130:104865. doi: 10.1016/j.envint.2019.05.059. [Epub ahead of print]

**BACKGROUND:** Radon is an inert gas formed from the decay of naturally-occurring materials in the earth's crust. It infiltrates into homes from soil, water, and construction materials. Its decay products are radionuclides, which attach to ambient particles. Residential radon is one of the leading risk factors for lung cancer. The scarce evidence for associations with other mortality causes originates mostly from occupational studies. **METHODS:** In a cohort study with 14 years of follow-up (2000-2013), we evaluated the association between chronic radon exposure and all-cause mortality, and explored whether there are subpopulations who are more vulnerable to radon effects. We included 87,296,195 person-years of follow-up from all Medicare beneficiaries in the Mid-Atlantic and Northeastern U.S. states. We examined the association between the logarithm of county-averaged radon ( $\ln(\text{Rn})$ ) and mortality and assessed effect modification by chronic conditions. **RESULTS:** An interquartile range increase in the  $\ln(\text{Rn})$  was associated with a 2.62% increase (95% CI 2.52%; 2.73%) in mortality, independent of PM<sub>2.5</sub> exposure. Larger mortality risks were observed among individuals with respiratory, cardiovascular and metabolic diseases, with the highest associations observed among those with diabetes (4.98% increase), heart failure (4.58% increase), and chronic obstructive pulmonary disease (4.49% increase).

**CONCLUSION:** We found an increased risk for all-cause mortality associated with increased radon exposure. The risk was enhanced among susceptible individuals with chronic conditions. We believe this is the first cohort study to identify populations at higher risk for non-malignant health consequences of radon exposure. Due to the limitations in exposure assessment and availability of individual confounders, these findings should be interpreted with caution.