



Caring Ambassadors Lung Cancer Program

Literature Review, July 2019

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BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[IL-6/JAK1 pathway drives PD-L1 Y112 phosphorylation to promote cancer immune evasion.](#) Chan LC1,2, Li CW1, Xia W1, et al. J Clin Invest. 2019 Jul 15;130:3324-3338. doi: 10.1172/JCI126022. eCollection 2019 Jul 15.

Glycosylation of immune receptors and ligands, such as T cell receptor and coinhibitory molecules, regulates immune signaling activation and immune surveillance. However, how oncogenic signaling initiates glycosylation of coinhibitory molecules to induce immunosuppression remains unclear. Here we show that IL-6-activated JAK1 phosphorylates programmed death-ligand 1 (PD-L1) Tyr112, which recruits the endoplasmic reticulum-associated N-glycosyltransferase STT3A to catalyze PD-L1 glycosylation and maintain PD-L1 stability. Targeting of IL-6 by IL-6 antibody induced synergistic T cell killing effects when combined with anti-T cell immunoglobulin mucin-3 (anti-Tim-3) therapy in animal models. A positive correlation between IL-6 and PD-L1 expression was also observed in hepatocellular carcinoma patient tumor tissues. These results identify a mechanism regulating PD-L1 glycosylation initiation and suggest the combination of anti-IL-6 and anti-Tim-3 as an effective marker-guided therapeutic strategy.

[Investigation of Leukocyte Telomere Length and Genetic Variants in Chromosome 5p15.33 as Prognostic Markers in Lung Cancer.](#) Kachuri L1,2,3, Helby J4, Bojesen SE4,5, et al. Cancer Epidemiol Biomarkers Prev. 2019 Jul;28(7):1228-1237. doi: 10.1158/1055-9965.EPI-18-1215.

BACKGROUND: Lung cancer remains the leading cause of cancer mortality with relatively few prognostic biomarkers. We investigated associations with overall survival for telomere length (TL) and genetic variation in chromosome 5p15.33, an established telomere maintenance locus. **METHODS:** Leukocyte TL was measured after diagnosis in 807 patients with non-small cell lung cancer (NSCLC) from the Princess Margaret Cancer Center in Toronto and assessed prospectively in 767 NSCLC cases from the Copenhagen City Heart Study and the Copenhagen General Population Study. Associations with all-cause mortality were tested for 723 variants in 5p15.33, genotyped in 4,672 NSCLC cases.

RESULTS: Short telomeres (≤ 10 th percentile) were associated with poor prognosis for adenocarcinoma in both populations: TL measured 6 months after diagnosis [HR = 1.65; 95% confidence intervals (CI),

1.04-2.64] and for those diagnosed within 5 years after blood sampling (HR = 2.42; 95% CI, 1.37-4.28). Short TL was associated with mortality in never smokers with NSCLC (HR = 10.29; 95% CI, 1.86-56.86) and adenocarcinoma (HR = 11.31; 95% CI, 1.96-65.24). Analyses in 5p15.33 identified statistically significant prognostic associations for rs56266421-G in LPCAT1 (HR = 1.86; 95% CI, 1.38-2.52; $P = 4.5 \times 10^{-5}$) in stage I-IIIa NSCLC, and for the SLC6A3 gene with OS in females with NSCLC ($P = 1.6 \times 10^{-3}$). **CONCLUSIONS:** Our findings support the potential clinical utility of TL, particularly for adenocarcinoma patients, while associations in chromosome 5p15.33 warrant further exploration. **IMPACT:** This is the largest lung cancer study of leukocyte TL and OS, and the first to examine the impact of the timing of TL measurement. Our findings suggest that extremely short telomeres are indicative of poor prognosis in NSCLC.

[IL-32 \$\gamma\$ suppresses lung cancer stem cell growth via inhibition of ITGAV-mediated STAT5 pathway.](#)

Lee YS1, Kim KC1, Mongre RK1, et al. Cell Death Dis. 2019 Jul 1;10(7):506. doi: 10.1038/s41419-019-1737-4.

The cancer stem cells (CSCs) are thought to be responsible for cancer initiation, recurrence, and metastasis via a multifactorial process. IL-32 γ has been known to inhibit several tumor developments. However, the role of IL-32 γ in CSCs is unknown. The role of IL-32 γ on tumor development was assessed in IL-32 γ transgenic (Tg) mice allograft and xenograft model. In the in vitro assay, we analyzed CSC growth and apoptosis in cells with IL-32 γ overexpression by cell viability assay and tumor-sphere formation assay. In addition, expression of cell proliferation, apoptosis markers, and signaling molecules was determined by western blot analysis. IL-32 γ suppressed CD133+ CSC-induced allograft model in IL-32 γ Tg mice and xenograft model. Tumor-sphere formation and cell viability assay revealed a greater inhibition of CSC proliferation and antineoplastic activity of IL-32 γ in CD133+ CSCs as compared with normal cancer cells. The inhibitory effects of IL-32 γ on tumor development were associated with inhibition of the STAT5 pathway. In addition, inhibition of STAT5 increased cleavage of caspase-3, but suppressed CD133 expression and colony formation. Web-based gene network analysis showed that IL-32 is correlated with ITGAV, an integrin gene. Our result revealed that knockdown of ITGAV by siRNA inhibited the phosphorylation of STAT5. Moreover, we identified that ITGAV overexpression reversed the effect of IL-32 γ on phosphorylation of STAT5 and the expression of CD133. **Our results demonstrate** that IL-32 γ negatively regulates CD133+ CSC proliferation and tumor development and suggest that IL-32 γ has great potential for use in the treatment of cancer progression.

[Proximity proteomics identifies cancer cell membrane cis-molecular complex as a potential cancer target.](#)

Kotani N1, Yamaguchi A2, Ohnishi T2, Kuwahara R3, Nakano T1, Nakano Y1, Ida Y1, Murakoshi T1, Honke K2. Cancer Sci. 2019 Aug;110(8):2607-2619. doi: 10.1111/cas.14108. Epub 2019 Jul 23.

Cancer-specific antigens expressed in the cell membrane have been used as targets for several molecular targeted strategies in the last 20 years with remarkable success. To develop more effective cancer treatments, novel targets and strategies for targeted therapies are needed. Here, we examined the cancer cell membrane-resident "cis-bimolecular complex" as a possible cancer target (cis-bimolecular cancer target: BiCAT) using proximity proteomics, a technique that has attracted attention in the last 10 years. BiCAT were detected using a previously developed method termed the enzyme-mediated activation of radical source (EMARS), to label the components proximal to a given cell membrane molecule. EMARS analysis identified some BiCAT, such as close homolog of L1 (CHL1), fibroblast growth factor 3 (FGFR3) and $\alpha 2$ integrin, which are commonly expressed in mouse primary lung cancer cells and human lung squamous cell carcinoma cells. Analysis of cancer specimens from 55 lung cancer patients revealed that CHL1 and $\alpha 2$ integrin were highly co-expressed in almost all cancer tissues compared with normal lung tissues. As an example of BiCAT application, in vitro simulation of effective drug combinations

used for multiple drug treatment strategies was performed using reagents targeted to BiCAT molecules. The combination treatment based on BiCAT information moderately suppressed cancer cell proliferation compared with single administration, suggesting that the information about BiCAT in cancer cells is useful for the appropriate selection of the combination among molecular targeted reagents. Thus, BiCAT has the potential to contribute to several molecular targeted strategies in future.

SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

[Increasing Numbers and Reported Adverse Events in Patients with Lung Cancer Undergoing Inpatient Lung Biopsies: A Population-Based Analysis.](#) von Itzstein MS1, Gupta A1,2, Mara KC3, Khanna S4, Gerber DE5,6,7,8. *Lung*. 2019 Jul 31. doi: 10.1007/s00408-019-00255-y. [Epub ahead of print]

INTRODUCTION: The use of molecular biomarkers to guide lung cancer management has led to increasing frequency and amounts of tissue required for repeat lung biopsies. While patient safety and reporting of adverse events has been increasingly emphasized in recent decades, the safety of lung biopsies in patients with lung cancer has only been studied in small cohorts. We therefore analyzed adverse events in patients with lung cancer undergoing lung biopsies in the National Hospital Discharge Survey (NHDS) database. **METHODS:** Data were abstracted using ICD-9 lung cancer diagnosis (162.X) and lung biopsy procedure codes (33.20, 33.24, 33.25, 33.26, 33.27, 33.28) from 2001 to 2010. Agency for Healthcare Research and Quality (AHRQ) Patient-Safety Indicators (PSI) were used to identify hospital-acquired adverse events. Weighted analyses were performed using SAS version 9.4. **RESULTS:** A total of 540,747 patients were included for analysis. The number of biopsies increased over time, from 51,221 in 2001, to 63,239 in 2010 ($P < 0.001$). Overall, 159,683 (30%) patients suffered ≥ 1 -PSI event during their hospitalization. Incidence of PSI varied by biopsy type: bronchoscopic (26%), percutaneous (34%), surgical (39%). The proportion of patients with ≥ 1 PSI event increased from 24% in 2001 to 38% in 2010 ($P < 0.001$). Patients with ≥ 1 PSI had longer length of stay (mean, 11.6 vs 8.1 days; $P < 0.001$) and higher in-hospital mortality (adjusted odds ratio, 5.9, 95% CI 3.9-8.9; $P < 0.001$). **CONCLUSIONS:** The frequency of lung biopsies performed and rate of documented adverse events in hospitalized lung cancer patients have increased. These findings have policy, funding, research, and practice implications.

[Identifying Smoking-Related Disease on Lung Cancer Screening CT Scans: Increasing the Value.](#) Regan EA1,2, Lowe KE1,2, Make BJ1, et al. *Chronic Obstr Pulm Dis*. 2019 Jul 24;6(3):233-245. doi: 10.15326/jcopdf.6.3.2018.0142.

BACKGROUND: Lung cancer screening (LCS) via chest computed tomography (CT) scans can save lives by identifying early-stage tumors. However, most smokers die of comorbid smoking-related diseases. LCS scans contain information about smoking-related conditions that is not currently systematically assessed. Identifying these common comorbid diseases on CT could increase the value of screening with minimal impact on LCS programs. We determined the prevalence of 3 comorbid diseases from LCS eligible scans and quantified related adverse outcomes. **METHODS:** We studied COPD Genetic Epidemiology study (COPDGene®) participants ($n=4078$) who met criteria for LCS screening at enrollment (age > 55 years, and < 80 years, > 30 pack years smoking, current smoker or former smoker within 15 years of smoking cessation). CT scans were assessed for coronary artery calcification (CAC), emphysema, and vertebral bone density. We tracked the following clinically significant events: myocardial infarctions (MIs), strokes, pneumonia, respiratory exacerbations, and hip and vertebral fractures. **RESULTS:** Overall, 77% of eligible CT scans had one or more of these diagnoses identified. CAC (> 100 mg) was identified in 51% of scans, emphysema in 44%, and osteoporosis in 54%. Adverse events related to the underlying smoking-related diseases were common, with 50% of participants reporting at least one. New diagnoses of cardiovascular disease, emphysema and osteoporosis were made

in 25%, 7% and 46%, of participants respectively. New diagnosis of disease was associated with significantly more adverse events than in participants who did not have CT diagnoses for both osteoporosis and cardiovascular risk. **CONCLUSIONS:** Expanded analysis of LCS CT scans identified individuals with evidence of previously undiagnosed cardiovascular disease, emphysema or osteoporosis that corresponded with adverse events. LCS CT scans can potentially facilitate diagnoses of these smoking-related diseases and provide an opportunity for treatment or prevention.

[A Geospatial Analysis of Factors Affecting Access to CT Facilities: Implications for Lung Cancer Screening.](#) Tailor TD1, Tong BC2, Gao J3, Choudhury KR4, Rubin GD5. J Am Coll Radiol. 2019 Jul 11. pii: S1546-1440(19)30751-3. doi: 10.1016/j.jacr.2019.06.020. [Epub ahead of print]

OBJECTIVE: The association between access to CT facilities for lung cancer screening and population characteristics is understudied. We aimed to determine the relationship between census tract-level socioeconomic characteristics (SEC) and driving distance to an ACR-accredited CT facility.

METHODS: Census tract-level SEC were determined from the US Census Bureau. Distance to nearest ACR-accredited CT facility was derived at the census tract level. Census tract-level multivariable regression modeling was used to determine the relationship between driving distance to a CT facility and census tract SEC, including population density (a marker of rural versus urban), gender, race, insurance status or type, and education level. **RESULTS:** In an adjusted multivariable model, census tract-level population density was the greatest relative determinant of distance to a CT facility. Namely, rural census tracts had relatively longer distances to CT facilities than urban census tracts ($P < .001$). Census tracts with higher uninsured and undereducated (less than high school degree) people and Medicaid beneficiaries had relatively greater distances to CT facilities ($P < .001$), whereas those with higher nonwhite, female, and Medicare-recipient populations had shorter distances ($P < .001$). **DISCUSSION:** Rural populations have relatively less geographic access to CT facilities. Furthermore, other vulnerable populations, such as the uninsured, those on Medicaid, and the undereducated, may also have relatively less access to CT imaging facilities. These variations in access to CT may affect the uptake and utilization of lung cancer screening.

[Will That Pulmonary Nodule Become Cancerous? A Risk Prediction Model for Incident Lung Cancer.](#) Nemesure B1, Clouston S2,3, Albano D4, Kuperberg S5, Bilfinger TV4. Cancer Prev Res (Phila). 2019 Jul;12(7):463-470. doi: 10.1158/1940-6207.CAPR-18-0500.

This prospective investigation derived a prediction model for identifying risk of incident lung cancer among patients with visible lung nodules identified on computed tomography (CT). Among 2,924 eligible patients referred for evaluation of a pulmonary nodule to the Stony Brook Lung Cancer Evaluation Center between January 1, 2002 and December 31, 2015, 171 developed incident lung cancer during the observation period. Cox proportional hazard models were used to model time until disease onset. The sample was randomly divided into discovery ($n = 1,469$) and replication ($n = 1,455$) samples. In the replication sample, concordance was computed to indicate predictive accuracy and risk scores were calculated using the linear predictions. Youden index was used to identify high-risk versus low-risk patients and cumulative lung cancer incidence was examined for high-risk and low-risk groups. Multivariable analyses identified a combination of clinical and radiologic predictors for incident lung cancer including ln-age, ln-pack-years smoking, a history of cancer, chronic obstructive pulmonary disease, and several radiologic markers including spiculation, ground glass opacity, and nodule size. The final model reliably detected patients who developed lung cancer in the replication sample ($C = 0.86$, sensitivity/specificity = 0.73/0.81). Cumulative incidence of lung cancer was elevated in high-risk versus low-risk groups [HR = 14.34; 95% confidence interval (CI), 8.17-25.18]. Quantification of reliable risk scores has high clinical utility, enabling physicians to better stratify treatment protocols to manage patient

care. The final model is among the first tools developed to predict incident lung cancer in patients presenting with a concerning pulmonary nodule.

[Optimal route planning for image-guided EBUS bronchoscopy.](#) Zang X1, Gibbs JD2, Cheirsilp R3, Byrnes PD4, Toth J5, Bascom R5, Higgins WE6. *Comput Biol Med.* 2019 Jul 26;112:103361. doi: 10.1016/j.compbiomed.2019.103361. [Epub ahead of print]

The staging of the central-chest lymph nodes is a major lung-cancer management procedure. To perform a staging procedure, the physician first uses a patient's 3D X-ray computed-tomography (CT) chest scan to interactively plan airway routes leading to selected target lymph nodes. Next, using an integrated EBUS bronchoscope (EBUS = endobronchial ultrasound), the physician uses videobronchoscopy to navigate through the airways toward a target node's general vicinity and then invokes EBUS to localize the node for biopsy. Unfortunately, during the procedure, the physician has difficulty in translating the preplanned airway routes into safe, effective biopsy sites. We propose an automatic route-planning method for EBUS bronchoscopy that gives optimal localization of safe, effective nodal biopsy sites. To run the method, a 3D chest model is first computed from a patient's chest CT scan. Next, an optimization method derives feasible airway routes that enables maximal tissue sampling of target lymph nodes while safely avoiding major blood vessels. In a lung-cancer patient study entailing 31 nodes (long axis range: [9.0 mm, 44.5 mm]), 25/31 nodes yielded safe airway routes having an optimal tissue sample size = 8.4 mm (range: [1.0 mm, 18.6 mm]) and sample adequacy = 0.42 (range: [0.05, 0.93]). Quantitative results indicate that the method potentially enables successful biopsies in essentially 100% of selected lymph nodes versus the 70-94% success rate of other approaches. The method also potentially facilitates adequate tissue biopsies for nearly 100% of selected nodes, as opposed to the 55-77% tissue adequacy rates of standard methods. The remaining nodes did not yield a safe route within the preset safety-margin constraints, with 3 nodes never yielding a route even under the most lenient safety-margin conditions. Thus, the method not only helps determine effective airway routes and expected sample quality for nodal biopsy, but it also helps point out situations where biopsy may not be advisable. We also demonstrate the methodology in an image-guided EBUS bronchoscopy system, used successfully in live lung-cancer patient studies. During a live procedure, the method provides dynamic real-time sample size visualization in an enhanced virtual bronchoscopy viewer. In this way, the physician vividly sees the most promising biopsy sites along the airway walls as the bronchoscope moves through the airways.

[Spatial and temporal heterogeneity of panel-based tumor mutational burden \(TMB\) in pulmonary adenocarcinoma: separating biology from technical artifacts.](#) Kazdal D1, Endris V2, Allgäuer M2, et al. *J Thorac Oncol.* 2019 Jul 23. pii: S1556-0864(19)30563-5. doi: 10.1016/j.jtho.2019.07.006. [Epub ahead of print]

INTRODUCTION: Tumor mutational burden (TMB) is an emerging biomarker used to identify patients more likely to benefit from immuno-oncology therapy. Aside from various unsettled technical aspects, biological variables like tumor cell content and intratumor heterogeneity (ITH) may play an important role in determining TMB. **METHODS:** TMB estimates were determined applying the TruSight™ Oncology 500 targeted sequencing panel. Spatial and temporal heterogeneity was analyzed by multi-region sequencing (2-6 samples) of 24 pulmonary adenocarcinomas and by sequencing a set of matched primary tumors, locoregional lymph node metastases, and distant metastases in 5 patients. **RESULTS:** On average, a coding region of 1.28 Mbp was covered with a mean read depth of 609x. Manual validation of the mutation-calls confirmed a good performance, but revealed noticeable misclassification during germline filtering. Different regions within a tumor showed considerable spatial TMB variance in 30% (7/24) of the cases (max difference 14.13 mut/Mbp). Lymph node derived TMB was significantly lower ($p=0.016$). In 13 cases, distinct mutational profiles were exclusive to different regions of a tumor, leading to higher values for simulated aggregated TMB. Combined, ITH and the aggregated TMB could result in

divergent TMB designation in 17% of the analyzed patients. TMB variation between primary tumor and distant metastases existed but was not profound. **CONCLUSIONS:** Our data demonstrate that, in addition to technical aspects like germline filtering, the tumor content and spatially divergent mutational profiles within a tumor are relevant factors influencing TMB estimation, revealing limitations of single sample based TMB estimations in a clinical context.

[Liquid Biopsy in Lung Cancer Screening: The Contribution of Metabolomics. Results of A Pilot Study.](#) Singhal S1, Rolfo C2, Maksymiuk AW3,4, et al. *Cancers (Basel)*. 2019 Jul 29;11(8). pii: E1069. doi: 10.3390/cancers11081069.

BACKGROUND: Lung cancer is the most common cause of cancer-related deaths worldwide. Early diagnosis is crucial to increase the curability chance of the patients. Low dose CT screening can reduce lung cancer mortality, but it is associated with several limitations. Metabolomics is a promising technique for cancer diagnosis due to its ability to provide chemical phenotyping data. The intent of our study was to explore metabolomic effects and profiles of lung cancer patients to determine if metabolic perturbations in the SSAT-1/polyamine pathway can distinguish between healthy participants and lung cancer patients as a diagnostic and treatment monitoring tool. **PATIENTS AND METHODS:** Plasma samples were collected as part of the SSAT1 Amantadine Cancer Study. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to identify and quantify metabolite concentrations in lung cancer patient and control samples. Standard statistical analyses were performed to determine whether metabolite concentrations could differentiate between healthy subjects and lung cancer patients, as well as risk prediction modeling applied to determine whether metabolic profiles could provide an indication of cancer progression in later stage patients. **RESULTS:** A panel consisting of 14 metabolites, which included 6 metabolites in the polyamine pathway, was identified that correctly discriminated lung cancer patients from controls with an area under the curve of 0.97 (95% CI: 0.875-1.0). **CONCLUSION:** When used in conjunction with the SSAT-1/polyamine pathway, these metabolites may provide the specificity required for diagnosing lung cancer from other cancer types and could be used as a diagnostic and treatment monitoring tool.

[Multidisciplinary approach to low-dose CT screening for lung cancer in a metropolitan community.](#) Shields LB1, Wilkett Barnes JG2, Buckley C2, Mikos GJ2, Rogers KN2, Hamm JT2, Flynn JM2, Hester ST3, Honaker JT3. *Fam Pract*. 2019 Jul 4. pii: cmz036. doi: 10.1093/fampra/cmz036. [Epub ahead of print]

BACKGROUND: Lung cancer is the primary cause of cancer death in men and women in the USA, led by Kentucky. In 2015, the Centers for Medicare and Medicaid Services initiated annual lung cancer screening with a low-dose computed tomography (LDCT) scan. This observational cohort study evaluated the multidisciplinary approach to this screening in our metropolitan community. **METHODS:** We present the prospective findings of patients who underwent a screening lung LDCT scan over a 2-year period at our institution in Kentucky. Patients who fulfilled the screening criteria were identified during an office visit with their primary care provider. **RESULTS:** Of the 4170 patients who underwent a screening lung LDCT scan, a total of 838 (20.9%) patients had nodules >4 mm. Of the 70 patients diagnosed with lung cancer, Stage 1 non-small cell lung cancer was most commonly detected [38 cases (54.3%)]. A follow-up lung LDCT scan (n = 897), pulmonary function test (n = 157), positron emission tomography scan (n = 12) and a lung biopsy (n = 53) were performed for certain individuals who had anomalies observed on the screening lung LDCT scan. A total of 42% of patients enrolled in group tobacco cessation classes quit smoking. **CONCLUSIONS:** This study provides a unique perspective of a lung LDCT scan screening program driven by primary care providers in a state plagued by cigarette smoking and lung cancer deaths and offers a valuable message into the prevention, high-risk screening and diagnosis of lung cancer.

[Prediction of Lung Cancer Screening Eligibility Using Simplified Criteria.](#) Triplette M1,2, Donovan LM3,4, Crothers K5, Madtes DK1,5, Au DH6,4. Ann Am Thorac Soc. 2019 Jul 12. doi: 10.1513/AnnalsATS.201903-239OC. [Epub ahead of print]

RATIONALE: Lung cancer screening with low-dose chest CT decreases mortality for high-risk current or former smokers. An essential eligibility criteria, lifetime smoking intensity (cigarette pack-years) is poorly recorded in electronic health records (EHRs), which may contribute to the overall low appropriate utilization of screening. **OBJECTIVES:** We sought to assess whether elements commonly extractable from the EHR may be useful as pre-screening tools to identify individuals for formal assessment of eligibility. **METHODS:** This is a cross-sectional cohort study of the National Health and Nutrition Examination Survey (NHANES) continuous survey, years 2011-2016. We included all adult participants with complete smoking interview data, weighted to construct a nationally representative cohort. We determined test characteristics for 5 criteria including eligibility age, smoking status (current, former or never) and current smoking intensity to predict lung cancer screening eligibility as defined by the United States Preventive Services Task Force and Centers for Medicare and Medicaid Services. **RESULTS:** Almost 9 million individuals, 3.8% of the population, may qualify for screening. Simplified criteria including the appropriate age range (55-77) and smoking status correctly discriminated individuals eligible for screening in most cases (AUC 0.92). When restricting to those of eligible age, smoking status retained fair predictive value (AUC 0.85). Incorporating additional information about current smoking behavior would allow for refinement in approaches to identify specific populations for screening. **CONCLUSIONS:** These simplified criteria may be useful in identifying individuals who are eligible for lung cancer screening. Applying these criteria as a pre-screening tool may improve appropriate referral and implementation of screening.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[Second Primary Lung Cancers Demonstrate Similar Survival with Wedge Resection and Lobectomy.](#) Lee DS, LaChappelle C, Taioli E, Kaufman A, Wolf A, Nicastrì D, Flores RM. Ann Thorac Surg. 2019 Jul 31. pii: S0003-4975(19)31064-1. doi: 10.1016/j.athoracsur.2019.06.023. [Epub ahead of print]

BACKGROUND: Patients who have undergone curative surgery for Stage I lung cancer require continued surveillance due to the risk of developing a second primary lung cancer. Early diagnosis allows for prompt intervention. However, as in primary cancers, the role of wedge versus lobar resections remains controversial. **METHODS:** The Surveillance Epidemiology and End Results (SEER) database was examined from 2004 to 2012 and all pathologically proven Stage I lung cancer cases that underwent cancer-directed surgery were selected. Cases which developed a second primary lung cancer 6 or more months after diagnosis of the first cancer were analyzed for survival after surgical treatment. **RESULTS:** Second primary lung cancer was identified in 625 cases, of which 331 (53.0%) were diagnosed with Stage I disease; 43.8% of patients underwent surgery alone, 30.9% received radiation alone, and 21.0% received neither surgery nor radiation. Of the patients who underwent surgery, 57.7% received wedge resection and 36.5% received a lobectomy. Surgical intervention was a positive predictor of survival - both wedge resection and lobectomy exhibited improved outcomes versus no surgery - but there was no statistically significant difference between the two surgical modalities. **CONCLUSIONS:** Wedge and lobar resections demonstrate similar survival for second primary lung cancers.

[Uniport video assisted thoracoscopic surgery \(U-VATS\) exhibits increased feasibility, non-inferior tolerance, and equal efficiency compared with multiport VATS and open thoracotomy in the elderly non-small cell lung cancer patients at early stage.](#) Zhao R1, Shi Z2, Cheng S1. *Medicine* (Baltimore). 2019 Jul;98(28):e16137. doi: 10.1097/MD.00000000000016137.

This study aimed to compare the feasibility, efficacy and safety among uniport video assisted thoracoscopic surgery (U-VATS), multiport VATS (M-TATS), and open thoracotomy in elderly non-small cell lung cancer (NSCLC) patients at early stage. One hundred ninety-one elderly NSCLC patients at early stage underwent U-VATS (N=73), M-VATS (N=56) or open thoracotomy (N=62) were included. Perioperative parameters, short-term outcomes, postoperative complications, and overall survival (OS) were assessed. Three-group analysis disclosed that operational duration, blood loss, drainage duration, hospital stay, pain score on the first day (D1) and D3, patients' global assessment (PGA), lasing air leak, infection, arrhythmia, and cardio-cerebrovascular events incidences were different among U-VATS, M-VATS, and open thoracotomy groups. Subsequently, 2-group analysis revealed that: In addition, there was no difference of OS among 3 groups, nor between any of the 2 groups. U-VATS presents with elevated feasibility, non-inferior tolerance, and similar efficacy compared with M-VATS and open thoracotomy in the elderly NSCLC patients at early stage.

[Evaluation of the residual lung function after thoracoscopic segmentectomy compared with lobectomy.](#) Tane S1, Nishio W2, Nishioka Y1, Tanaka H1, Ogawa H1, Kitamura Y1, Takenaka D3, Yoshimura M1. *Ann Thorac Surg*. 2019 Jul 11. pii: S0003-4975(19)31005-7. doi: 10.1016/j.athoracsur.2019.05.052. [Epub ahead of print]

BACKGROUND: Segmentectomy has shown a beneficial effect on preserving the lung function after resection. However, the preservable lung volume and changes after thoracoscopic segmentectomy remain unknown. We compared the residual lung function after thoracoscopic segmentectomy and lobectomy, using a novel three-dimensional computed tomography (3DCT)-based volumetric method. **METHODS:** Seventy-four patients who received thoracoscopic segmentectomy were matched to the 74 patients who received thoracoscopic lobectomy. Spirometry and computed tomography were performed before and six months after resection, and the ipsilateral residual preserved and non-operated lobe volume, and the contralateral lung volume were calculated using 3D-CT. The percentage of actual/predicted regional forced expiratory volume in 1 second (the preservation rate) in each lobe (measured by volumetry and spirometry), was compared with the extent of resection and procedural difficulty (typical or atypical segmentectomy). **RESULTS:** The postoperative lung function was significantly more well-preserved in segmentectomy than in lobectomy. After segmentectomy and lobectomy, the regional forced expiratory volume in 1 second of the ipsilateral unaffected lobe were increased in comparison to the preoperative value, while that of the residual lobe rescued by segmentectomy was decreased. The preservation rates of the residual and unaffected lobes were inversely and positively correlated, respectively, with the extent of the resected segment. The preservation rates of the residual lobe after typical or atypical segmentectomy were not significantly different. **CONCLUSIONS:** Although the decrease in the actual lung function of the residual lobe was greater than predicted and increased with increasing extent of resection, segmentectomy preserved the whole lung function better than lobectomy.

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

[Clinical outcomes in non-small cell lung cancer patients with an ultra-high expression of programmed death ligand-1 treated using pembrolizumab as a first-line therapy: A retrospective multicenter cohort study in Japan.](#) Eda Hiro R1, Kanazu M1, Kurebe H1, et al. *PLoS One*. 2019 Jul 31;14(7):e0220570. doi: 10.1371/journal.pone.0220570. eCollection 2019.

BACKGROUND: Pembrolizumab is currently approved as a first-line therapy for advanced non-small cell lung cancer (NSCLC) patients with a programmed death ligand-1 (PD-L1) expression $\geq 50\%$. However, the association between the efficacy of pembrolizumab and PD-L1 expression levels in patients with PD-L1 expression $\geq 50\%$ has not been fully elucidated. **METHODS:** We retrospectively analyzed patients with advanced NSCLC and a PD-L1 tumor proportion score (TPS) of $\geq 50\%$ who received pembrolizumab as a first-line therapy at 11 institutions in Japan between February 2017 and January 2018. Patients were divided into TPS 50-89% and TPS 90-100% (ultra-high PD-L1 expression) cohorts. **RESULTS:** In total, 149 patients were included: 99 (66.4%) and 50 (33.6%) patients were in the TPS 50-89% and TPS 90-100% cohorts, respectively. Baseline characteristics were similar between the TPS 90-100% and TPS 50-89% cohorts. The objective response rates (ORR) in the TPS 90-100% and TPS 50-89% cohorts were 58.0% and 46.5%, respectively ($p = 0.23$). Time to treatment failure (TTF) was longer in the TPS 90-100% cohort than in the TPS 50-89% cohort (hazard ratio [HR]: 0.67, 95% confidence interval (CI): 0.42-1.07; $p = 0.09$). Although TTF within 120 days after the initiation of pembrolizumab therapy was comparable between both cohorts ($p = 0.54$), TTF after 120 days was significantly longer in the TPS 90-100% cohort than in the TPS 50-89% cohort (HR: 0.22, 95% CI: 0.06-0.87; $p = 0.031$). Immune related adverse events of grade 3 or more occurred in 16.0% and 19.2% of patients in the TPS 90-100% and TPS 50-89% cohorts, respectively. **CONCLUSIONS:** The patients with an ultra-high PD-L1 expression continued pembrolizumab therapy longer, driven by a reduced risk of treatment failure in the late phase. PD-L1 expression levels might be a predictive biomarker of a first-line immunotherapy benefit in the late phase among NSCLC patients with TPS $\geq 50\%$.

[Treatment with Next-Generation ALK Inhibitors Fuels Plasma ALK Mutation Diversity.](#) Dagogo-Jack II, Rooney MM1, Lin JJ2, et al. Clin Cancer Res. 2019 Jul 29. pii: clincanres.1436.2019. doi: 10.1158/1078-0432.CCR-19-1436. [Epub ahead of print]

PURPOSE: Resistance to ALK tyrosine kinase inhibitors (TKIs) is often driven by ALK mutations. Here we investigated utility of plasma genotyping for identifying ALK resistance mutations at relapse on next-generation ALK TKIs. **EXPERIMENTAL DESIGN:** We analyzed 106 plasma specimens from 84 patients with advanced ALK-positive lung cancer treated with second- and third-generation ALK TKIs using a commercially available next-generation sequencing (NGS) platform (Guardant360). Tumor biopsies from TKI-resistant lesions underwent targeted NGS to identify ALK mutation. **RESULTS:** By genotyping plasma, we detected an ALK mutation in 46 (66%) of 70 patients relapsing on a second-generation ALK TKI. When post-alectinib plasma and tumor specimens were compared, there was no difference in frequency of ALK mutations (67% vs 63%), but plasma specimens were more likely to harbor ≥ 2 ALK mutations (24% vs 2%, $p=0.004$). Among 29 patients relapsing on lorlatinib, plasma genotyping detected an ALK mutation in 22 (76%), including 14 (48%) with ≥ 2 ALK mutations. The most frequent combinations of ALK mutations were G1202R/L1196M and D1203N/1171N. Detection of ≥ 2 ALK mutations was significantly more common in patients relapsing on lorlatinib compared to second-generation ALK TKIs (48% vs 23%, $p=0.017$). Among 15 patients who received lorlatinib after a second-generation TKI, serial plasma analysis demonstrated that 8 (53%) acquired ≥ 1 new ALK mutations on lorlatinib. **CONCLUSIONS:** ALK resistance mutations increase with each successive generation of ALK TKI and may be underestimated by tumor genotyping. Sequential treatment with increasingly potent ALK TKIs may promote acquisition of ALK resistance mutations leading to treatment-refractory compound ALK mutations.

[Patient-reported outcomes and quality of life in advanced ALK+ non-small-cell lung cancer trial of brigatinib \(ALTA\).](#) Lenderking WR1, Lin H2, Speck RM1, Zhu Y2, Huang H2, Huang J2, Kerstein D2, Langer CJ2. Future Oncol. 2019 Jul 31. doi: 10.2217/fon-2019-0185. [Epub ahead of print]

AIM: Patient-reported outcomes (PRO) can support clinically relevant primary end points.

MATERIALS & METHODS: The ALTA trial, an open-label, Phase II, randomized dose-comparison study, evaluated the safety and efficacy of brigatinib in ALK+ non-small-cell lung cancer. PRO data collection included the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (QLQ-C30). A linear mixed model for repeated measures was used to analyze change from baseline in the Global Health Status/Quality of Life subscale (GHS/QOL), with a change of greater than or equal to ten points deemed meaningful. **RESULTS:** Improvement in mean GHS/QOL scores was statistically significant in the majority of treatment cycles; <10% of patients experienced a meaningful worsening of their GHS/QOL and symptom scores. **CONCLUSION:** PRO-measured benefits are consistent with objective response benefits associated with brigatinib.

[Clinical outcomes to pemetrexed-based versus non-pemetrexed-based platinum doublets in patients with KRAS-mutant advanced non-squamous non-small cell lung cancer.](#)

Ricciuti B1, Brambilla M2, Cortellini A3, Clin Transl Oncol. 2019 Jul 22. doi: 10.1007/s12094-019-02175-y. [Epub ahead of print]

PURPOSE: KRAS mutation has been associated with enhanced dependency on the folate metabolism in preclinical studies. However, whether KRAS mutation correlates to increased sensitivity to pemetrexed in patients with advanced NSCLC is unknown. **METHODS:** Patients with advanced non-squamous NSCLC who had a documented EGFR and ALK WT genotype with simultaneous KRAS mutation assessment were evaluated for clinical outcome to pemetrexed- and non-pemetrexed-based first-line platinum doublet according to KRAS mutation status. **RESULTS:** Of 356 patients identified, 138 harbored a KRAS mutation. Among KRAS-mutant NSCLCs, those treated with platinum/pemetrexed (81/138) had significantly lower ORR (30.9% versus 47.4%, $P = 0.05$), DCR (51.8% versus 71.9%, $P = 0.02$) and shorter median progression-free survival [mPFS 4.1 versus 7.1 months, HR 1.48 (95% CI 1.03-2.12), $P = 0.03$] and median overall survival [mOS 9.7 versus 26.9 months, HR 1.93 (95% CI 1.27-2.94), $P = 0.002$] compared to those who received a non-pemetrexed-based platinum doublet (57/138). No difference in ORR, DCR, mPFS and mOS was observed between KRAS WT patients who received a pemetrexed-based (124/218) versus non-pemetrexed base platinum doublets (94/218). After adjusting for performance status, age and the presence of brain metastasis at baseline, treatment with pemetrexed-based platinum doublet was associated with an increased risk of death [HR 2.27 (95% CI 1.12-4.63), $P = 0.02$] among KRAS-mutant patients in multivariate analysis. **CONCLUSION:** Patients with KRAS-mutant lung adenocarcinoma have a poorer outcome on pemetrexed-based first-line chemotherapy. Whether KRAS-mutant NSCLCs should be excluded from pemetrexed-containing regimens should be assessed prospectively.

[Pemetrexed, Bevacizumab, or the Combination As Maintenance Therapy for Advanced](#)

[Nonsquamous Non-Small-Cell Lung Cancer: ECOG-ACRIN 5508.](#) Ramalingam SS1, Dahlberg SE2, Belani CP3, et al. J Clin Oncol. 2019 Jul 30;JCO1901006. doi: 10.1200/JCO.19.01006. [Epub ahead of print]

PURPOSE: Pemetrexed or bevacizumab is used for maintenance therapy of advanced nonsquamous non-small-cell lung cancer (NSCLC). The combination of bevacizumab and pemetrexed has also demonstrated efficacy. We conducted a randomized study to determine the optimal maintenance therapy. **PATIENTS AND METHODS:** Patients with advanced nonsquamous NSCLC and no prior systemic therapy received carboplatin (area under the curve, 6), paclitaxel (200 mg/m²), and bevacizumab (15 mg/kg) for up to four cycles. Patients without progression after four cycles were randomly assigned to maintenance therapy with bevacizumab (15 mg/kg), pemetrexed (500 mg/m²), or a combination of the two agents. The primary end point was overall survival, with bevacizumab serving as the control group. **RESULTS:** Of the 1,516 patients enrolled, 874 (57%) were randomly assigned after induction therapy to one of the three

maintenance therapy groups. With a median follow-up of 50.6 months, median survival with pemetrexed was 15.9 months, compared with 14.4 months with bevacizumab (hazard ratio [HR], 0.86; P = .12); median survival with pemetrexed and bevacizumab was 16.4 months (HR, 0.9; P = .28); median progression-free survival was 4.2, 5.1 (HR, 0.85; P = .06), and 7.5 months (HR, 0.67; P < .001) for the three groups, respectively. Incidence of worst grade 3 to 4 toxicity was 29%, 37%, and 51%, respectively, for bevacizumab, pemetrexed, and the combination regimen. **CONCLUSION:** Single-agent bevacizumab or pemetrexed is efficacious as maintenance therapy for advanced nonsquamous NSCLC. Because of a lack of survival benefit and higher toxicity, the combination of bevacizumab and pemetrexed cannot be recommended.

Brief Report: SWOG S1400C (NCT02154490)-A Phase II Study of Palbociclib for Previously Treated Cell Cycle Gene Alteration Positive Patients with Stage IV Squamous Cell Lung Cancer (Lung-MAP Sub-study). Edelman MJ1, Redman MW2, Albain KS3, et al. J Thorac Oncol. 2019 Jul 11. pii: S1556-0864(19)30557-X. doi: 10.1016/j.jtho.2019.06.027. [Epub ahead of print]

PURPOSE: Lung-MAP (SWOG S1400) is a master platform trial assessing targeted therapies in squamous non-small cell lung cancer (sqNSCLC). The objective of study C (S1400C) was to evaluate the response rate to palbociclib, a CDK 4/6 inhibitor, in patients with cell cycle gene abnormalities. **METHODS:** Patients with sqNSCLC, Performance status (PS) 0-2, normal organ function, who had progressed after at least one prior platinum-based chemotherapy with CDK 4 or CCND1/2/3 amplifications on tumor specimens were eligible. The study was originally designed as a phase II/III trial comparing palbociclib to docetaxel, but was modified to a single arm phase II trial with primary endpoint of response when immunotherapy was approved. If two or fewer responses were seen in the first 20 pts, then the study would cease enrollment. **RESULTS:** Eighty-eight patients (9% of patients screened) were assigned to S1400C, and 53 patients enrolled (including 17 to docetaxel). One patient registered to docetaxel was re-registered to receive palbociclib after progression on docetaxel. The frequency of cell cycle gene alterations in the eligible palbociclib patients (N=32) were: CCND1 (n=26, 81%), CCND2 (n=3, 9%), CCND3 (n=2, 6%), CDK4 (n=1, 3%). Thirty-two eligible patients received palbociclib. There were two partial responses (6% RR, 95% CI: 0%-15%), both with CCND1 amplification. Twelve patients had stable disease (38%, 95% CI: 21%-54%). Median progression-free survival was 1.7 months (95% CI: 1.6-2.9 months) and median overall survival was 7.1 months (95% CI: 4.2-12.5). **CONCLUSIONS:** Palbociclib as monotherapy failed to demonstrate the pre-specified criteria for advancement to phase III testing.

Establishment of a non-small-cell lung cancer-liver metastasis patient-derived tumor xenograft model for the evaluation of patient-tailored chemotherapy. Yang X1, Meng G2. Biosci Rep. 2019 Jul 5;39(7). pii: BSR20182082. doi: 10.1042/BSR20182082. Print 2019 Jul 31.

In order to optimize patient-tailored chemotherapy, a non-small-cell lung cancer (NSCLC)-liver metastasis patient-derived tumor xenograft (PDTX) model is developed. Computed tomography (CT)-guided NSCLC percutaneous biopsy was subcutaneously inoculated into the flank of non-obese diabetic/severe combined immunodeficiency (NOD/SCID) female mice (PDTX F1) and allowed to reach 500 mm³ volume. Then, the tumors were re-transplanted into Balb/c nude mice and liver metastasis was confirmed (PDTX F2), which were further assigned into doxorubicin (DOX), docetaxel (DTX), and non-treatment control group. H&E staining and Keratin 20 (CK20) staining were applied to determine the consistency of PDTX models and primary tumors. Tumor growth curve, body weight, and the expression of p65 nuclear factor (NF)- κ B and the secretion of interferon (IFN)- γ were investigated. The successive transplant procedure can induce the NSCLC-liver metastasis PDTX model, and morphological and structural characteristics of PDTX models (F2) were in accordance with primary tumors. DOX and DTX could delay tumor growth, activate the NF- κ B pathway, and promote IFN- γ secretion in the PDTX

models. The NSCLC-liver metastasis PDTX model is established and provides a powerful mean to assess chemotherapeutic efficacy.

Which Is Better EGFR-TKI Followed by Osimertinib: Afatinib or Gefitinib/Erlotinib? Tamiya M1, Tamiya A2, Suzuki H3, et al. *Anticancer Res.* 2019 Jul;39(7):3923-3929. doi: 10.21873/anticancer.13544.

BACKGROUND/AIM: Treatment with EGFR-tyrosine kinase inhibitor (TKI) shows a durable response against NSCLC harboring EGFR mutation; however, treatment resistance occurs within 1-1.5 years following first-line EGFR-TKIs [first- and second-generation (G) TKIs]. When resistant NSCLC exhibits T790M mutations, osimertinib is the standard therapy. However, intratumoral heterogeneity and clonal evolution may occur in NSCLC. Afatinib may overcome tumor heterogeneity, leading to T790M clonal purity. We aimed to determine whether NSCLC treatment with afatinib followed by osimertinib (afatinib group) provides higher therapeutic efficacy than other 1st-G EGFR-TKIs followed by osimertinib (1st-G group). **MATERIALS AND METHODS:** This multicenter retrospective study evaluated outcomes between afatinib group and 1st-G group. We analyzed clinical data from NSCLC patients receiving osimertinib after progression following 1st- or 2nd-G EGFR-TKIs between March 28, 2016 and March 31, 2018. Patients with performance status (PS) 0-2 were enrolled to reduce bias of patients' conditions. **RESULTS:** We enrolled 111 patients treated with osimertinib. The median age was 69 (range: 39-88) years. Out of 111 patients, 33 (29.7%) were men, 100 (90%) had PS 0-1, and 35 (31.5%) were in the afatinib group. The objective RR and DCR were significantly higher in the afatinib group than in the 1st-G group [82.9% vs. 53.9% (p=0.0065); 91.4% vs. 71.1% (p=0.032)]. The median PFS tended higher in the afatinib group than in the 1st-G group (15.6 vs. 8.9 months, p=0.195). **CONCLUSION:** Afatinib followed by osimertinib may provide better outcomes for T790M-positive NSCLC than 1st-G EGFR-TKIs. Afatinib followed by osimertinib may be a therapeutic option for NSCLC harboring EGFR mutation.

NSCLC - RADIOTHERAPY

Predictors of Respiratory Decline Following Stereotactic Ablative Radiotherapy to Multiple Lung Tumors.

Moding EJ1, Liang R1, Lartey FM1, Maxim PG1, Sung A2, Diehn M3, Loo BW Jr4, Gensheimer MF5. *Clin Lung Cancer.* 2019 Jul 4. pii: S1525-7304(19)30142-1. doi: 10.1016/j.clcc.2019.05.015. [Epub ahead of print]

INTRODUCTION: Stereotactic ablative radiotherapy (SABR) is highly effective at controlling early stage primary lung cancer and lung metastases. Although previous studies have suggested that treating multiple lung tumors with SABR is safe, post-treatment changes in respiratory function have not been analyzed in detail. **PATIENTS AND METHODS:** We retrospectively identified patients with 2 or more primary lung cancers or lung metastases treated with SABR and analyzed clinical outcomes and predictors of toxicity. We defined a composite respiratory decline endpoint to include increased oxygen requirement, increased dyspnea scale, or death from respiratory failure not owing to disease progression.

Clinical Outcomes Following Stereotactic Body Radiation Therapy (SBRT) for Stage I Medically Inoperable Small Cell Lung Carcinoma: A Multi-Institutional Analysis From the RSSearch Patient Registry.

Singh R1, Ansinelli H2, Sharma D3, Jenkins J4, Davis J4, Vargo JA5, Sharma S3,6. *Am J Clin Oncol.* 2019 Jul;42(7):602-606. doi: 10.1097/COC.0000000000000561.

OBJECTIVES: To utilize the RSSearch Patient Registry (RSSPR) to examine local control (LC), overall survival (OS), and toxicities following stereotactic body radiation therapy (SBRT) for stage I (T1-T2/N0) medically inoperable small cell lung carcinoma (SCLC). **MATERIALS AND METHODS:** We searched the RSSPR for medically inoperable stage I SCLC patients treated with definitive SBRT. Potential predictive factors of OS were estimated using the Kaplan-Meier method as well as a Cox proportional

hazards model. **RESULTS:** Twenty-one patients were identified with medically inoperable stage I SCLC that met inclusion criteria. Fourteen patients had stage IA SCLC (T1N0) and 7 patients had stage IB SCLC (T2N0) with a median gross tumor volume of 10.1 cm (range: 0.72 to 41.4 cm). The median number of fractions was 4 (range: 3 to 5), and the median BED10 was 105.6 Gy10 (range: 72 to 239.7 Gy10). Four patients received adjuvant chemotherapy. One- and 2-year actuarial OS rates were 73.1% (95% confidence interval [CI]: 36.8%-90.1%) and 36.6% (95% CI: 9.0%-65.7%), respectively. Factors found to be associated with 1-year OS on univariate analysis included T2 disease (85.5% vs. 33.3%; P=0.03), adjuvant chemotherapy (100% vs. 66.3%; P=0.11), and gross tumor volume \geq 10 cm (100% vs. 52.5%; P=0.10). On multivariate analysis, adjuvant chemotherapy was associated with improved OS (hazard ratio=0.07 [95% CI: 0.13-0.37; P=0.002]). The 1-, 2-, and 3-year LC rates were 100%, and 1- and 2-year progression-free survival (PFS) rates were 85.7% (95% CI: 33.4-97.9%) and 42.9% (95% CI: 1.1-85.3%), respectively. Similar to OS, patients with T1N0 disease had superior PFS as compared to T2N0 disease (P=0.01). Toxicities were reported by 3/21 (14.3%) of patients with none \geq grade 3 and no esophageal toxicities. **CONCLUSIONS:** SBRT was well-tolerated in the treatment of stage I SCLC with excellent LC achieved. Patients with T1N0 stage IA SCLC were noted to have improved PFS and OS following SBRT as compared with T2N0 Stage IB SCLC. Adjuvant chemotherapy was found to result in improved OS for stage I SCLC patients over SBRT alone.

[Comparing survival predicted by the diagnosis-specific Graded Prognostic Assessment \(DS-GPA\) to actual survival in patients with 1-10 brain metastases treated with stereotactic radiosurgery.](#)

Nagtegaal S1, Claes A2, Suijkerbuijk K3, Schramel F4, Snijders T5, Verhoeff J2. *Radiother Oncol.* 2019 Jul 11;138:173-179. doi: 10.1016/j.radonc.2019.06.033. [Epub ahead of print]

BACKGROUND AND PURPOSE: Multiple prognostic models for predicting survival after treatment for brain metastases have been developed. One of them, the diagnosis-specific Graded Prognostic Assessment (DS-GPA), has been developed to predict the median survival for brain metastases from the most frequent primary sites: lung carcinoma, breast cancer, melanoma, renal cell cancer and gastrointestinal tumours. In this study we aim to compare the survival predicted by the DS-GPA to actual survival, and to assess this models performance on both population and individual levels. **METHODS:** We identified a consecutive cohort of patients treated with SRS for brain metastases in our institute. DS-GPA scores were calculated for each patient, and the median survival for each DS-GPA group was calculated. Differences in survival between DS-GPA groups were tested with Wilcoxon Signed Rank tests and log-rank tests. **RESULTS:** In total 367 patients were included in the analysis. Median survival in our cohort is largely comparable to corresponding DS-GPA cohorts, but some notable differences are present. There was a significantly shorter median survival (15.4 months, compared to 26.5 months) in the adenocarcinoma NSCLC subgroup with a GPA score of 2.3-3. We confirmed the significant differences in survival time for most cancer-specific subgroups. **CONCLUSION:** DS-GPA seems to be a reliable tool to classify patients with brain metastases treated with SRS into prognostic subgroups. However, we found some aberrations from predicted median survival times, which may be due to specific characteristics of the populations of patients treated with SRS versus other patients.

[Synchronous Oligometastatic Non-small Cell Lung Cancer Managed With Curative-Intent Chemoradiation Therapy: Long-term Outcomes From a Single Institution.](#)

Yegya-Raman N1, Aisner J2, Kim S3,4, Sayan M1, Li D1, Langenfeld J5, Patel M2, Malhotra J2, Jabbour SK1. *Adv Radiat Oncol.* 2019 Mar 22;4(3):541-550. doi: 10.1016/j.adro.2019.03.005. eCollection 2019 Jul-Sep.

PURPOSE: We examined long-term clinical outcomes among patients with synchronous oligometastatic non-small cell lung cancer (NSCLC) treated at our institution with definitive thoracic chemoradiation therapy (CRT) and local therapy to all oligometastatic lesions. **METHODS AND MATERIALS:** A retrospective review identified 38 patients with synchronous oligometastatic NSCLC (\leq 3 metastatic

lesions) who were treated with definitive CRT to the primary tumor and regional lymph nodes between 1999 and 2017 at our institution. Of the 38 patients, 27 patients (71%) received induction chemotherapy, all of whom responded or stabilized with initial systemic therapy before consideration of CRT. Most patients received chemotherapy concurrently with radiation therapy (n = 32; 84%) and local therapy to the metastatic disease site(s) (n = 34; 89%). We assessed patterns of progression or failure, overall survival (OS), progression-free survival (PFS), and toxicities. **RESULTS:** The median follow-up duration was 54.9 months. Most patients (84%) presented with N2 to N3 disease. The brain or central nervous system was the most common site of disease progression and occurred in 16 of 28 patients (57%) experiencing any progression and 10 of 16 patients (63%) who initially presented with brain oligometastases. Median OS was 21.1 months (95% confidence interval [CI], 15.6-49.0 months), and median PFS 9.7 months (95% CI, 8.2-14.4 months). The 1-, 2-, and 4-year OS rates were 75.7%, 45.0%, and 33.7%, respectively. On multivariate analysis, both locoregional progression (hazard ratio: 5.8; 95% CI, 2.2-15.0; P = .0003) and distant progression (hazard ratio: 6.0; 95% CI, 2.3-15.4; P = .0002), when treated as time-dependent covariates, were associated with inferior OS. Grade ≥ 3 esophagitis occurred in 9% and grade ≥ 3 pneumonitis in 5% of patients with evaluable data. **CONCLUSIONS:** Patients with synchronous oligometastatic NSCLC and a high regional nodal burden treated with definitive thoracic CRT experienced favorable survival outcomes and low toxicity. At our institution, treating oligometastatic disease with CRT after systemic therapy is incorporated into the treatment plan from the onset of therapy, and we monitor the neuraxis closely for progression during and after treatment. Future research should focus on novel treatment combinations, such as immunotherapy or targeted systemic therapy as appropriate to further improve tumor control and survival. **RESULTS:** A total of 86 patients treated with SABR to 203 lung tumors were analyzed. A total of 21.8% and 41.8% of patients developed composite respiratory decline at 2 and 4 years, respectively. When accounting for intrathoracic disease progression, 12.7% of patients developed composite respiratory decline at 2 years. Of the patients, 7.9% experienced grade 2 or greater radiation pneumonitis. No patient- or treatment-related factor predicted development of respiratory decline. The median overall survival was 46.9 months, and the median progression-free survival was 14.8 months. The cumulative incidence of local failure was 9.7% at 2 years. **CONCLUSION:** Although our results confirm that SABR is an effective treatment modality for patients with multiple lung tumors, we observed a high rate of respiratory decline after treatment, which may be owing to a combination of treatment and disease effects. Future studies may help to determine ways to avoid pulmonary toxicity from SABR.

[Stereotactic Ablative Body Radiotherapy Versus Radical Radiotherapy: Comparing Real-World Outcomes in Stage I Lung Cancer.](#) Phillips II, Sandhu S2, Lichtenborg M3, Harden S4. Clin Oncol (R Coll Radiol). 2019 Jul 31. pii: S0936-6555(19)30293-6. doi: 10.1016/j.clon.2019.07.013. [Epub ahead of print]

AIMS: Stereotactic ablative body radiotherapy (SABR) is now considered the standard of care for medically inoperable stage I non-small cell lung cancer (NSCLC). The English National Cancer Registration and Analysis Service (NCRAS) collects data on all patients diagnosed with lung cancer, including information on treatment. We wanted to compare outcomes for patients with stage I NSCLC treated with radical radiotherapy with either SABR or fractionated radiotherapy. **MATERIALS AND METHODS:** All patients diagnosed with stage I NSCLC in 2015 and 2016 were identified from the CRAS dataset, validated by the National Lung Cancer Audit, and their treatment data were collated. For patients who received radiotherapy, those receiving radical dose fractionations, including SABR, were identified through linkage to the national Radiotherapy Dataset. Clinical outcomes for those receiving SABR or more fractionated radical radiotherapy were compared using univariate and fully adjusted Cox proportional hazards models. **RESULTS:** In total, 12 384 patients with stage I NSCLC were identified during the study period; 53.5% underwent surgical resection, 24.3% received no documented treatment,

18.6% received radical radiotherapy and 3.5% received other non-curative-intent treatments. For those receiving radical radiotherapy, 69% received SABR and 31% received fractionated treatment. The hazard ratio of death for the 1587 patients who received SABR was 0.69 (95% confidence interval 0.61-0.79) compared with 717 patients who received radical fractionated radiotherapy; this benefit was seen for both stage Ia and stage Ib disease. The median overall survival was also longer for SABR versus radical radiotherapy (715 days versus 648 days). Exploratory travel time analysis shows that compared with stage I NSCLC patients receiving SABR, those receiving fractionated radiotherapy and those receiving no active treatment would have to travel longer and further to reach their nearest radiotherapy SABR centre. **CONCLUSION:** This study adds to the data that SABR has a survival benefit when compared with fractionated radical radiotherapy. Although the use of SABR increased in England over this study period, it has still not reached levels of use seen in other countries. This study also highlights that one quarter of stage I NSCLC patients overall received no active treatment.

[Stereotactic radiosurgery with and without checkpoint inhibition for patients with metastatic non-small cell lung cancer to the brain: a matched cohort study.](#) Shepard MJ1, Xu Z1, Donahue J2, et al. *J Neurosurg.* 2019 Jul 26;1-8. doi: 10.3171/2019.4.JNS19822. [Epub ahead of print]

OBJECTIVE: Immune checkpoint inhibitors (ICIs) improve survival in patients with advanced non-small cell lung cancer (NSCLC). Clinical trials examining the efficacy of ICIs in patients with NSCLC excluded patients with untreated brain metastases (BMs). As stereotactic radiosurgery (SRS) is commonly employed for NSCLC-BMs, the authors sought to define the safety and radiological and clinical outcomes for patients with NSCLC-BMs treated with concurrent ICI and SRS. **METHODS:** A retrospective matched cohort study was performed on patients who had undergone SRS for one or more NSCLC-derived BMs. Two matched cohorts were identified: one that received ICI before or after SRS within a 3-month period (concurrent ICI) and one that did not (ICI naive). Locoregional tumor control, peritumoral edema, and central nervous system (CNS) adverse events were compared between the two cohorts. **RESULTS:** Seventeen patients (45 BMs) and 34 patients (92 BMs) composed the concurrent-ICI and ICI-naive cohorts, respectively. There was no statistically significant difference in overall survival (HR 0.99, 95% CI 0.39-2.52, $p = 0.99$) or CNS progression-free survival (HR 2.18, 95% CI 0.72-6.62, $p = 0.11$) between the two groups. Similarly, the 12-month local tumor control rate was 84.9% for tumors in the concurrent-ICI cohort versus 76.3% for tumors in the ICI-naive cohort ($p = 0.94$). Further analysis did reveal that patients receiving concurrent ICI had increased rates of CNS complete response for BMs treated with SRS (8/16 [50%] vs 5/32 [15.6%], $p = 0.012$) per the Response Assessment in Neuro-Oncology (RANO) criteria. There was also a shorter median time to BM regression in the concurrent-ICI cohort (2.5 vs 3.1 months, $p < 0.0001$). There was no increased rate of radiation necrosis or intratumoral hemorrhage in the patients receiving concurrent ICI (5.9% vs 2.9% in ICI-naive cohort, $p = 0.99$). There was no significant difference in the rate of peritumoral edema progression between the two groups (concurrent ICI: 11.1%, ICI naive: 21.7%, $p = 0.162$). **CONCLUSIONS:** The concurrent use of ICI and SRS to treat NSCLC-BM was well tolerated while providing more rapid BM regression. Concurrent ICI did not increase peritumoral edema or rates of radiation necrosis. Further studies are needed to evaluate whether combined ICI and SRS improves progression-free survival and overall survival for patients with metastatic NSCLC.

[Change in apparent diffusion coefficient is associated with local failure after stereotactic body radiation therapy for non-small cell lung cancer: a prospective clinical trial.](#)

Sampath S1, Rahmanuddin S2, Sahoo P3, Frankel P4, Boswell S5, Wong J2, Rotter A2, Rockne R3, Wong J6, Park JM7. *Int J Radiat Oncol Biol Phys.* 2019 Jul 1. pii: S0360-3016(19)33424-8. doi: 10.1016/j.ijrobp.2019.06.2536. [Epub ahead of print]

PURPOSE: Response assessment with computed tomography (CT) following stereotactic body radiation therapy (SBRT) for non-small cell lung cancer (NSCLC) is challenging due to a myriad of anatomical changes that can occur after treatment. Diffusion weighted magnetic resonance imaging (DW-MRI) may provide additional data to guide therapy response. The primary objective was to evaluate the effect of SBRT on the mean apparent diffusion coefficient (ADC). **MATERIALS/METHODS:** This is a prospective clinical study of patients with NSCLC who received SBRT to the primary lung lesion. Patients underwent MRI scans prior to, and at 1 month after completion of SBRT. MRI consisted of T1- and T2-weighted sequences, along with post-contrast, dynamic-contrast, and diffusion weighted sequences with construction of ADC maps. Two blinded radiologists generated the ADC. SBRT was given over 5 fractions. **RESULTS:** A total of 13 patients were enrolled. Twelve patients were eligible for analysis. An average increase of 50% and 46% in mean single-plane ADC was observed after treatment by readers 1 and 2, respectively ($p < 0.01$, both reviewers). There was good inter-observer agreement of single-plane ADC values between the 2 radiologists (Pearson correlation 0.85 [baseline], 0.89 [1 month post-SBRT], $p < 0.001$ for both). There was also a significant 18% increase in mean volumetric ADC on the 1 month scan, (Wilcoxon $p = 0.02$). Two patients developed a local failure after SBRT, one at 6 months, the other at 34 months. Using a threshold of volumetric ADC increase of greater than 40%, 2/2 patients demonstrated local failure compared to 0/10 patients below this limit. **CONCLUSION:** A statistically significant increase in ADC was observed 1 month after treatment. An ADC increase of 40% at 1 month was associated with a higher rate of local failure. This pilot study provides impetus for studying ADC as a radiomic biomarker in patients receiving lung SBRT for NSCLC.

SMALL CELL LUNG CANCER - SCLC

[CDYL promotes the chemoresistance of small cell lung cancer by regulating H3K27 trimethylation at the CDKN1C promoter.](#) Qiu Z1,2, Zhu W1, Meng H1, Tong L1,3, Li X1, Luo P1, Yi L1, Zhang X1, Guo L4, Wei T1, Zhang J1. *Theranostics*. 2019 Jul 9;9(16):4717-4729. doi: 10.7150/thno.33680. eCollection 2019.

RATIONALE: Chemoresistance frequently occurs in patients with small cell lung cancer (SCLC) and leads to a dismal prognosis. However, the mechanisms underlying this process remain largely unclear. **METHODS:** The effects of chromodomain Y-like (CDYL) on chemoresistance in SCLC were determined using Western blotting, immunohistochemistry, cell counting kit-8 assays, flow cytometry, and tumorigenicity experiments, and the underlying mechanisms were investigated using mRNA sequencing, chromatin immunoprecipitation-qPCR, electrophoretic mobility shift assays, co-immunoprecipitation, GST pull down assays, bisulfite sequencing PCR, ELISA, and bioinformatics analyses. **RESULTS:** CDYL is expressed at high levels in chemoresistant SCLC tissues from patients, and elevated CDYL levels correlate with an advanced clinical stage and a poor prognosis. Furthermore, CDYL expression is significantly upregulated in chemoresistant SCLC cells. Using gain- and loss-of-function methods, we show that CDYL promotes chemoresistance in SCLC in vitro and in vivo. Mechanistically, CDYL promotes SCLC chemoresistance by silencing its downstream mediator cyclin-dependent kinase inhibitor 1C (CDKN1C). Further mechanistic investigations showed that CDYL recruits the enhancer of zeste homolog 2 (EZH2) to regulate trimethylation of lysine 27 in histone 3 (H3K27me3) at the CDKN1C promoter region and promotes transcriptional silencing. Accordingly, the EZH2 inhibitor GSK126 de-represses CDKN1C and decreases CDYL-induced chemoresistance in SCLC. Principal conclusions: **BASED ON THESE RESULTS**, the CDYL/EZH2/CDKN1C axis promotes chemoresistance in SCLC, and these markers represent promising therapeutic targets for overcoming chemoresistance in patients with SCLC.

Prognostic value of metabolic parameters on baseline 18F-FDG PET/CT in small cell lung cancer.

Araz M1, Soydal C2, Özkan E2, Sen E3, Nak D2, Kucuk ON2, Gönüllü U3, Kir KM2. Q J Nucl Med Mol Imaging. 2019 Jul 1. doi: 10.23736/S1824-4785.19.03169-8. [Epub ahead of print]

BACKGROUND: Maximum standardized uptake value (SUVmax) is the primary quantitative parameter given in 18F-FDG PET/CT reports. Calculations derived from three dimensional metabolic volumetric images have been proposed to be more successful than SUVmax alone in prognostication with a lower interobserver variability in many cancers. We aimed to determine the prognostic value of metabolic parameters derived from 18F-FDG PET/CT studies in small cell lung cancer (SCLC) patient population with a long follow up time. **METHODS:** In this study, 38 consecutive SCLC patients (34M, 4F, age:65.76 ±8.18 years) who were referred to 18F-FDG PET/CT for staging between October 2006-January 2011 were included. SUVmax, SUVmean, SUVpeak, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were calculated. Overall survival (OS) was calculated from the date of the initial PET/CT to death from any cause. Survival tables were obtained and Kaplan Meier curves were reconstructed. Mantel- Cox regression analysis was performed in order to investigate if any of these parameters have an effect on survival along with other clinical risk factors. **RESULTS:** Median SUVmax, SUVmean, SUVpeak, MTV, TLG and LDH values were calculated as 13.9g/dL, 6.4g/dL,10.69g/dL, 147 cm³, 1898.52 and 375U/L respectively. Median follow-up was 761.23±873.21 days (25,37 months, range:110-3338 days). Since basal 18F-FDG PET/CT scans, all patients were lost in the follow up except for two patients. MTV was a significant prognostic factor in SCLC patients. Estimated mean survival times were 261.0±45.6 (95%CI:171.6-350.3) days in patients with MTV value above the calculated median 147, and 577.0±124.0 (95%CI 333.7-820.2) days in patients with MTV<147. The difference was statistically significant with a p=0.037. **CONCLUSIONS:** Baseline whole body MTV reflecting total tumor load is a prognostic index in SCLC. SUV is insufficient to predict prognosis.

Determination of Risk Factors Related to Supraclavicular Recurrence for Limited-Stage Small Cell Lung Cancer (SCLC) Patients.

Guan Y1, Zhang X1. Med Sci Monit. 2019 Jul 5;25:4968-4973. doi:

10.12659/MSM.916279.

BACKGROUND: This research aimed to determine high-risk factors of supraclavicular recurrence for limited-stage small cell lung cancer (LS-SCLC) patients to discover a potential subpopulation that can benefit from prophylactic supraclavicular irradiation (PSCI). **MATERIAL AND METHODS:** Between July 2006 and July 2011, LS-SCLC patients without supraclavicular lymph node (SCLN) involvement consecutively treated with concurrent chemo-radiation but without PSCI in the Radiotherapy Department of the Cancer Institute and Hospital of Tianjin Medical University, were retrospectively analyzed. SCLN recurrence rate, overall survival (OS), and distant metastasis-free survival (DMFS) were assessed. Binary logistic regression analysis was conducted to discover the high-risk factors related to the SCLN recurrence. The receiver operating characteristic (ROC) curves were drawn to evaluate logistic regression model prediction performance. **RESULTS:** Eighty-eight LS-SCLC patients were analyzed in this study. During 99 months (ranging from 72 months to 124 months) for survivors, 28 (31.8%) had SCLN recurrence. There were significant differences for median DMFS and OS between LS-SCLC patients with and without SCLN recurrence. The logistic regression model revealed that lymphadenopathy at mediastinal level 2 and level 3 prior to chemotherapy were significantly associated with SCLN recurrence, which was validated by ROC. **CONCLUSIONS:** Lymphadenopathy at mediastinal level 2 and level 3 prior to chemotherapy were the high-risk factors associated with SCLN recurrence for patients with LS-SCLC. Further work is needed to determine whether patients with these factors can benefit from PSCI.

[**A prospective evaluation of whole brain volume loss and neurocognitive decline following hippocampal-sparing prophylactic cranial irradiation for limited-stage small-cell lung cancer.**](#)

Gui C1, Chintalapati N1, Hales RK1, et al. J Neurooncol. 2019 Jul 13. doi: 10.1007/s11060-019-03235-7. [Epub ahead of print]

INTRODUCTION: This study evaluated an association between whole brain volume loss and neurocognitive decline following prophylactic cranial irradiation (PCI) for limited-stage small-cell lung cancer (SCLC). **METHODS:** This was a secondary analysis of a prospective clinical trial that accrued patients at a single institution from 2013 to 2016. Patients with limited-stage SCLC treated with standard chemo-radiation received PCI 25 Gy/10 fractions, with mean hippocampal dose limited to < 8 Gy. Whole brain volumes were measured using MR imaging obtained before and at 6, 12, 18, and 24 months after PCI. Verbal memory was measured by the Hopkins Verbal Learning Test-Revised (HVLТ-R) before and at 6 and 12 months after PCI. Univariate and multivariate linear regression evaluated associations between changes in whole brain volume and verbal memory. **RESULTS:** Twenty-two patients enrolled. The median whole brain volume before PCI was 1301 mL. Subsequent reduction in whole brain volume was greatest at 18 months after PCI (median change - 23 mL, range - 142 to 20, p = 0.03). At 6 months after PCI, reduction in volume was independently associated with decline in verbal memory, measured by two components of the HVLТ-R (Delayed Recall: 0.06/mL volume change, p = 0.046; Percent Retained: 0.66/mL volume change, p = 0.030), when controlling for education and global cognitive function at baseline. **CONCLUSION:** This is the first study to correlate reduction in whole brain volume and decline in neurocognitive function following whole brain radiation therapy (WBRT). This suggests that loss of brain volume after WBRT may be clinically significant and subsequently impact cognition and quality of life.

[**The Hemoglobin, Albumin, Lymphocyte, and Platelet \(HALP\) Score in Patients with Small Cell Lung Cancer Before First-Line Treatment with Etoposide and Progression-Free Survival.**](#)

Shen XB1,2, Zhang YX1,2, Wang W2, Pan YY1,2. Med Sci Monit. 2019 Jul 29;25:5630-5639. doi: 10.12659/MSM.917968.

The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is a prognostic factor in patients who have some types of malignant tumors. The aim of this study was to investigate the prognostic significance of the HALP score in patients with small cell lung cancer (SCLC) before first-line treatment with etoposide. **MATERIAL AND METHODS:** A retrospective study included 178 patients with SCLC who received first-line chemotherapy with etoposide between September 2015 and May 2019. The baseline clinical characteristics and blood parameters were recorded. Univariate and multivariate analysis and Kaplan-Meier plots were used to identify the factors associated with progression-free survival (PFS). **RESULTS:** The optimal cut-off values of the HALP score was determined by X-tile software to be 25.8. Univariate and multivariate analysis showed that in 178 patients, the HALP score, body mass index (BMI), and serum albumin levels had no prognostic significance. In the patient age group <65 years, a BMI ≥ 24 kg/m² was an independent prognostic factor (HR, 1.943; 95% CI, 1.251-3.018) (P=0.003). In the patient age group ≥ 65 years, a HALP score >25.8 was an independent positive prognostic factor for outcome following first-line treatment with etoposide (HR, 0.483; 95% CI, 0.270-0.865) (P=0.014). **CONCLUSIONS:** patients <65 years with SCLC who underwent first-line treatment with etoposide, a BMI ≥ 24 kg/m² an independent prognostic factor, and in patients ≥ 65 years, a HALP score >25.8 was an independent predictor of improved outcome, associated with increased PFS.

[**Limited-Stage Small Cell Lung Cancer: Is Prophylactic Cranial Irradiation Necessary?**](#)

Farris MK1, Wheless WH2, et al. Pract Radiat Oncol. 2019 Jul 1. pii: S1879-8500(19)30185-7. doi: 10.1016/j.prro.2019.06.014. [Epub ahead of print]

PURPOSE/OBJECTIVE(S): Prophylactic cranial irradiation (PCI) reduces the incidence of brain metastases in patients with limited stage small cell lung cancer (LS-SCLC). However, PCI is associated with neurotoxicity. Previous studies have not consistently utilized pretreatment magnetic resonance imaging (MRI). Modern imaging improvements continue to enhance early metastasis detection, potentially decreasing the utility of PCI. We sought to determine if PCI was associated with improved outcomes in LS-SCLC patients with modern imaging. **MATERIALS/METHODS:** We identified LS-SCLC patients with no intracranial disease who were treated between 2007-2018. Kaplan-Meier estimates of overall Survival (OS) and progression free survival (PFS) were calculated and multivariate Cox proportional hazards models were generated. The cumulative incidence (CI) of brain metastases was estimated using competing risks methodology. **RESULTS:** Ninety-two patients were identified without intracranial disease at initial staging, 39 of whom received PCI. Median follow-up was 56.7 months. The median OS for the cohort was 35.5 months (95% CI 25.8-49.3) and median PFS was 19.1 months (95% CI 12.3-30.5). Median OS with PCI versus observation was 37.9 months (95% CI 31.8-NR) v. 30.5 months (95% CI 14.6-56.1, p=0.07) while median PFS was 26.3 months (95% CI 19.1-NR) v. 12.3 months (95% CI 8.5-30.5, p=0.02) respectively. Overall, at 2 years, the cumulative incidence of brain metastases was 10% with PCI and 29% without; this increased to 32% and 29% by 4 years (p=0.66). In those patients who had negative magnetic resonance imaging (MRI) of the brain after completing initial treatment, the 1-year CI of brain metastasis was not significantly different at 8% versus 11% (p=0.46) respectively. Both PCI and treatment response were independent predictors for PFS on multivariate analysis. Stratified by disease response, patients with a complete response (CR) did not benefit from PCI (p=0.50), while those with partial response (PR)/stable disease (SD) experienced improved PFS (p=0.01). **CONCLUSION:** Overall, PCI was associated with improved PFS and reduced early incidence of brain metastases. Patients achieving a CR to initial therapy did not experience a PFS benefit with PCI. This may indicate that subsets of LS-SCLC patients can potentially be spared from PCI in the era of modern imaging.

[Clinical Outcomes Following Stereotactic Body Radiation Therapy \(SBRT\) for Stage I Medically Inoperable Small Cell Lung Carcinoma: A Multi-Institutional Analysis From the RSSearch Patient Registry.](#) Singh R1, Ansinelli H2, Sharma D3, Jenkins J4, Davis J4, Vargo JA5, Sharma S3,6. Am J Clin Oncol. 2019 Jul;42(7):602-606. doi: 10.1097/COC.0000000000000561.

OBJECTIVES: To utilize the RSSearch Patient Registry (RSSPR) to examine local control (LC), overall survival (OS), and toxicities following stereotactic body radiation therapy (SBRT) for stage I (T1-T2/N0) medically inoperable small cell lung carcinoma (SCLC). **MATERIALS AND METHODS:** We searched the RSSPR for medically inoperable stage I SCLC patients treated with definitive SBRT. Potential predictive factors of OS were estimated using the Kaplan-Meier method as well as a Cox proportional hazards model. **RESULTS:** Twenty-one patients were identified with medically inoperable stage I SCLC that met inclusion criteria. Fourteen patients had stage IA SCLC (T1N0) and 7 patients had stage IB SCLC (T2N0) with a median gross tumor volume of 10.1 cm (range: 0.72 to 41.4 cm). The median number of fractions was 4 (range: 3 to 5), and the median BED10 was 105.6 Gy10 (range: 72 to 239.7 Gy10). Four patients received adjuvant chemotherapy. One- and 2-year actuarial OS rates were 73.1% (95% confidence interval [CI]: 36.8%-90.1%) and 36.6% (95% CI: 9.0%-65.7%), respectively. Factors found to be associated with 1-year OS on univariate analysis included T2 disease (85.5% vs. 33.3%; P=0.03), adjuvant chemotherapy (100% vs. 66.3%; P=0.11), and gross tumor volume ≥ 10 cm (100% vs. 52.5%; P=0.10). On multivariate analysis, adjuvant chemotherapy was associated with improved OS (hazard ratio=0.07 [95% CI: 0.13-0.37; P=0.002]). The 1-, 2-, and 3-year LC rates were 100%, and 1- and 2-year progression-free survival (PFS) rates were 85.7% (95% CI: 33.4-97.9%) and 42.9% (95% CI: 1.1-85.3%), respectively. Similar to OS, patients with T1N0 disease had superior PFS as compared to T2N0 disease (P=0.01). Toxicities were reported by 3/21 (14.3%) of patients with none \geq

grade 3 and no esophageal toxicities. **CONCLUSIONS:** SBRT was well-tolerated in the treatment of stage I SCLC with excellent LC achieved. Patients with T1N0 stage IA SCLC were noted to have improved PFS and OS following SBRT as compared with T2N0 Stage IB SCLC. Adjuvant chemotherapy was found to result in improved OS for stage I SCLC patients over SBRT alone.

PALLIATIVE AND SUPPORTIVE CARE

Heart Rate Variability and Heart Rate Recovery in Lung Cancer Survivors Eligible for Long-Term Cure. Ha D1, Malhotra A2, Ries AL2, O'Neal WT3, Fuster MM4. *Respir Physiol Neurobiol.* 2019 Jul 31:103264. doi: 10.1016/j.resp.2019.103264. [Epub ahead of print]

Lung cancer survivors are at risk for physical fitness and autonomic function impairments. In a cross-sectional study of consecutive lung cancer survivors post-curative intent therapy, we assessed and identified predictors of resting heart rate variability (HRV) and heart rate recovery (HRR), defined as standard deviation of normal-to-normal-R-to-R intervals (SDNN) and root-mean-square-of-successive-differences (rMSSD) from routine outpatient single 10-s electrocardiographs (ECGs) and difference in heart rate (HR) at 1-minute following and the end of the six-minute-walk-test (6MWT), respectively. In 69 participants, the mean (SD) HRR was -10.6 (6.7) beats. Significant independent predictors of HRR were age and HR change associated with the 6MWT. In a subset of 41 participants with available ECGs, the mean (SD) SDNN and rMSSD were 19.1 (15.6) and rMSSD 18.2 (14.6) ms, respectively. Significant independent predictors of HRV were supine HR, HRR, and total lung capacity. HRV/HRR may be useful physiological measures in studies aimed at improving physical fitness and/or autonomic function in lung cancer survivors.

Factors Associated with Anxiety and Depression among Family Caregivers of Patients Undergoing Palliative Radiotherapy. Govina O1, Vlachou E1, Kalemikerakis I1, Papageorgiou D2, Kavga A1, Konstantinidis T3. *Asia Pac J Oncol Nurs.* 2019 Jul-Sep;6(3):283-291. doi: 10.4103/apjon.apjon_74_18.

OBJECTIVE: The family caregivers of patients receiving palliative care experience high levels of anxiety and depression. The aim of the present study was to investigate the factors associated with family caregivers' anxiety and depression when caring for patients with advanced cancer in Greece.

METHODS: The sample consisted of 100 patients undergoing palliative radiotherapy and their respective caregivers. Patients completed the Hospital Anxiety and Depression Scale (HADS) and the MD Anderson Symptom Inventory. Their respective caregivers completed the Oberst Caregiving Burden Scale, the Bakas Caregiving Outcomes Scale, and the HADS. Correlational and multiple regression analyses were conducted to identify potential predictors of anxiety and depression. **RESULTS:** The majority of patients were male (63.0%), whereas the majority of their caregivers were female (76.0%). The mean ages of patients and caregivers were 63.9 ± 10.8 and 53.3 ± 12.6 years, respectively. Caregiving anxiety and depression were associated with patients' variables, such as gender ($P < 0.0005$), primary cancer ($P = 0.008$), and past surgery ($P = 0.002$), and caregiver's variables, such as gender ($P = 0.001$), co-residence ($P = 0.05$), previous care experience ($P = 0.04$), and means of transport ($P = 0.038$). In multiple regression analyses, caregiving anxiety and depression were significantly predicted by caregivers' and patients' characteristics, in a model that accounted for 48% of the anxiety variance ($P < 0.0005$) and 39% of the depression variance ($P < 0.0005$). **CONCLUSION:** The caregivers who experienced more anxiety and depression shared the following traits: they were women, cared for men with lung cancer, cared for patients not undergoing surgery, lived together, were younger, went to the hospital by private means of transport, had previous care experience, and perceived an increased degree of general burden. Further investigation of the factors that may affect caregivers' psychological state is required to better identify parameters that may predict it.

[The relation between psychological profiles and quality of life in patients with lung cancer.](#)

van Montfort E1, de Vries J2,3, Arts R3, Aerts JG4, Kloover JS3, Traa MJ3. Support Care Cancer. 2019 Jul 1. doi: 10.1007/s00520-019-04923-w. [Epub ahead of print]

OBJECTIVE: Previous studies in patients with lung cancer examined the association between psychological factors with quality of life (QoL), as well as the association between psychological factors with sociodemographic and medical characteristics. However, knowledge about the impact of combinations of psychological characteristics on QoL is still lacking. Therefore, the current study aimed to identify psychological profiles, covering multiple psychological factors. Additionally, the association between these profiles with QoL and with sociodemographic and medical characteristics was explored.

METHODS: Patients with lung cancer (n = 130, mean age = 68.3 ± 8.6 years; 49% men) completed questionnaires focusing on sociodemographic information, anxiety and depressive symptoms (HADS), coping (COPE-easy), perceived social support (PSSS), and QoL (WHOQOL-BREF). Medical information was extracted from patients' medical records. A step-3 latent profile analysis was performed to identify the psychological profiles. Multinomial logit models were used to explore the medical and sociodemographic correlates of the profiles and the relation with QoL. **RESULTS:** Four psychological profiles were identified as follows: (1) anxious, extensive coping repertoire (33%); (2) depressive, avoidant coping (23%); (3) low emotional symptoms, active/social coping (16%); and (4) low emotional symptoms, limited coping repertoire (29%). QoL in profile 1 (QoL = 6.59) was significantly different from QoL in profile 3 (QoL = 8.11, p = .001) and profile 4 (QoL = 7.40, p = .01). QoL in profile 2 (QoL = 6.43) was significantly different from QoL in profile 3 (QoL = 8.11, p = .003) and profile 4 (QoL = 7.40, p = .02). Regarding QoL, no other significant differences were found. Sociodemographic and medical characteristics were not distinctive for the profiles (all p values > .05). **CONCLUSION:** Determining psychological profiles of patients with lung cancer in an early stage provides information that may be helpful in aligning care with patients' unique needs, as it will help in more adequately selecting those patients who are in need of psychological screening and/or psychological treatment as compared with determining scores on single psychological factors.

[Understanding Symptom Burden in Patients With Advanced Cancer Living in Rural Areas.](#)

Gilbertson-White S1, Perkhounkova Y1, Saeidzadeh S1, Hein M1, Dahl R1, Simons-Burnett A1. Oncol Nurs Forum. 2019 Jul 1;46(4):428-441. doi: 10.1188/19.ONF.428-441.

OBJECTIVES: To evaluate the feasibility of using a biobehavioral approach to examine symptom burden in rural residents with advanced cancer. **SAMPLE & SETTING:** 21 patients with advanced lung, colorectal, or pancreatic cancer were enrolled at the University of Iowa in Iowa City. **METHODS & VARIABLES:** Using Cleeland's cytokine-immunologic model of symptom expression, symptom burden (i.e., severity, count, and interference) and inflammatory cytokines were measured for 24 weeks. Potential predictors included demographics, clinical characteristics, optimism, social support, and cancer-related stress. Descriptive statistics, Wilcoxon rank-sum, and Fisher's exact test were used for analysis. **RESULTS:** Recruitment and retention rates were similar for rural and nonrural patients. Demographics, optimism, and social support were no different between groups. The cancer-related stress total score for rural patients was nearly half of the score of nonrural patients, with rural patients reporting significantly less avoidance. Symptom severity for the five worst symptoms remained moderate during the 24 weeks, whereas nonrural residents reported steady declines in severity of their five worst symptoms. Significant differences in inflammatory cytokines between groups were only found at one time point. **IMPLICATIONS FOR NURSING:** Rural residents who seek care at a cancer center may be clinically and demographically more similar to their nonrural counterparts than to rural residents seeking local care.

[Retrospective Prognostic Study of Death at Home or Hospice Versus at a Hospital Among Patients With Advanced Non-Small Cell Lung Cancer.](#) Hamamoto Y1, Ibe T1, Kodama H1, Mouri A2, Mineshita M3. *Am J Hosp Palliat Care*. 2019 Jul 31;1049909119865865. doi: 10.1177/1049909119865865. [Epub ahead of print]

BACKGROUND: Patients with advanced non-small cell lung cancer greatly care about where they will die. Most people in Japan preferred their location of death as their homes. But only 8.2% of patients with cancer spend their last days at home with palliative care in Japan. Many patients with cancer are still going to spend their last days at a hospital (81.7%). **OBJECTIVE:** We examined the survival times of such patients according to their place of death; that is, whether they died at home, at a hospice, or at a hospital, and investigated patient characteristics. **RESULTS:** Among the 313 patients recruited, 214 were analyzed in this study: 90, 49, and 75 received hospital-based, home-based, and hospice-based palliative care, respectively. The patients who died at a hospice exhibited significantly longer survival than those who died at hospital (estimated median survival time, 420 days [95% confidence interval [CI]: 325-612 days] versus 252 days [95% CI: 201-316 days]; $P < .0001$). The characteristics of patients did not differ significantly according to place of death. **CONCLUSIONS:** Patients who died at a hospice or at home exhibited significantly longer survival than those who died at a hospital for advanced non-small cell lung cancer.

[Co-occurring Gastrointestinal Symptoms Are Associated with Taste Changes in Oncology Patients Receiving Chemotherapy.](#) Nolden A1, Joseph PV2, Kober KM3, et al. *J Pain Symptom Manage*. 2019 Jul 23. pii: S0885-3924(19)30389-6. doi: 10.1016/j.jpainsymman.2019.07.016. [Epub ahead of print]

BACKGROUND: Over 80% of cancer patients report taste changes. Despite the high prevalence of this symptom and its negative effects on health, few studies have assessed its association with other gastrointestinal (GI) symptoms. **OBJECTIVES:** Determine the occurrence, frequency, severity and distress of patient-reported "change in the way food tastes" (CFT) and identify phenotypic and GI symptoms characteristics associated with its occurrence. **METHODS:** Patients receiving chemotherapy for breast, GI, gynecological, or lung cancer completed demographic and symptom questionnaires prior to their 2nd or 3rd cycle of chemotherapy. CFT was assessed using the Memorial Symptom Assessment Scale. Differences in demographic, clinical, and GI symptom characteristics were evaluated using parametric and nonparametric tests. **RESULTS:** Of the 1,329 patients, 49.4% reported experiencing CFT in the week prior to their 2nd or 3rd cycle of chemotherapy. In the univariate analysis, patients who reported CFT had fewer years of education; were more likely to be Black or Hispanic, Mixed race, or other, and had a lower annual household income. A higher percentage of patients with CFT reported the occurrence of thirteen GI symptoms (e.g., constipation, diarrhea, abdominal cramps, feeling bloated). In a multivariable logistic regression analysis, Compared to patients with breast cancer, patients with lung (OR=0.55; $p=0.004$) had a decrease in the odds of being in the CFT group. Patients who received a neurokinin-1 receptor antagonist and two other antiemetics were at an increased odds of being in the CFT group (OR=2.51; $p=0.001$). Eight of the thirteen GI symptoms evaluated were associated with an increased odds of being in the CFT group. **CONCLUSIONS:** This study provides new evidence on the frequency, severity, and distress of CFT in oncology patients undergoing chemotherapy. These findings suggest that CFT is a important problem that warrants ongoing assessments and nutritional interventions.

[Psychological correlates of sleep quality in lung cancer patients under chemotherapy: A single-center cross-sectional study.](#) Papadopoulos D1, Kiagia M1, Charpidou A1, Gkiozos I1, Syrigos K1. *Psychooncology*. 2019 Jul 2. doi: 10.1002/pon.5167. [Epub ahead of print]

OBJECTIVES: Disturbed sleep is a common complaint of lung cancer patients undergoing active oncologic treatment. We aimed to clarify the extent to which psychological symptoms, coping strategies,

and social support interfere with sleep quality and whether they mediate the relationship between sleep quality and fatigue or functional capacity in a sample of chemotherapy treated lung cancer patients.

METHODS: Lung cancer patients attending an oncology unit for scheduled chemotherapy cycles completed questionnaires assessing their sleep quality, fatigue, depression, anxiety, stress, coping, social support, symptoms of pain, dyspnea, and cough, and sleep hygiene practices. Demographic and disease-related characteristics were obtained from patients' medical records and treating physicians rated their functional status. Multivariate regression and mediation analyses were applied to test the study's hypotheses. **RESULTS:** One hundred nineteen patients were enrolled, 58.2% of whom were identified as poor sleepers. After adjusting for age, gender, comorbidities, concomitant medications, cancer stage, prior and ongoing treatment, sleep hygiene, and symptoms, there was a statistically significant association between poor sleep quality and anxiety (odds ratio [OR] 1.17 [95% CI, 1.01-1.35]), stress (OR 1.14 [95% CI, 1.04-1.25]), and positive coping (OR 1.15 [95% CI, 1.02-1.31]). Poor sleep quality was an independent correlate of fatigue (B 1.56 [95% CI, 0.61-2.50]) and low performance status (OR 5.17 [95% CI, 1.60-16.72]); stress symptoms partially mediated the relationship between sleep quality and fatigue ($P = .030$). **CONCLUSIONS:** Higher psychological burden predict sleep disturbances and contribute to increased fatigue in lung cancer patients undergoing chemotherapy. Effective psychoeducational interventions may benefit these populations.

[The relation between psychological profiles and quality of life in patients with lung cancer.](#) van Montfort E1, de Vries J2,3, Arts R3, Aerts JG4, Kloover JS3, Traa MJ3. Support Care Cancer. 2019 Jul 1. doi: 10.1007/s00520-019-04923-w. [Epub ahead of print]

OBJECTIVE: Previous studies in patients with lung cancer examined the association between psychological factors with quality of life (QoL), as well as the association between psychological factors with sociodemographic and medical characteristics. However, knowledge about the impact of combinations of psychological characteristics on QoL is still lacking. Therefore, the current study aimed to identify psychological profiles, covering multiple psychological factors. Additionally, the association between these profiles with QoL and with sociodemographic and medical characteristics was explored. **METHODS:** Patients with lung cancer ($n = 130$, mean age = 68.3 ± 8.6 years; 49% men) completed questionnaires focusing on sociodemographic information, anxiety and depressive symptoms (HADS), coping (COPE-easy), perceived social support (PSSS), and QoL (WHOQOL-BREF). Medical information was extracted from patients' medical records. A step-3 latent profile analysis was performed to identify the psychological profiles. Multinomial logit models were used to explore the medical and sociodemographic correlates of the profiles and the relation with QoL. **RESULTS:** Four psychological profiles were identified as follows: (1) anxious, extensive coping repertoire (33%); (2) depressive, avoidant coping (23%); (3) low emotional symptoms, active/social coping (16%); and (4) low emotional symptoms, limited coping repertoire (29%). QoL in profile 1 (QoL = 6.59) was significantly different from QoL in profile 3 (QoL = 8.11, $p = .001$) and profile 4 (QoL = 7.40, $p = .01$). QoL in profile 2 (QoL = 6.43) was significantly different from QoL in profile 3 (QoL = 8.11, $p = .003$) and profile 4 (QoL = 7.40, $p = .02$). Regarding QoL, no other significant differences were found. Sociodemographic and medical characteristics were not distinctive for the profiles (all p values $> .05$). **CONCLUSION:** Determining psychological profiles of patients with lung cancer in an early stage provides information that may be helpful in aligning care with patients' unique needs, as it will help in more adequately selecting those patients who are in need of psychological screening and/or psychological treatment as compared with determining scores on single psychological factors.

[Identification of subgroups of chemotherapy patients with distinct sleep disturbance profiles and associated co-occurring symptoms.](#) Tejada M1, Viele C1, Kober KM1, et al. Sleep. 2019 Jul 30. pii: zsz151. doi: 10.1093/sleep/zsz151. [Epub ahead of print]

STUDY OBJECTIVES: Purposes of this study were to identify subgroups of patients with distinct sleep disturbance profiles and to evaluate for differences in demographic, clinical, and various sleep characteristics, as well for differences in the severity of co-occurring symptoms among these subgroups. **METHODS:** Outpatients with breast, gynecological, gastrointestinal, or lung cancer (n = 1331) completed questionnaires six times over two chemotherapy cycles. Self-reported sleep disturbance was evaluated using the General Sleep Disturbance Scale (GSDS). Latent profile analysis was used to identify distinct subgroups. **RESULTS:** Three latent classes with distinct sleep disturbance profiles were identified (Low [25.5%], High [50.8%], Very High [24.0%]) across the six assessments. Approximately 75% of the patients had a mean total GSDS score that was above the clinically meaningful cutoff score of at least 43 across all six assessments. Compared to the Low class, patients in High and Very High classes were significantly younger, had a lower functional status, had higher levels of comorbidity, and were more likely to be female, more likely to have childcare responsibilities, less likely to be employed, and less likely to have gastrointestinal cancer. For all of the GSDS subscale and total scores, significant differences among the latent classes followed the expected pattern (Low < High < Very High). For trait and state anxiety, depressive symptoms, morning and evening fatigue, decrements in attentional function, and decrements in morning and evening energy, significant differences among the latent classes followed the expected pattern (Low < High < Very High). **CONCLUSIONS:** Clinicians need to perform in-depth assessments of sleep disturbance and co-occurring symptoms to identify high-risk patients and recommend appropriate interventions.

[**A Model-Based Cost-Effectiveness Analysis of an Exercise Program for Lung Cancer Survivors Following Curative-Intent Treatment.**](#) Ha D1,2, Kerr J3, Ries AL2, Fuster MM4,2, Lippman SM5, Murphy JD6. Am J Phys Med Rehabil. 2019 Jul 26. doi: 10.1097/PHM.0000000000001281. [Epub ahead of print]

OBJECTIVE: The cost-effectiveness of exercise interventions in lung cancer survivors is unknown. We performed a model-based cost-effectiveness analysis of an exercise intervention in lung cancer survivors. **DESIGN:** We used Markov modeling to simulate the impact of the Lifestyle Interventions and Independence for Elders (LIFE) exercise intervention compared to usual care for stage I-IIIa lung cancer survivors following curative-intent treatment. We calculated and considered incremental cost-effectiveness ratios (ICERs) <\$100,000/quality-adjusted life-year (QALY) as cost-effective and assessed model uncertainty using sensitivity analyses. **RESULTS:** The base-case model showed that the LIFE exercise program would increase overall cost by \$4,740 and effectiveness by 0.06 QALYs compared to usual care and have an ICER of \$79,504/QALY. The model was most sensitive to the cost of the exercise program, probability of increasing exercise, and utility benefit related to exercise. At a willingness-to-pay threshold of \$100,000/QALY, LIFE had a 71% probability of being cost-effective compared to 27% for usual care. When we included opportunity costs, LIFE had an ICER of \$179,774/QALY, exceeding the cost-effectiveness threshold. **CONCLUSIONS:** A simulation of the LIFE exercise intervention in lung cancer survivors demonstrates cost-effectiveness from an organization but not societal perspective. A similar exercise program for lung cancer survivors may be cost-effective.

[**"All boats will rise": Physicians' perspectives on multidisciplinary lung cancer care in a community-based hospital setting.**](#) Kedia SK1, Ward KD2, Collins AC2, Jackson BM3, Stewart FR3, Faris NR3, Roark KS3, Osarogiagbon RU3. Support Care Cancer. 2019 Jul 15. doi: 10.1007/s00520-019-04950-7. [Epub ahead of print]

PURPOSE: We explored the perceived strengths, barriers to implementation, and suggestions for sustainable implementation of a multidisciplinary model within a community-based hospital system from the physicians' perspectives. **METHODS:** We conducted 9 focus groups with 37 physicians involved in the care of lung cancer patients. Grounded theory methodology guided the identification of recurrent

themes that emerged from the qualitative data analysis. **RESULTS:** The majority of study participants agreed that the multidisciplinary model could benefit patients by promoting high quality, efficient, and well-coordinated care. Co-location, financial disincentives, and time constraints were identified as major deterrents to full participation in a multidisciplinary clinic. Other perceived challenges were the integration of a multidisciplinary care model into the existing healthcare system, maintenance of referral streams, and designation of the physician primarily responsible for a patient's care. Educating physicians about the availability of a multidisciplinary clinic, establishing efficient processes for initial consultations, implementing technology for virtual participation, and using a nurse navigator with reliable closed-loop communication were suggested to improve the implementation of the multidisciplinary model. **CONCLUSIONS:** Physicians generally agreed that the multidisciplinary model could improve lung cancer care, but they perceived significant personal, institutional, and system-level barriers that need to be addressed for its successful implementation in a community healthcare setting.

Lung Cancer Patient and Caregiver Health Vulnerabilities and Interest in Health Promotion

Interventions: An Exploratory Study. Nightingale CL1, Steffen LE1, Tooze JA2, Petty W3, Danhauer SC1, Badr H4, Weaver KE1. *Glob Adv Health Med.* 2019 Jul 17;8:2164956119865160. doi: 10.1177/2164956119865160. eCollection 2019.

INTRODUCTION: Lung cancer patients and their caregivers are at risk for negative health behaviors and poor psychosocial functioning, but few interventions exist that target this population. To inform intervention development, we explored potential targets and interest and concordance in health promotion interventions among lung cancer patients and their caregivers. **METHODS:** Lung cancer patients (n = 18) with a smoking history and their caregivers (n = 15) participated in a cross-sectional, observational survey study (an average of 1 month postdiagnosis) to assess health behaviors, psychosocial functioning, and interest in health promotion interventions. Fisher's exact and Wilcoxon rank-sum tests examined factors associated with intervention interest. McNemar's test examined concordance in interest. **RESULTS:** Many caregivers (40%) reported providing care at least 4 days per week, and over half (53.3%) reported a smoking history. Patients reported high cancer self-blame (mean = 3.1, standard deviation = 0.9, range = 1-4). Patients (55.6%) and caregivers (60%) reported clinically significant depressive symptoms. There was high interest and concordance in interest in cancer education (patients, 77.8%; caregivers, 86.7%) and diet and exercise (patients, 66.7%; caregivers, 80%) interventions. Significantly more caregivers were interested in stress reduction (patients, 53.3%; caregivers, 73.3%; P = .05) and yoga (patients, 16.7%; caregivers, 50%; P = .03) than patients. Caregivers interested in stress reduction interventions had higher levels of distress than those not interested. **DISCUSSION:** Health promotion interventions are needed and of interest to lung cancer patients and caregivers. Shared interests in interventions suggest dyadic interventions may be appropriate, yet interventions should also address distinct patient and caregiver needs.

Effects of Home-Based Exercise Training for Patients With Lung Cancer. Wang YQ1, Liu X1, Yin YY1, Ma RC1, Yang Z1, Cao HP1, Xie J1. *Oncol Nurs Forum.* 2019 Jul 1;46(4):E119-E134. doi: 10.1188/19.ONF.E119-E134.

PROBLEM IDENTIFICATION: To investigate the effectiveness of home-based exercise training on exercise capacity, dyspnea, anxiety, depression, and health-related quality of life (HRQOL). **LITERATURE SEARCH:** A systematic literature search of the Cochrane Central Register of Randomized Controlled Trials, Embase®, PubMed®, and Web of Science databases was performed for articles published through July 22, 2018. **DATA EVALUATION:** The meta-analysis was conducted with Review Manager, version 5.3, following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. **SYNTHESIS:** 10 articles with a total of 453 patients met the inclusion criteria. Home-based exercise training was found to increase the six-minute walk distance. In addition,

anxiety was also improved after the intervention. However, no improvements in dyspnea, depression, or HRQOL were observed. **IMPLICATIONS FOR RESEARCH:** Home-based exercise training as a nursing intervention for promoting the rehabilitation of patients with lung cancer can be recommended, but more research should be undertaken to determine the most effective exercises and follow-up methods.

COMPLEMENTARY & ALTERNATIVE THERAPY

[Effect of Xiao-Ai-Ping injection on paclitaxel pharmacokinetics in rats by LC-MS/MS method.](#) Shi MZ1, Xing TY2, et al. *J Pharm Biomed Anal.* 2019 Sep 10;174:728-733. doi: 10.1016/j.jpba.2019.07.003. Epub 2019 Jul 3.

Xiao-Ai-Ping injection (XAP) has been shown to be clinically effective in treatment of gastric carcinoma, liver cancer and lung cancer, when it was combined with anticancer drug paclitaxel (PTX). To analyze the effect of XAP on the pharmacokinetics of PTX, a liquid chromatography-tandem mass spectroscopy (LCMS/MS) assay method was developed and validated to quantify PTX simultaneously and its main metabolite 3'-p-hydroxypaclitaxel (C3'-OHP) in rat plasma. PTX and C3'-OHP were quantified using positive MRM mode. The analysis method was validated for specificity, recovery, carry-over, accuracy, precision, sample stability and dilution integrity under various storage conditions. The pharmacokinetic parameters were determined in rats after tail intravenous administration of 6 mg/mL PTX in the absence (control group) or presence of intraperitoneal administration of 10 mL/kg, 20 mL/kg XAP (study groups). Compared to control group, the area under the plasma concentration-time curve (AUC) of PTX and C3'-OHP in study groups increased significantly following consecutive administration with XAP for 10 days. In conclusion, pretreatment with XAP enhanced the exposure of PTX and C3'-OHP. There would be herb-drug interaction happening between XAP and PTX in rats.

MISCELLANEOUS WORKS

[Sex-Based Disparities Among Cancer Clinical Trial Participants.](#) Ludmir EB1, Fuller CD1, Moningi S1, et al. *J Natl Cancer Inst.* 2019 Jul 27. pii: djz154. doi: 10.1093/jnci/djz154. [Epub ahead of print] Landmark investigation two decades ago demonstrated sex-based disparities among participants in cancer cooperative group trials. While federal efforts have aimed to improve representation of female patients in government-sponsored research, less is known about sex disparities in the broader landscape of modern oncologic randomized controlled trials (RCTs). Using ClinicalTrials.gov, we identified RCTs related to colorectal or lung cancer (the 2 most common non-sex-specific disease sites). Among the 147 included trials, the proportion of female patients enrolled on trial was on average 6.8% (95%CI = -8.8% to -4.9%) less than the proportion of female patients in the population by disease site ($p < 0.001$). While no statistically significant underrepresentation of women was noted within the 26 cooperative group trials, sex disparities were markedly heightened for the 121 non-cooperative-group-sponsored trials. Furthermore, underrepresentation of women did not improve with time. Future efforts should therefore focus on addressing these pervasive sex-based enrollment disparities beyond cooperative group trials alone.

[Healthcare resource utilization and costs associated with patients prescribed afatinib or erlotinib as first-line therapy for EGFR mutation-positive NSCLC in the United States.](#) Samuelsen C1, Lim J2, Golembesky A1, Shrestha S3, Wang L3, Griebisch II. *J Med Econ.* 2019 Jul 17:1. doi: 10.1080/13696998.2019.1645681. [Epub ahead of print]

AIMS: To assess healthcare resource utilization (HCRU) and costs in patients with non-small cell lung cancer treated with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors afatinib or erlotinib as first-line treatment. **MATERIALS AND METHODS:** This retrospective analysis used data

from three large administrative claims databases in the United States: Truven MarketScan, IMS PharMetrics Plus and Optum Clinformatics Data Mart. Patients with diagnosis codes of lung cancer treated with afatinib or erlotinib were included in the sample. Treatment cohorts were matched on baseline characteristics using propensity scores to account for potential selection bias. HCRU and healthcare costs were compared between the matched afatinib and erlotinib cohorts. **RESULTS:** 3,152 patients met the study inclusion criteria; propensity score matching of the afatinib and erlotinib patients yielded 525 matched pairs with well-balanced baseline characteristics. The afatinib cohort had significantly fewer patients with ≥ 1 inpatient visits (40.4% versus 52.2%, $p = 0.0001$) and outpatient emergency room (ER) visits (45.7% versus 54.1%, $p = 0.0066$). Per patient per month (PPPM) visits were significantly different between afatinib compared to erlotinib for inpatient visits (0.1 versus 0.2, $p = 0.0152$), other outpatient visits PPPM (2.6 versus 3.0, $p = 0.022$) and outpatient office visits (2.0 versus 1.7, $p = 0.0059$). Although costs of outpatient office (\$1,624 versus \$1,070; $p = 0.0086$) and pharmacy (\$6,709 versus \$5,932; $p < 0.0001$) visits were higher for afatinib versus erlotinib, total costs did not differ significantly between cohorts (\$14,972 versus \$14,412; $p = 0.4415$). Limitations: Retrospective claims data can be subject to coding errors or data omissions; patients were required to have continuous health plan enrolment; EGFR mutation status was not confirmed. **CONCLUSIONS:** Patients treated with afatinib as first-line monotherapy experienced fewer inpatient stays and ER visits compared with erlotinib. Total costs were not significantly different between the two treatment cohorts.

[Association of Rurality With Survival and Guidelines-Concordant Management in Early-stage Non-Small Cell Lung Cancer.](#) Nicoli CD1, Sprague BL2, Anker CJ3, Lester-Coll NH3. *Am J Clin Oncol.* 2019 Jul;42(7):607-614. doi: 10.1097/COC.0000000000000549.

BACKGROUND: Rural populations of the United States have not experienced a similar degree of decline in lung cancer mortality recently seen nationwide. Several investigations examining survival differences in rural lung cancer patients have been incongruent. We investigated the association of rural residence with survival outcomes and receipt of guidelines-concordant treatment in early-stage non-small cell lung cancer (NSCLC). **METHODS:** Retrospective study of National Cancer Data Base patients with NSCLC diagnosed from 2004 to 2015. Comparisons of survival outcomes and guidelines-concordant management with lobectomy or stereotactic body radiation therapy among rural and nonrural patients, classified according to the US Department of Agriculture's Rural-Urban Continuum Codes. **RESULTS:** We identified 840,566 patients; 18.7% resided in rural areas. Rurality was associated with greater proportions of males, white patients, and higher comorbidities. Larger proportions of rural stage I patients (53.4%) did not undergo guidelines-concordant management with lobectomy or stereotactic body radiation therapy relative to nonrural patients (50.1%, $P < 0.001$). Although rural patients within each stage at diagnosis have a significant disparity in overall survival (OS), stage I NSCLC had the largest absolute difference (nonrural=61.4 mo, rural=50.3 mo, difference of 11.1 mo, $P < 0.0001$). In multivariable Cox regression, rurality was independently associated with impaired survival in both all-stages (hazard ratio=1.08, $P < 0.001$) and stage I NSCLC (hazard ratio=1.09, $P < 0.001$). **CONCLUSIONS:** Small differences exist in OS among all rural NSCLC patients, but rural patients with stage I NSCLC have a marked disadvantage in OS. Rurality is an independent risk factor for decreased survival in all-stages and stage I NSCLC.

[Exploring Stigma Among Lung Cancer Survivors: A Scoping Literature Review.](#) Webb LA1, McDonnell KK1, Adams SA1, Davis RE1, Felder TM1. *Oncol Nurs Forum.* 2019 Jul 1;46(4):402-418. doi: 10.1188/19.ONF.402-418.

PROBLEM IDENTIFICATION: Lung cancer survivors face many challenges that affect their quality of life and survival. A growing concern is the layered effect of stigma related to cigarette smoking and the perceived life-threatening diagnosis of lung cancer. This experience may affect lung cancer survivors'

physical, psychological, and social well-being, negatively influencing their quality of life.

LITERATURE SEARCH: CINAHL®, PubMed®, PsycINFO®, and Web of Science were searched from January 2000 through August 2017, using combinations of four keywords. **DATA EVALUATION:** Extracted data included research aims, design, method, analytical approach, sample size, gender, ethnicity/race, setting, stigma measure, smoking status, and major results. **SYNTHESIS:** Of 163 studies initially identified, 30 (19 quantitative, 8 qualitative, 2 theoretical reviews, and 1 mixed method) were included. Quantitative studies were analyzed by statistical significance and relevant findings. Thematic analysis was used to evaluate qualitative studies. **IMPLICATIONS FOR RESEARCH:** Future research should focus on the development and testing of tailored and multilevel interventions to support the management of stigma and lessen the negative impact it has on quality of life, with special considerations for vulnerable subpopulations.