Caring Ambassadors Lung Cancer Program
Literature Review, February 2018

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

The effect of ethanolic extract of Thymus kotschyanus on cancer cell growth in vitro and depression-like behavior in the mouse. Doosti MH1, Ahmadi K1, Fasihi-Ramandi M1. J Tradit Complement Med. 2017 Apr 17;8(1):89-94. doi: 10.1016/j.jtcme.2017.03.003. eCollection 2018 Jan. suggest an urgent need for new therapeutic agents with lower toxicity and high efficacy. Some Thyme species extracts have remarkably been shown to positively affect depression and cancer cells. In the present study, we investigated the effect of Thymus kotschyanus on depression and cancer cells. To this end, in experiment 1, NMRI mice were treated orally with the ethanolic extract of T. kotschyanus (50, 150 and 250 mg/ml) for seven days and then depression-like behavior was measured by Forced Swim Test (FST) and Tail Suspension Test (TST). In experiment 2, the pharmacological effect of the extract on the lung (A549) and cervical (Hela) cancer cell lines was also evaluated by MTT (3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide) in various concentration_(10, 5, 2.5, 1.25, 0.63, 0.31, 0.15 and 0.08 mg/ml). The results indicated that T. kotschyanus extract treatment (150 and 250 mg/kg) decreased depression-like behavior in the FST and TST tests in adult mice. Moreover, the treatment inhibited cancer cell growth and viability in a dose and time-dependent manner. Collectively these findings suggest that T. kotschyanus have antidepressant and anticancer effects.

Carvacrol Targets AXL to Inhibit Cell Proliferation and Migration in Non-small Cell Lung Cancer Cells. Jung CY1, Kim SY2, Lee C3. Anticancer Res. 2018 Jan;38(1):279-286.
BACKGROUND/AIM: AXL has been reported to be overexpressed and highly activated in various cancer types. In this study, we demonstrated the effect of carvacrol on cell proliferation and migration in non-small cell lung cancer (NSCLC) cells by impeding the expression and activation of AXL.
MATERIALS AND METHODS: The levels of AXL protein, mRNA and promoter activity were evaluated by western blot, reverse transcription polymerase chain reaction (RT-PCR) and luciferase assay, respectively. AXL-overexpressing cells were established by ectopic expression of AXL cDNA. Cell viability, clonogenicity, and migration were measured in carvacrol-treated NSCLC cells. **RESULTS:**

Carvacrol treatment of NSCLC cells caused down-regulation of AXL expression at the transcriptional level and also inhibited phosphorylation of AXL upon ligand stimulation. Carvacrol suppressed cell proliferation and migration and its inhibitory effect was attenuated in AXL-overexpressing NSCLC cells. **CONCLUSION:** Our data demonstrate that AXL is a crucial therapeutic target of carvacrol-induced inhibition of NSCLC cell proliferation and migration.

Fenofibrate prevents skeletal muscle loss in mice with lung cancer. Goncalves MD1,2,3, Hwang SK1,2, Pauli C4, et al. Proc Natl Acad Sci U S A. 2018 Jan 23;115(4):E743-E752. doi: 10.1073/pnas.1714703115. Epub 2018 Jan 8.
The cancer anorexia cachexia syndrome is a systemic metabolic disorder characterized by the catabolism of stored nutrients in skeletal muscle and adipose tissue that is particularly prevalent in nonsmall cell lung cancer (NSCLC). Loss of skeletal muscle results in functional impairments and increased mortality. The aim of the present study was to characterize the changes in systemic metabolism in a genetically engineered mouse model of NSCLC. We show that a portion of these animals develop loss of skeletal muscle, loss of adipose tissue, and increased inflammatory markers mirroring the human cachexia syndrome. Using noncachexic and fasted animals as controls, we report a unique cachexia metabolite phenotype that includes the loss of peroxisome proliferator-activated receptor-α (PPARα) -dependent ketone production by the liver. In this setting, glucocorticoid levels rise and correlate with skeletal muscle degradation and hepatic markers of gluconeogenesis. Restoring ketone production using the PPARα agonist, fenofibrate, prevents the loss of skeletal muscle mass and body weight. These results demonstrate how targeting hepatic metabolism can prevent muscle wasting in lung cancer, and provide evidence for a therapeutic strategy.

SCREENING, DIAGNOSIS AND STAGING

An Assessment of Primary Care and Pulmonary Provider Perspectives on Lung Cancer Screening. Triplette M1, Kross EK1, Mann BA2, Elmore JG1, Slatore CG3,4, Shahrir S1, Romine PE1, Frederick PD1, Crothers K1. Ann Am Thorac Soc. 2018 Jan;15(1):69-75. doi: 10.1513/AnnalsATS.201705-392OC.
RATIONALE: Lung cancer screening has a mortality benefit to high-risk smokers, but implementation remains suboptimal. Providers represent the key entry point to screening, and an understanding of provider perspectives on lung cancer screening is necessary to improve referral and overall implementation. **OBJECTIVES:** The objective of this study was to understand knowledge, beliefs, attitudes, barriers, and facilitators to screening in a diverse group of referring pulmonologists and primary care providers. **METHODS:** We conducted an electronic survey of primary care and pulmonary providers within a tertiary care medical center across different practice sites. The survey covered the following domains: 1) beliefs and assessment of evidence, 2) knowledge of lung cancer screening and guidelines, 3) current screening practices, 4) barriers and facilitators, and 5) demographic and practice characteristics. **RESULTS:** The 196 participants included 80% primary care clinicians and 19% pulmonologists (1% others). Forty-one percent practiced at university-based or affiliated clinics, 47% at county hospital-based clinics, and 12% at other or unidentified sites. The majority endorsed lung cancer screening effectiveness (74%); however, performance on knowledge-based assessments of screening eligibility, documentation, and nodule management was suboptimal. Key barriers included inadequate time (36%), inadequate staffing (36%), and patients having too many other illnesses to address screening (38%). Decision aids, which are used at the point of referral, were commonly identified both as important lung cancer screening clinical facilitators (51%) and as provider knowledge facilitators (59%). There were several differences by provider specialty, including primary care providers more frequently reporting time constraints and their patients having too many other illnesses to address screening as significant barriers to lung cancer screening. **CONCLUSIONS:** Providers endorsed the benefits of lung cancer screening, but

there are limitations in provider knowledge of key screening components. The most frequently reported barriers to screening represent a lack of clinical time or resources to address lung cancer screening in clinical practice. Facilitators for nodule management as well as point-of-care referral materials may be helpful in reducing knowledge gaps and the clinical burden of referral. These are all modifiable factors, which could be addressed to increase screening referral. Differences in attitudes and barriers by specialty should also be considered to optimize screening implementation.

Impact of Concurrent Genomic Alterations Detected by Comprehensive Genomic Sequencing on Clinical Outcomes in East-Asian Patients with EGFR-Mutated Lung Adenocarcinoma.

Sato S1, Nagahashi M2, Koike T1, et al. Sci Rep. 2018 Jan 17;8(1):1005. Doi: 10.1038/s41598-017-18560-y.

Next-generation sequencing (NGS) has enabled comprehensive detection of genomic alterations in lung cancer. Ethnic differences may play a critical role in the efficacy of targeted therapies. The aim of this study was to identify and compare genomic alterations of lung adenocarcinoma between Japanese patients and the Cancer Genome Atlas (TCGA), which majority of patients are from the US. We also aimed to examine prognostic impact of additional genomic alterations in patients harboring EGFR mutations. Genomic alterations were determined in Japanese patients with lung adenocarcinoma (N = 100) using NGS-based sequencing of 415 known cancer genes, and correlated with clinical outcome. EGFR active mutations, i.e., those involving exon 19 deletion or an L858R point mutation, were seen in 43% of patients. Some differences in driver gene mutation prevalence were observed between the Japanese cohort described in the present study and the TCGA. Japanese cohort had significantly more genomic alterations in cell cycle pathway, i.e., CDKN2B and RB1 than TCGA. Concurrent mutations, in genes such as CDKN2B or RB1, were associated with worse clinical outcome in patients with EGFR active mutations. Our data support the utility of comprehensive sequencing to detect concurrent genomic variations that may affect clinical outcomes in this disease.

Lung Cancer Screening and Smoking Cessation Clinical Trials. SCALE (Smoking Cessation within the Context of Lung Cancer Screening) Collaboration.

Joseph AM1, Rothman AJ2, Almirall D3, et al. Am J Respir Crit Care Med. 2018 Jan 15;197(2):172-182. doi: 10.1164/rccm.201705-0909CI.

National recommendations for lung cancer screening for former and current smokers aged 55-80 years with a 30-pack-year smoking history create demand to implement efficient and effective systems to offer smoking cessation on a large scale. These older, high-risk smokers differ from participants in past clinical trials of behavioral and pharmacologic interventions for tobacco dependence. There is a gap in knowledge about how best to design systems to extend reach and treatments to maximize smoking cessation in the context of lung cancer screening. Eight clinical trials, seven funded by the National Cancer Institute and one by the Veterans Health Administration, address this gap and form the SCALE (Smoking Cessation within the Context of Lung Cancer Screening) collaboration. This paper describes methodological issues related to the design of these clinical trials: clinical workflow, participant eligibility criteria, screening indication (baseline or annual repeat screen), assessment content, interest in stopping smoking, and treatment delivery method and dose, all of which will affect tobacco treatment outcomes. Tobacco interventions consider the "teachable moment" offered by lung cancer screening, how to incorporate positive and negative screening results, and coordination of smoking cessation treatment with clinical events associated with lung cancer screening. Unique data elements, such as perceived risk of lung cancer and costs of tobacco treatment, are of interest. Lung cancer screening presents a new and promising opportunity to reduce morbidity and mortality resulting from lung cancer that can be amplified by effective smoking cessation treatment. SCALE teamwork and collaboration promise to maximize knowledge gained from the clinical trials.

Association of Pathologic Nodal Staging Quality With Survival Among Patients With Non-Small Cell Lung Cancer After Resection With Curative Intent. Smeltzer MP1, Faris NR2, Ray MA1, Osarogiagbon RU2. JAMA Oncol. 2018 Jan 1;4(1):80-87. doi: 10.1001/jamaoncol.2017.2993.
IMPORTANCE: Pathologic nodal stage is the most significant prognostic factor in resectable non-small cell lung cancer (NSCLC). The International Association for the Study of Lung Cancer NSCLC staging project revealed intercontinental differences in N category-stratified survival. These differences may indicate differences not only in cancer biology but also in the thoroughness of the nodal examination. **OBJECTIVE:** To determine whether survival was affected by sequentially more stringent definitions of pN staging quality in a cohort of patients with NSCLC after resection with curative intent. **DESIGN:** This observational study used the Mid-South Quality of Surgical Resection cohort, a population-based database of lung cancer resections with curative intent. A total of 2047 consecutive patients who underwent surgical resection at 11 hospitals with at least 5 annual lung cancer resections in 4 contiguous US Dartmouth hospital referral regions in northern Mississippi, eastern Arkansas, and western Tennessee (>90% of the eligible population) were included. Resections were performed from January 1, 2009, through January 25, 2016. Survival was evaluated with the Kaplan-Meier method and Cox proportional hazards models. **EXPOSURES:** Eight sequentially more stringent pN staging quality strata included the following: all patients (group 1); those with complete resections only (group 2); those with examination of at least 1 mediastinal lymph node (group 3); those with examination of at least 10 lymph nodes (group 4); those with examination of at least 3 hilar or intrapulmonary and at least 3 mediastinal lymph nodes (group 5); those with examination of at least 10 lymph nodes, including at least 1 mediastinal lymph node (group 6); those with examination of at least 1 hilar or intrapulmonary and at least 3 mediastinal nodal stations (group 7); and those with examination of at least 1 hilar or intrapulmonary lymph node, at least 10 total lymph nodes, and at least 3 mediastinal nodal stations (group 8). **MAIN OUTCOMES AND MEASURES:** N category-stratified overall survival. **RESULTS:** Of the total 2047 patients (1046 men [51.1%] and 1001 women [48.9%]; mean [SD] age, 67.0 [9.6] years) included in the analysis, the eligible analysis population ranged from 541 to 2047, depending on stringency. Sequential improvement in the N category-stratified 5-year survival of pN0 and pN1 tumors was found from the least stringent group (0.63 [95% CI, 0.59-0.66] for pN0 vs 0.46 [95% CI, 0.38-0.54] for pN1) to the most stringent group (0.71 [95% CI, 0.60-0.79] for pN0 vs 0.60 [95% CI, 0.43-0.73] for pN1). The pN1 cohorts with 3 or more mediastinal nodal stations examined had the most striking survival improvements. More stringently defined mediastinal nodal examination was associated with better separation in survival curves between patients with pN1 and pN2 tumors. **CONCLUSIONS AND RELEVANCE:** The prognostic value of pN stratification depends on the thoroughness of examination. Differences in thoroughness of nodal staging may explain a large proportion of intercontinental survival differences. More thorough nodal examination practice must be disseminated to improve the prognostic value of the TNM staging system. Future updates of the TNM staging system should incorporate more quality restraints.

EBUS: Faster, cheaper and most effective in lung cancer staging. Sampsonas F1, Kakoullis L1, Lykouras D1, Karkoulias K1, Spiropoulos K1. Int J Clin Pract. 2018 Jan 3. doi: 10.1111/ijcp.13053. [Epub ahead of print]
The use of endobronchial ultrasound trans-bronchial needle aspiration (EBUS-TBNA) as the initial diagnostic and staging procedure in patients with suspected, non-metastatic lung cancer has gained substantial support, and is now recommended by numerous guidelines. Whereas considerable attention has been pointed to the reductions in costs achieved by EBUS-TBNA, that has not been the case for some of its more significant benefits, namely the reduction of the diagnostic work-up time and its ability to accurately assess and restage lymph nodes, which were previously stated incorrectly by CT or PET scan. Both these benefits translate into improved outcomes for patients, as delays are reduced, futile surgeries

are prevented and curable operations can be performed on patients previously excluded by CT or PET scan. Indeed, the use of EBUS as the initial diagnostic and staging procedure has been proven to significantly increase survival, compared with conventional diagnostic and staging procedures, in a pragmatic, randomised controlled trial (Navani N. et al, 2015). The instalment of EBUS will have the greatest effect on overwhelmed, suboptimally functioning national healthcare systems, by decreasing the number of required diagnostic and staging procedures, therefore reducing both treatment delays and costs. The improved selection of surgical candidates by EBUS will result in improved patient outcomes. The latest findings regarding the benefits of EBUS are outlined in this review, which, to the best of our knowledge, is the first to emphasise the impact of the procedure, both on timing and costs of lung cancer staging, as well as on survival.

Improving the Implementation of Lung Cancer Screening Guidelines at an Academic Primary Care Practice. Brenner AT, Cubillos L, Birchard K, et al. J Healthc Qual. 2018 Jan/Feb;40(1):27-35. doi: 10.1097/JHQ.0000000000000089.
Expert groups recommend annual chest computed tomography for lung cancer screening (LCS) in high-risk patients. Lung cancer screening in primary care is a complex process that includes identification of the at-risk population, comorbidity assessment, and shared decision making. We identified three key processes required for high-quality screening implementation in our academic primary care practice: (1) systematic collection of lifetime cumulative smoking history to identify potentially eligible patients; (2) visit-based clinical reminders and order sets embedded in the electronic health record (EHR); and (3) tools to facilitate shared decision making and appropriate test ordering. We applied quality improvement techniques to address gaps in these processes. Over 12 months, we developed and implemented a nurse protocol for collecting complete smoking history and entering that data into discrete EHR fields. We obtained histories on over 50% of the clinic's more than 2,300 known current and former smokers, aged 55-80 years. We then built and pilot tested an automated visit-based reminder (VBR) system, driven by the discrete smoking history data. The VBR included an order set and template for documentation of shared decision making. Physicians interacted with the VBR in approximately 30% of opportunities for use. Further work is needed to better understand how to systematically provide appropriate LCS in primary care environments.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Post-Treatment Mortality After Surgery and Stereotactic Body Radiotherapy for Early-Stage Non-Small-Cell Lung Cancer.
Stokes WA1, Bronsert MR1, Meguid RA1, et al. J Clin Oncol. 2018 Jan 18:JCO2017756536. doi: 10.1200/JCO.2017.75.6536. [Epub ahead of print]
PURPOSE: In early-stage non-small cell lung cancer (NSCLC), post-treatment mortality may influence the comparative effectiveness of surgery and stereotactic body radiotherapy (SBRT), with implications for shared decision making among high-risk surgical candidates. We analyzed early mortality after these interventions using the National Cancer Database. **PATIENTS AND METHODS:** We abstracted patients with cT1-T2a, N0, M0 NSCLC diagnosed between 2004 and 2013 undergoing either surgery or SBRT. Thirty-day and 90-day post-treatment mortality rates were calculated and compared using Cox regression and propensity score-matched analyses. **RESULTS:** We identified 76,623 patients who underwent surgery (78% lobectomy, 20% sublobar resection, 2% pneumonectomy) and 8,216 patients who received SBRT. In the unmatched cohort, mortality rates were moderately increased with surgery versus SBRT (30 days, 2.07% v 0.73% [absolute difference (Δ), 1.34%]; P < .001; 90 days, 3.59% v

2.93% [Δ, 0.66%]; P < .001). Among the 27,200 propensity score-matched patients, these differences increased (30 days, 2.41% v 0.79% [Δ, 1.62%]; P < .001; 90 days, 4.23% v 2.82% [Δ, 1.41%]; P < .001). Differences in mortality between surgery and SBRT increased with age, with interaction P < .001 at both 30 days and 90 days (71 to 75 years old: 30-day Δ, 1.87%; 90-day Δ, 2.02%; 76 to 80 years old: 30-day Δ, 2.80%; 90-day Δ, 2.59%; > 80 years old: 30-day Δ, 3.03%; 90-day Δ, 3.67%; all P ≤ .001). Compared with SBRT, surgical mortality rates were higher with increased extent of resection (30-day and 90-day multivariate hazard ratio for mortality: sublobar resection, 2.85 and 1.37; lobectomy, 3.65 and 1.60; pneumonectomy, 14.5 and 5.66; all P < 0.001). **CONCLUSION:** Differences in 30- and 90-day post-treatment mortality between surgery and SBRT increased as a function of age, with the largest differences in favor of SBRT observed among patients older than 70 years. These representative mortality data may inform shared decision making among patients with early-stage NSCLC who are eligible for both interventions.

Left sleeve lobectomy versus left pneumonectomy for the management of patients with non-small cell lung cancer. Wang L1, Pei Y1, Li S1, Zhang S1, Yang Y1. Thorac Cancer. 2018 Jan 17. doi: 10.1111/1759-7714.12583. [Epub ahead of print]
BACKGROUND: The study was conducted to compare the outcomes of sleeve lobectomy (SL) and pneumonectomy (PN) for management of the left lung in patients with non-small cell lung cancer (NSCLC). **METHODS:** One hundred and thirty-five patients who underwent left SL (n = 87) or left PN (n = 48) for NSCLC from January 2006 to December 2011 were enrolled in this retrospective study. Left SL was performed when technically possible. The clinicopathological features and treatment outcomes in both groups were compared. Survival was evaluated using the Kaplan-Meier method, and significant differences were calculated using the log-rank test. Multivariate analysis was conducted using the Cox proportional hazards model to analyze significant variables associated with the outcomes of left SL. **RESULTS:** There were no significant differences in general clinicopathological features (age, gender, lymph node metastasis, pathological stage, and complications of bronchial fistula) between patients who underwent left SL and left PN. The operation duration was markedly longer and the extent of bleeding was greater for left SL than left PN; however patients who underwent left SL achieved significantly longer overall survival than patients who underwent left PN. The outcomes of left SL were only associated with pathological stage. **CONCLUSIONS:** Our results indicate that left SL may offer superior survival than left PN in selected patients. If anatomically feasible, left SL may be a preferred alternative to left PN for NSCLC patients. Pathological stage is an important factor to determine the outcome of SL.

A SUVmax-based propensity matched analysis of stereotactic body radiotherapy versus surgery in stage I non-small cell lung cancer: unveiling the role of 18F-FDG PET/CT in clinical decision-making. Ye L1, Xu F2, Shi S1, Zeng Z1, Jin X3, Huang Y1, Lu C2, Gu J2, Ge D4, He J5. Clin Transl Oncol. 2018 Jan 11. doi: 10.1007/s12094-017-1819-7. [Epub ahead of print]
BACKGROUND: The value of maximum standard uptake value (SUVmax) was overlooked in current studies comparing stereotactic body radiotherapy (SBRT) versus surgery for stage I non-small cell lung cancer (NSCLC). Herein, we aimed to compare the 3-year outcomes based on patients for whom SUVmax were available, and to explore the role of SUVmax in clinical decision-making. **METHODS:** From January 2010 to June 2016, data of eligible patients were collected. Patient variables and clinical outcomes were compared in both unmatched and matched groups using propensity score matching (PSM). Multivariate analysis was performed for predictors of poor outcome. The relationship between treatment approach and survival outcome was also evaluated in subgroup patients stratified by SUVmax level. **RESULTS:** A total of 425 patients treated with either surgery (325) or SBRT (100) were included. Patients receiving SBRT were significantly older, had a higher level of SUVmax and were more likely to have tumor of centrally located. Multivariate analysis showed that SUVmax and tumor size were

significant predictors for 3-year OS, LRC, and PFS, while better PFS was also related to peripheral tumor and surgery. The result of PSM analysis also showed that compared to SBRT, surgery could only achieve better PFS. Subgroup analysis indicated that surgery had added advantage of 3-year LRC and PFS for patients in high SUVmax group (SUVmax > 8), but not in low SUVmax group. **CONCLUSIONS:** The study found a superior PFS after surgery while OS and LRC did not differ between SBRT and surgery. Surgery should be recommended for tumor of high SUVmax.

Outcomes after Video-assisted Thoracoscopic Lobectomy versus Open Lobectomy for Early-Stage Lung Cancer in Older Adults. Ezer N1, Kale M2, Sigel K2, et al. Ann Am Thorac Soc. 2018 Jan;15(1):76-82. doi: 10.1513/AnnalsATS.201612-980OC.
RATIONALE: Video-assisted thoracoscopic surgery (VATS) and open lobectomy are both standard of care for the treatment of early-stage non-small cell lung cancer (NSCLC) because of equivalent long-term survival. **OBJECTIVES:** To evaluate whether the improved perioperative outcomes associated with VATS lobectomy are explained by surgeon characteristics, including case volume and specialty training. **METHODS:** We analyzed the Surveillance, Epidemiology, and End Results-Medicare-linked registry to identify stage I-II NSCLC in patients above 65 years of age. We used a propensity score model to adjust for differences in patient characteristics undergoing VATS versus open lobectomy. Perioperative complications, extended length of stay, and perioperative mortality among patients were compared after adjustment for surgeon's volume and specialty using linear mixed models. We compared survival using a Cox model with robust standard errors. **RESULTS:** We identified 9,508 patients in the registry who underwent lobectomy for early-stage NSCLC. VATS lobectomies were more commonly performed by high-volume surgeons ($P < 0.001$) and thoracic surgeons ($P = 0.01$). VATS lobectomy was associated with decreased adjusted odds of cardiovascular complications (odds ratio [OR] = 0.65; 95% confidence interval [CI] = 0.47-0.90), thromboembolic complications (OR = 0.47; 95% CI = 0.38-0.58), extrapulmonary infections (OR = 0.75; 95% CI = 0.61-0.94), extended length of stay (OR = 0.47; 95% CI = 0.40-0.56), and perioperative mortality (OR = 0.33; 95% CI = 0.23-0.48) even after controlling for differences in surgeon volume and specialty. Long-term survival was equivalent for VATS and open lobectomy (hazard ratio = 0.95; 95% CI = 0.85-1.08) after controlling for patient and tumor characteristics, surgeon volume, and specialization. **CONCLUSIONS:** VATS lobectomy for NSCLC is associated with better postoperative outcomes, but similar long-term survival, compared with open lobectomy among older adults, even after controlling for surgeon experience.

Left sleeve lobectomy versus left pneumonectomy for the management of patients with non-small cell lung cancer. Wang L1, Pei Y1, Li S1, Zhang S1, Yang Y1. Thorac Cancer. 2018 Jan 17. doi: 10.1111/1759-7714.12583. [Epub ahead of print]
BACKGROUND: The study was conducted to compare the outcomes of sleeve lobectomy (SL) and pneumonectomy (PN) for management of the left lung in patients with non-small cell lung cancer (NSCLC). **METHODS:** One hundred and thirty-five patients who underwent left SL (n = 87) or left PN (n = 48) for NSCLC from January 2006 to December 2011 were enrolled in this retrospective study. Left SL was performed when technically possible. The clinicopathological features and treatment outcomes in both groups were compared. Survival was evaluated using the Kaplan-Meier method, and significant differences were calculated using the log-rank test. Multivariate analysis was conducted using the Cox proportional hazards model to analyze significant variables associated with the outcomes of left SL. **RESULTS:** There were no significant differences in general clinicopathological features (age, gender, lymph node metastasis, pathological stage, and complications of bronchial fistula) between patients who underwent left SL and left PN. The operation duration was markedly longer and the extent of bleeding was greater for left SL than left PN; however patients who underwent left SL achieved significantly longer overall survival than patients who underwent left PN. The outcomes of left SL were only

associated with pathological stage. **CONCLUSIONS:** Our results indicate that left SL may offer superior survival than left PN in selected patients. If anatomically feasible, left SL may be a preferred alternative to left PN for NSCLC patients. Pathological stage is an important factor to determine the outcome of SL.

Significance of Body Mass Index for Postoperative Outcomes after Lung Cancer Surgery in Elderly Patients. Matsuoka K1, Yamada T2, Matsuoka T2, Nagai S2, Ueda M2, Miyamoto Y2. World J Surg. 2018 Jan;42(1):153-160. doi: 10.1007/s00268-017-4142-0.
BACKGROUND: Although the frequency of elderly patients undergoing surgery for lung cancer has been increasing, indications for surgery in elderly patients are still controversial. Low body mass index is a significant predictor of poor prognosis in elderly patients with various medical conditions. Then, we examined the long-term outcome of elderly patients who had undergone thoracic surgery for lung cancer, focusing especially on body mass index. **PATIENTS AND METHODS:** Between January 2004 and March 2011, 1673 patients with lung cancer underwent surgical resection at our institution. Among these patients, we retrospectively examined 158 patients aged 80 years or older. **RESULTS:** Perioperative morbidity and mortality rates were 41.8 and 1.3%, respectively. Among 149 patients who were completely followed up, 80 patients (53.7%) died. The overall postoperative survival rates at 3 and 5 years were 66.9 and 49.9%, respectively. Univariate analysis demonstrated that sex (female), smoking index (pack-years <20), histology (non-squamous cell carcinoma), pathological stage (stage I) and BMI (within normal BMI) were statistically significant factors associated with better outcome. Multivariate analysis revealed that patients with a low (<18.5 kg/m2) or high (≥25 kg/m2) body mass index had a significantly and poorer prognosis than patients with a normal body mass index. **CONCLUSION:** Body mass index is a more useful prognostic factor than other clinical factors including pathological stage in elderly patients. Because elderly patients with low and high body mass index have a significant poor prognosis, surgeons and pulmonologist should take this into account when consider surgical indication for such elderly patients.

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

Detection of EGFR, KRAS and BRAF mutations in metastatic cells from cerebrospinal fluid. Frankel D1, Nanni-Metellus I2, Robaglia-Schlupp A1, et al. Clin Chem Lab Med. 2018 Jan 8. pii: /j/cclm.ahead-of-print/cclm-2017-0527/cclm-2017-0527.xml. doi: 10.1515/cclm-2017-0527. [Epub ahead of print]
BACKGROUND: In lung adenocarcinoma, molecular profiling of actionable genes has become essential to set up targeted therapies. However, the feasibility and the relevance of molecular profiling from the cerebrospinal fluid (CSF) in the context of meningeal metastasis have been poorly assessed. **METHODS:** We selected patients with stage IV lung adenocarcinoma harbouring metastatic cells in the CSF after cytological analysis. Seven samples from six patients were eligible for molecular testing of epidermal growth factor receptor (EGFR), V-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue (KRAS), v-Raf murine sarcoma viral oncogene homologue B1 (BRAF) and human epidermal growth factor receptor 2 (HER2) mutations using quantitative polymerase chain reaction (PCR) high-resolution melting curve analysis and Sanger sequencing after DNA extraction from the cell pellets of the CSF. **RESULTS:** Five patients showed mutations in one or two actionable genes, two harboured an EGFR mutation (exons 19 and 21), one only a KRAS mutation, one both EGFR and KRAS mutations and one a BRAF mutation. In all cases, the results of mutation testing provided new major information for patient management, leading to therapeutic adaptation. CSF molecular analysis identified mutations not detected in other neoplastic sites for two patients. In one case, the EGFR p.Thr790Met was identified. CSF was also the only sample available for genetic testing for almost all patients at the time of disease progression. **CONCLUSIONS:** When cancer cells are present in the CSF, the molecular profiling from the cell pellets is relevant, as it can

detect supplemental or different mutations compared to a previous analysis of the primitive tumour or plasma cell-free DNA and allows the adaptation of the treatment strategy.

Immune-Modified Response Evaluation Criteria In Solid Tumors (imRECIST): Refining Guidelines to Assess the Clinical Benefit of Cancer Immunotherapy. Hodi FS1, Ballinger M1, Lyons B1,et al. J Clin Oncol. 2018 Jan 17:JCO2017751644. doi: 10.1200/JCO.2017.75.1644. [Epub ahead of print]

PURPOSE: Treating solid tumors with cancer immunotherapy (CIT) can result in unconventional responses and overall survival (OS) benefits that are not adequately captured by Response Evaluation Criteria In Solid Tumors (RECIST) v1.1. We describe immune-modified RECIST (imRECIST) criteria, designed to better capture CIT responses. **PATIENTS AND METHODS**: Atezolizumab data from clinical trials in non-small-cell lung cancer, metastatic urothelial carcinoma, renal cell carcinoma, and melanoma were evaluated. Modifications to imRECIST versus RECIST v1.1 included allowance for best overall response after progressive disease (PD) and changes in PD definitions per new lesions (NLs) and nontarget lesions. imRECIST progression-free survival (PFS) did not count initial PD as an event if the subsequent scan showed disease control. OS was evaluated using conditional landmarks in patients whose PFS differed by imRECIST versus RECIST v1.1. **RESULTS:** The best overall response was 1% to 2% greater, the disease control rate was 8% to 13% greater, and the median PFS was 0.5 to 1.5 months longer per imRECIST versus RECIST v1.1. Extension of imRECIST PFS versus RECIST v1.1 PFS was associated with longer or similar OS. Patterns of progression analysis revealed that patients who developed NLs without target lesion (TL) progression had a similar or shorter OS compared with patients with RECIST v1.1 TL progression. Patients infrequently experienced a spike pattern (TLs increase, then decrease) but had longer OS than patients without TL reversion. **CONCLUSION:** Evaluation of PFS and patterns of response and progression revealed that allowance for TL reversion from PD per imRECIST may better identify patients with OS benefit. Progression defined by the isolated appearance of NLs, however, is not associated with longer OS. These results may inform additional modifications to radiographic criteria (including imRECIST) to better reflect efficacy with CIT agents.

Real-world usage and clinical outcomes of alectinib among post-crizotinib progression anaplastic lymphoma kinase positive non-small-cell lung cancer patients in the USA. DiBonaventura MD1, Wong W2, Shah-Manek B3,4, Schulz M2. Onco Targets Ther. 2017 Dec 22;11:75-82. doi: 10.2147/OTT.S144960. eCollection 2018.

BACKGROUND: Alectinib is an approved treatment for anaplastic lymphoma kinase (ALK)-positive patients with advanced non-small-cell lung cancer. Despite positive supporting clinical data, there is a lack of real-world information on the usage and patient outcomes of those treated with alectinib post-crizotinib progression. **METHODS:** Participating oncologists (N=95) in the USA were recruited from an online physician panel to participate in a retrospective patient chart review. Physicians randomly selected eligible patients (ie, patients who progressed on crizotinib as their first ALK inhibitor and were treated with alectinib as their second ALK inhibitor), collected demographics and clinical history from their medical charts, and entered the data into an online data collection form. **RESULTS:** A total of N=207 patient charts were included (age: 60.1±10.4 years; 53.6% male). The patients in our sample were older (median age of 60 vs 53 years), were more likely to be current smokers (12% vs 1%), had better performance status (45% vs 33% had an Eastern Cooperative Oncology Group [ECOG] of 0), and were less likely to have an adenocarcinoma histology (83% vs 96%) relative to published clinical trials. The objective response rate was higher than in clinical trials (67.1% vs 51.3%, respectively) as was the disease control rate (89.9% vs 78.8%, respectively), though it varied by race/ethnicity, ECOG, and prior treatment history. Discontinuation (0.0%) and dose reductions (3.4%) due to adverse events were uncommon in alectinib. **CONCLUSION:** Patients using alectinib post-crizotinib in clinical practice are older, more

racially/ethnically and histologically diverse than patients in published trials. Real-world response rates were high and similar to those reported in clinical studies, though there is some variation by patient characteristics. Alectinib was well tolerated in clinical practice as reflected by the rates of discontinuation, dose reductions, and dose interruptions.

Carcinoembryonic Antigen as a Predictive Biomarker of Response to Nivolumab in Non-small Cell Lung Cancer. Kataoka Y1, Hirano K2, Narabayashi T3, Hara S4, Fujimoto D5, Tanaka T6, Ebi N7, Tomii K5, Yoshioka H8. Anticancer Res. 2018 Jan;38(1):559-563.
AIM: To find new predictive factors for the efficient use of immune checkpoint inhibitors in patients with non-small-cell lung cancer (NSCLC). **PATIENTS AND METHODS:** In this multicenter retrospective cohort study, we evaluated consecutive patients treated with nivolumab between January and October 2016 after second-line systemic chemotherapy. The endpoint was progression-free survival (PFS), as defined by Response Evaluation Criteria in Solid Tumors version 1.1. **RESULTS:** A total of 189 patients were included in the study. Sixty-four percent had received two or more prior systemic therapies. In Cox proportional hazard analyses, Eastern Cooperative Oncology Group Performance Status of 2 or more, lactate dehydrogenase (LDH) ≥217 mg/dl, and carcinoembryonic antigen ≥13.8 ng/ml were independently associated with inferior PFS. LDH was not associated in the sensitivity analysis. **CONCLUSION:** In patients with NSCLC treated with nivolumab, worse pretreatment performance status, and higher carcinoembryonic antigen were associated with inferior PFS.

Imaging skeletal muscle volume, density, and FDG uptake before and after induction therapy for non-small cell lung cancer.
Goncalves MD1, Taylor S2, Halpenny DF3, et al. Clin Radiol. 2018 Jan 6. pii: S0009-9260(17)30568-8. doi: 10.1016/j.crad.2017.12.004. [Epub ahead of print]
AIM: To assess whether changes in body composition could be assessed serially using conventional thoracic computed tomography (CT) and positron-emission tomography (PET)/CT imaging in patients receiving induction chemotherapy for non-small cell lung cancer (NSCLC). **MATERIALS AND METHODS:** CT-based skeletal muscle volume and density were measured retrospectively from thoracic and lumbar segment CT images from 88 patients with newly diagnosed and untreated NSCLC before and after induction chemotherapy. Skeletal muscle 2-[18F]-fluoro-2-deoxy-d-glucose (FDG) uptake was measured from PET/CT images from a subset of patients (n=42). Comparisons of each metric before and after induction chemotherapy were conducted using the non-parametric Wilcoxon signed-rank test for paired data. The association between clinical factors and percentage change in muscle volume was examined using univariate linear regression models, with adjustment for baseline muscle volume. **RESULTS:** Following induction chemotherapy, thoracic (-3.3%, p=0.0005) and lumbar (-2.6%, p=0.0101) skeletal muscle volume were reduced (adiposity remained unchanged). The proportion of skeletal muscle with a density <0 HU increased (7.9%, p<0.0001), reflecting a decrease in skeletal muscle density and skeletal muscle FDG uptake increased (10.4-31%, p<0.05). No imaging biomarkers were correlated with overall survival. **CONCLUSION:** Changes in body composition can be measured from routine thoracic imaging. During chemotherapy skeletal muscle volume and metabolism are altered; however, there was no impact on survival in this retrospective series, and further validation in prospective, well-controlled studies are required.

EGFR-TKI-Associated Interstitial Pneumonitis in Nivolumab-Treated Patients With Non-Small Cell Lung Cancer. Oshima Y1, Tanimoto T2, Yuji K1, Tojo A1. JAMA Oncol. 2018 Jan 11. doi: 10.1001/jamaoncol.2017.4526. [Epub ahead of print]
IMPORTANCE: Nivolumab and epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are now the standard-of-care therapies in non-small cell lung cancer (NSCLC). Although EGFR-

TKIs are well understood and have well-defined safety profiles, our experience with immune checkpoint inhibitors is still growing, particularly regarding the use of combinations of different classes of antitumor agents, including both the concomitant and sequential use of such agents. **OBJECTIVE:** To determine whether nivolumab increases EGFR-TKI-associated interstitial pneumonitis (IP). **DESIGN, SETTING, AND PARTICIPANTS:** A database study of 20 516 participants with NSCLC in the US Food and Drug Administration Adverse Event Reporting System (FAERS) database, performed between April 2015 and March 2017. **MAIN OUTCOMES AND MEASURES:** We compared the incidence of EGFR-TKI-associated IP in patients receiving and not receiving nivolumab treatment. **RESULTS:** The mean (SD) age of participants treated with EGFR-TKI, with and without nivolumab, was 64.4 (15.5) and 68.9 (11.8) years, respectively, and the proportion of men was 40.0% and 53.8%, respectively. Of the 20 516 participants with NSCLC, 985 cases (4.80%; 95% confidence interval [CI], 4.51-5.10) developed IP. Of 5777 patients treated with EGFR-TKI, 265 developed IP (4.59%; 95% CI, 4.06-5.16). Of 70 patients treated with both EGFR-TKI and nivolumab, 18 developed IP (25.7%; 95% CI, 16.0-37.6). The adjusted odds ratio for an interaction between EGFR-TKI and nivolumab was 4.31 (95% CI, 2.37-7.86; $P < .001$), suggesting the existence of an interaction. When we further stratified the patients by treatment with and without nivolumab, the odds ratio of EGFR-TKI-associated IP in cases with and without nivolumab treatment was 5.09 (95% CI, 2.87-9.03) and 1.22 (95% CI, 1.00-1.47), respectively. **CONCLUSIONS AND RELEVANCE:** We found a higher proportion of reports of IP for nivolumab in combination with EGFR-TKI vs treatment with either drug alone. Owing to the limitations of this study, the results warrant further confirmation. However, careful consideration should be given to the possibility of an increased risk of IP when EGFR-TKI is administered in combination with nivolumab, including concomitant and sequential use, and careful monitoring for IP is recommended.

Beyond Concurrent Chemoradiation: The Emerging Role of PD-1/PD-L1 Inhibitors in Stage III Lung Cancer. McCall NS1, Dicker AP2, Lu B3. Clin Cancer Res. 2018 Jan 22. pii: clincanres.3269.2017. doi: 10.1158/1078-0432.CCR-17-3269. [Epub ahead of print]
Concurrent chemoradiation (cCRT) with platinum-based chemotherapy is standard of care therapy for patients with Stage III unresectable non-small cell lung cancer (NSCLC). Though potentially curative, five-year overall survival has hovered around 20%, despite extensive efforts to improve outcomes with increasing doses of conformal radiation and intensification of systemic therapy with either induction or consolidation chemotherapy. PD-1/PD-L1 immune checkpoint inhibitors have demonstrated unprecedented efficacy in patients with Stage IV NSCLC. Additionally, preclinical and early clinical evidence suggests that chemotherapy and radiation may work synergistically with anti-PD-1/PD-L1 therapy to promote anti-tumor immunity, which has led to the initiation of clinical trials testing these drugs in patients with Stage III NSCLC. A preliminary report of a randomized phase III trial, the PACIFIC trial, demonstrated an impressive increase in median progression-free survival with consolidative durvalumab, a PD-L1 inhibitor, compared to observation after cCRT. Here, we discuss the clinical and translational implications of integrating PD-1/PD-L1 inhibitors in the management of patients with unresectable Stage III NSCLC.

Outcomes of bevacizumab combined with chemotherapy in lung adenocarcinoma-induced malignant pleural effusion. Tao H1, Meng Q1, Li M1, Shi L1, Tang J1, Liu Z1. Thorac Cancer. 2018 Jan 3. doi: 10.1111/1759-7714.12582. [Epub ahead of print]
BACKGROUND: VEGF is critical in the pathogenesis of malignant pleural effusion (MPE). To understand the clinical benefits of antiangiogenic agents, the efficacy of chemotherapy containing bevacizmab was investigated in patients with lung adenocarcinoma-induced MPE. **METHODS:** The data of lung adenocarcinoma patients with MPE treated with bevacizumab plus chemotherapy on day 1, every three weeks, for ≤ 6 cycles was retrospectively collected. Patients who achieved a response or stable

disease were administered bevacizumab as maintenance therapy until progression. The primary outcomes of the study were MPE response rate (RR), MPE control rate, and pleural progression-free survival (PPFS), while the secondary outcomes were PFS, overall survival (OS), changes to the lung volume and thoracic cage, and safety profiles. **RESULTS:** A total of 21 cases were collected, and all were evaluable for response, including 15 chemotherapy-naïve patients and 6 who experienced relapse. The median cycle of treatments was 7 (1-42) and 5 (2-6) for bevacizumab and chemotherapy, respectively. The MPE RR reached 81.0%. The MPE control rate at 6, 12, 24, 48, and 96 weeks were 95.2%, 90.0%, 89.5%, 73.7%, and 43.8%, respectively. Median PPFS was significantly longer than PFS (22.2 vs. 7.8 months; P = 0.044), and median OS was 25.8 months. Nineteen (90.5%) patients experienced lung re-expansion after treatment. Only one (4.8%) patient suffered thoracic volume decrease during treatment and the follow-up period. No unexpected adverse events were observed. **CONCLUSIONS:** Bevacizumab combined with chemotherapy demonstrated efficacious, persistence, and safety in controlling lung cancer-induced MPE, indicating a potential superior therapeutic option.

Prognostic Factors as a Function of Disease-free Interval After Definitive (Chemo)radiation for Non-Small Cell Lung Cancer Using Conditional Survival Analysis. Hong J1, Liao Z1, Zhuang Y1, Levy LB1, Sheu T1, Heymach JV2, Nguyen QN1, Xu T1, Komaki R1, Gomez DR1. Am J Clin Oncol. 2018 Jan;41(1):46-52. doi: 10.1097/COC.0000000000000235.
PURPOSE: We analyzed overall and disease-free survival (OS and DFS) after definitive (chemo)radiation for stage III non-small cell lung cancer with 2 statistical methods: Kaplan-Meier (KM) analysis, with diagnosis as index date, and conditional survival (CS) analysis, with a variety of disease-free index dates, and determined whether prognostic factors varied based on the reference date.
MATERIALS AND METHODS: All 651 patients analyzed received definitive (chemo)radiotherapy for stage III non-small cell lung cancer in November 1998 to December 2010 at a single institution; all had Karnofsky performance status scores ≥60 and received ≥60 Gy. OS and DFS were first calculated with the KM method, and then CS was used to calculate 2 outcomes: OS conditioned on DFS time (OS|DFS) and DFS conditioned on DFS time (DFS|DFS). Factors predicting OS and DFS conditioned on 1-, 2-, and 3-year DFS were sought in univariate and multivariate analyses. **RESULTS:** KM analysis produced 1-, 2-, and 3-year DFS rates of 48%, 30%, and 26%; OS rates were 64%, 41%, and 29%. By CS analysis, both OS|DFS and DFS|DFS showed an increase in 5-year OS after 6 months, and CS after 30 months approached 100%. On multivariate analyses, age and concurrent chemoradiation predicted OS|DFS; age, smoking history, tumor histology, disease stage, and radiation dose predicted DFS|DFS.
CONCLUSIONS: CS analysis showed that the probability of long-term survival increases sharply after 6 months with no evidence of disease; factors predicting survival differed based on the method and endpoint used.

NSCLC - RADIOTHERAPY

Volumetric modulated arc therapy treatment planning of thoracic vertebral metastases using stereotactic body radiotherapy. Mallory M1, Pokhrel D2, Badkul R1, Jiang H1, Lominska C1, Wang F1. J Appl Clin Med Phys. 2018 Jan 19. doi: 10.1002/acm2.12252. [Epub ahead of print]
PURPOSE/OBJECTIVES: To retrospectively evaluate the plan quality, treatment efficiency, and accuracy of volumetric modulated arc therapy (VMAT) plans for thoracic spine metastases using stereotactic body radiotherapy (SBRT). **MATERIALS/METHODS:** Seven patients with thoracic vertebral metastases treated with noncoplanar hybrid arcs (NCHA) (1 to 2 3D-conformal partial arcs +7 to 9 IMRT beams) were re-optimized with VMAT plans using three coplanar arcs. Tumors were located between T2 and T7 and PTVs ranged between 24.3 and 240.1 cc (median 48.1 cc). All prescriptions were 30 Gy in 5 fractions with 6 MV beams treated using the Novalis Tx linac equipped with high definition

multileaf collimators (HDMLC). MR images were fused with planning CTs for target and OAR contouring. Plans were compared for target coverage using conformality index (CI), homogeneity index (HI), D90, D98, D2, and Dmedian. Normal tissue sparing was evaluated by comparing doses to the spinal cord (Dmax, D0.35, and D1.2 cc), esophagus (Dmax and D5 cc), heart (Dmax, D15 cc), and lung (V5 and V10). Data analysis was performed with a two-sided t-test for each set of parameters. Dose delivery efficiency and accuracy of each VMAT plan was assessed via quality assurance (QA) using a MapCHECK device. The Beam-on time (BOT) was recorded, and a gamma index was used to compare dose agreement between the planned and measured doses. **RESULTS:** VMAT plans resulted in improved CI (1.02 vs. 1.36, P = 0.05), HI (0.14 vs. 0.27, P = 0.01), D98 (28.4 vs. 26.8 Gy, P = 0.03), D2 (32.9 vs. 36.0 Gy, P = 0.02), and Dmedian (31.4 vs. 33.7 Gy, P = 0.01). D90 was improved but not statistically significant (30.4 vs. 31.0 Gy, P = 0.38). VMAT plans showed statistically significant improvements in normal tissue sparing: Esophagus Dmax (22.5 vs. 27.0 Gy, P = 0.03), Esophagus 5 cc (17.6 vs. 21.5 Gy, P = 0.02), and Heart Dmax (13.1 vs. 15.8 Gy, P = 0.03). Improvements were also observed in spinal cord and lung sparing as well but were not statistically significant. The BOT showed significant reduction for VMAT, 4.7 ± 0.6 min vs. 7.1 ± 1 min for NCHA (not accounting for couch kicks). VMAT plans demonstrated an accurate dose delivery of 95.5 ± 1.0% for clinical gamma passing rate of 3%/3 mm criteria, which was similar to NCHA plans. **CONCLUSIONS:** VMAT plans have shown improved dose distributions and normal tissue sparing compared to NCHA plans. Significant reductions in treatment time could potentially minimize patient discomfort and intrafraction movement errors. VMAT planning for SBRT is an attractive option for the treatment of metastases to thoracic vertebrae, and further investigation using alternative fractionation schedules is warranted.

Pretreatment 18F-Fluorodeoxyglucose Positron Emission Tomography Standardized Uptake Values and Tumor Size in Medically Inoperable Nonsmall Cell Lung Cancer Is Prognostic of Overall 2-Year Survival After Stereotactic Body Radiation Therapy. Kocher MR, Sharma A, Garrett-Mayer E, Ravenel JG. J Comput Assist Tomogr. 2018 Jan/Feb;42(1):146-150. doi: 10.1097/RCT.0000000000000653.

OBJECTIVE: The aim of this study was to determine prognostic value of tumor size and metabolic activity on survival for patients with early stage nonsmall cell lung cancer receiving stereotactic body radiation therapy. **METHODS:** We retrospectively evaluated the patients who underwent positron emission tomography-computed tomography scan before stereotactic body radiation therapy treatment. Tumor diameter, tumor volume, maximum standardized uptake value (SUVmax), standardized uptake value (SUV) average, and SUV volume were obtained. Cox regression analyses were performed to determine the associations between tumor characteristics and survival. **RESULTS:** The patients with large tumors and high SUVmax have worse survival than patients with small tumors and low SUVmax (hazard ratio [HR] = 3.47, P = 0.007). Patients with small tumors and high SUVmax (HR = 1.80; P = 0.24) and large tumors and low SUVmax (HR = 1.55; P = 0.43) had increased risk of death compared with patients with small tumors and low SUVmax. **CONCLUSIONS:** Both increased tumor size and metabolic activity are associated with increased risk of death. Combining size and metabolic activity together is superior for predicting 2-year survival and identifying patients for whom survival is statistically worse.

The Role of Prophylactic Cranial Irradiation for Non-small Cell Lung Cancer. Precival C1, Landy M1, Poole C1, Mullaney L2. Anticancer Res. 2018 Jan;38(1):7-14.

BACKGROUND: The use of prophylactic cranial irradiation (PCI) to treat brain metastases (BM) in non-small cell lung cancer (NSCLC) is restricted due to the potential associated toxicity and lack of survival benefit. BM can have a negative impact on neurocognitive function (NF) and quality of life (QOL). The aim of this review was to assess the impact of PCI on disease-specific and NF and QOL

outcomes. **MATERIALS AND METHODS:** An electronic database literature search was completed to identify relevant studies. **RESULTS:** Fourteen published articles were included. PCI significantly reduced the incidence of BM, but no significant survival advantage was found. NF decline was reported in one trial. No significant difference in QOL with PCI was reported. PCI was well tolerated by the majority of patients with NSCLC and associated with a relatively low toxicity. **CONCLUSION:** PCI reduces the incidence of BM without any significant survival advantage. PCI has the potential to be beneficial in practice for certain patients with locally advanced NSCLC, based on disease factors and patient preference.

Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. Iyengar P1, Wardak Z1, Gerber DE2, et al. JAMA Oncol. 2018 Jan 11;4(1):e173501. doi: 10.1001/jamaoncol.2017.3501. Epub 2018 Jan 11.
IMPORTANCE: Patterns-of-failure studies suggest that in metastatic non-small-cell lung cancer (NSCLC) sites of gross disease at presentation are the first to progress when treated with chemotherapy. This knowledge has led to increased adoption of local ablative radiation therapy in patients with stage IV NSCLC, though prospective randomized evidence is limited. **OBJECTIVE:** To determine if intervening with noninvasive stereotactic ablative radiotherapy (SAbR) prior to maintenance chemotherapy in patients with non-progressive limited metastatic NSCLC after induction therapy led to significant improvements in progression-free survival (PFS). **DESIGN, SETTING, AND PARTICIPANTS:** This is a single-institution randomized phase 2 study of maintenance chemotherapy alone vs SAbR followed by maintenance chemotherapy for patients with limited metastatic NSCLC (primary plus up to 5 metastatic sites) whose tumors did not possess EGFR-targetable or ALK-targetable mutations but did achieve a partial response or stable disease after induction chemotherapy. **INTERVENTIONS:** Maintenance chemotherapy or SAbR to all sites of gross disease (including SAbR or hypofractionated radiation to the primary) followed by maintenance chemotherapy. **MAIN OUTCOMES AND MEASURES:** The primary end point was PFS; secondary end points included toxic effects, local and distant tumor control, patterns of failure, and overall survival. **RESULTS:** A total of 29 patients (9 women and 20 men) were enrolled; 14 patients (median [range] age, 63.5 [51.0-78.0] years) were allocated to the SAbR-plus-maintenance chemotherapy arm, and 15 patients (median [range] age, 70.0 [51.0-79.0] years) were allocated to the maintenance chemotherapy-alone arm. The trial was stopped to accrual early after an interim analysis found a significant improvement in PFS in the SAbR-plus-maintenance chemotherapy arm of 9.7 months vs 3.5 months in the maintenance chemotherapy-alone arm ($P = .01$). Toxic effects were similar in both arms. There were no in-field failures with fewer overall recurrences in the SAbR arm while those patients receiving maintenance therapy alone had progression at existing sites of disease and distantly. **CONCLUSIONS AND RELEVANCE:** Consolidative SAbR prior to maintenance chemotherapy appeared beneficial, nearly tripling PFS in patients with limited metastatic NSCLC compared with maintenance chemotherapy alone, with no difference in toxic effects. The irradiation prevented local failures in original disease, the most likely sites of first recurrence. Furthermore, PFS for patients with limited metastatic disease appeared similar to those patients with a greater metastatic burden, further arguing for the potential benefits of local therapy in limited metastatic settings.

Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Tsao MN1, Xu W, Wong RK, Lloyd N, Laperriere N, Sahgal A, Rakovitch E, Chow E. Cochrane Database Syst Rev. 2018 Jan 25;1:CD003869. doi: 10.1002/14651858.CD003869.pub4. [Epub ahead of print]
BACKGROUND: This is an update to the review published in the Cochrane Library (2012, Issue 4).It is estimated that 20% to 40% of people with cancer will develop brain metastases during the course of their illness. The burden of brain metastases impacts quality and length of survival. **OBJECTIVES:** To assess

the effectiveness and adverse effects of whole brain radiotherapy (WBRT) given alone or in combination with other therapies to adults with newly diagnosed multiple brain metastases. **SEARCH METHODS:** We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase to May 2017 and the National Cancer Institute Physicians Data Query for ongoing trials. **SELECTION CRITERIA:** We included phase III randomised controlled trials (RCTs) comparing WBRT versus other treatments for adults with newly diagnosed multiple brain metastases. **DATA COLLECTION AND ANALYSIS:** Two review authors indepe ndently assessed trial quality and abstracted information in accordance with Cochrane methods. **MAIN RESULTS:** We added 10 RCTs to this updated review. The review now includes 54 published trials (45 fully published reports, four abstracts, and five subsets of data from previously published RCTs) involving 11,898 participants.Lower biological WBRT doses versus controlThe hazard ratio (HR) for overall survival (OS) with lower biological WBRT doses as compared with control (3000 cGy in 10 daily fractions) was 1.21 (95% confidence interval (CI) 1.04 to 1.40; P = 0.01; moderate-certainty evidence) in favour of control. The HR for neurological function improvement (NFI) was 1.74 (95% CI 1.06 to 2.84; P = 0.03; moderate-certainty evidence) in favour of control fractionation.Higher biological WBRT doses versus controlThe HR for OS with higher biological WBRT doses as compared with control (3000 cGy in 10 daily fractions) was 0.97 (95% CI 0.83 to 1.12; P = 0.65; moderate-certainty evidence). The HR for NFI was 1.14 (95% CI 0.92 to 1.42; P = 0.23; moderate-certainty evidence).WBRT and radiosensitisersThe addition of radiosensitisers to WBRT did not confer additional benefit for OS (HR 1.05, 95% CI 0.99 to 1.12; P = 0.12; moderate-certainty evidence) or for brain tumour response rates (odds ratio (OR) 0.84, 95% CI 0.63 to 1.11; P = 0.22; high-certainty evidence).Radiosurgery and WBRT versus WBRT aloneThe HR for OS with use of WBRT and radiosurgery boost as compared with WBRT alone for selected participants was 0.61 (95% CI 0.27 to 1.39; P = 0.24; moderate-certainty evidence). For overall brain control at one year, the HR was 0.39 (95% CI 0.25 to 0.60; P < 0.0001; high-certainty evidence) favouring the WBRT and radiosurgery boost group.Radiosurgery alone versus radiosurgery and WBRTThe HR for local brain control was 2.73 (95% CI 1.87 to 3.99; P < 0.00001; high-certainty evidence)favouring the addition of WBRT to radiosurgery. The HR for distant brain control was 2.34 (95% CI 1.73 to 3.18; P < 0.00001; high-certainty evidence) favouring WBRT and radiosurgery. The HR for OS was 1.00 (95% CI 0.80 to 1.25; P = 0.99; moderate-certainty evidence). Two trials reported worse neurocognitive outcomes and one trial reported worse quality of life outcomes when WBRT was added to radiosurgery.We could not pool data from trials related to chemotherapy, optimal supportive care (OSC), molecular targeted agents, neurocognitive protective agents, and hippocampal sparing WBRT. However, one trial reported no differences in quality-adjusted life-years for selected participants with brain metastases from non-small-cell lung cancer randomised to OSC and WBRT versus OSC alone. **AUTHORS' CONCLUSIONS:** None of the trials with altered higher biological WBRT dose-fractionation schemes reported benefit for OS, NFI, or symptom control compared with standard care. However, OS and NFI were worse for lower biological WBRT dose-fractionation schemes than for standard dose schedules. The addition of WBRT to radiosurgery improved local and distant brain control in selected people with brain metastases, but data show worse neurocognitive outcomes and no differences in OS. Selected people with multiple brain metastases from non-small-cell lung cancer may show no difference in OS when OSC is given and WBRT is omitted. Use of radiosensitisers, chemotherapy, or molecular targeted agents in conjunction with WBRT remains experimental. Further trials are needed to evaluate the use of neurocognitive protective agents and hippocampal sparing with WBRT. As well, future trials should examine homogeneous participants with brain metastases with focus on prognostic features and molecular markers.

Differences in lung injury after IMRT or proton therapy assessed by 18FDG PET imaging.
Shusharina N1, Liao Z2, Mohan R3, Liu A3, Niemierko A1, Choi N1, Bortfeld T1. Radiother Oncol. 2018 Jan 15. pii: S0167-8140(18)30012-4. doi: 10.1016/j.radonc.2017.12.027. [Epub ahead of print]

BACKGROUND AND PURPOSE: To compare lung injury among non-small cell lung cancer (NSCLC) patients treated with IMRT or proton therapy as revealed by 18F-FDG post-treatment uptake and to determine factors predictive for clinically symptomatic radiation pneumonitis. **MATERIAL AND METHODS:** For 83 patients treated with IMRT or proton therapy, planning CT and follow up 18F-FDG PET-CT were analyzed. Post-treatment PET-CT was aligned with planning CT to establish a voxel-to-voxel correspondence between PET and planning dose images. 18F-FDG uptake as a function of radiation dose to normal lung was obtained for each patient. PET image-derived parameters as well as demographic, clinical, treatment and dosimetric patient characteristics were correlated with clinical symptoms of pneumonitis. **RESULTS:** The dose distributions for the two modalities were significantly different; V5 was higher for IMRT, whereas V60 was higher for protons. The mean lung dose (MLD) was similar for the two modalities. The slope of linear 18F-FDG-uptake - dose response did not differ significantly between the two modalities. The MLD, slope, and 95th percentile of SUV were identified as three major factors associated with radiation pneumonitis. **CONCLUSIONS:** Despite significantly different dose distributions for IMRT and for protons, the slope of the SUV-dose linear regression line previously shown to be associated with RP did not differ between IMRT and protons. Patients who developed radiation pneumonitis had statistically significantly higher MLD and higher slope regardless of treatment modality.

SMALL CELL LUNG CANCER - SCLC

Barriers to Combined-Modality Therapy for Limited-Stage Small-Cell Lung Cancer. Pezzi TA1, Schwartz DL1,2, Mohamed ASR1,3, et al. JAMA Oncol. 2018 Jan 4. doi: 10.1001/jamaoncol.2017.4504. [Epub ahead of print]

IMPORTANCE: Combined-modality therapy with chemotherapy and radiation therapy plays a crucial role in the upfront treatment of patients with limited-stage small-cell lung cancer (SCLC), but there may be barriers to utilization in the United States. **OBJECTIVE:** To estimate utilization rates and factors associated with chemotherapy and radiation therapy delivery for limited-stage SCLC using the National Cancer Database. **DESIGN, SETTING, AND PARTICIPANTS:** Analysis of initial management of all limited-stage SCLC cases from 2004 through 2013 in the National Cancer Database. **MAIN OUTCOMES AND MEASURES:** Utilization rates of chemotherapy and radiation therapy at time of initial treatment. Multivariable analysis identified independent clinical and socioeconomic factors associated with utilization and overall survival. **RESULTS:** A total of 70 247 cases met inclusion criteria (55.3% female; median age, 68 y [range, 19-90 y]). Initial treatment was 55.5% chemotherapy and radiation therapy, 20.5% chemotherapy alone, 3.5% radiation therapy alone, and 20.0% neither (0.5% not reported). Median survival was 18.2 (95% CI, 17.9-18.4), 10.5 (95% CI, 10.3-10.7), 8.3 (95% CI, 7.7-8.8), and 3.7 (95% CI, 3.5-3.8) months, respectively. Being uninsured was associated with a lower likelihood of both chemotherapy (odds ratio [OR], 0.65; 95% CI, 0.56-0.75; $P < .001$) and radiation therapy (OR, 0.75; 95% CI, 0.67-0.85; $P < .001$) administration on multivariable analysis. Medicare/Medicaid insurance had no impact on chemotherapy use, whereas Medicaid (OR, 0.79; 95% CI, 0.72-0.87; $P < .001$) and Medicare (OR, 0.86; 95% CI, 0.82-0.91; $P < .001$) were independently associated with a lower likelihood of radiation therapy delivery. Lack of health insurance (HR, 1.19; 95% CI, 1.13-1.26; $P < .001$), Medicaid (HR, 1.27; 95% CI, 1.21-1.32; $P < .001$), and Medicare (HR, 1.12; 95% CI, 1.09-1.15; $P < .001$) coverage were independently associated with shorter survival on adjusted analysis, while chemotherapy (HR, 0.55; 95% CI, 0.54-0.57; $P < .001$) and radiation therapy (HR, 0.62; 95% CI, 0.60-0.63; $P < .001$) were associated with a survival benefit. **CONCLUSIONS AND RELEVANCE:** Substantial proportions of patients documented in a major US cancer registry did not receive radiation therapy or chemotherapy as part of initial treatment for limited-stage SCLC, which, in turn, was associated with poor survival. Lack of radiation therapy delivery was uniquely associated with

government insurance coverage, suggesting a need for targeted access improvement in this population. Additional work will be necessary to conclusively define exact population patterns, specific treatment deficiencies, and causative factors leading to heterogeneous care delivery.

Target engagement imaging of PARP inhibitors in small-cell lung cancer. Carney B1,2, Kossatz S1, Lok BH3,4, et al. Nat Commun. 2018 Jan 12;9(1):176. doi: 10.1038/s41467-017-02096-w. Insufficient chemotherapy response and rapid disease progression remain concerns for small-cell lung cancer (SCLC). Oncologists rely on serial CT scanning to guide treatment decisions, but this cannot assess in vivo target engagement of therapeutic agents. Biomarker assessments in biopsy material do not assess contemporaneous target expression, intratumoral drug exposure, or drug-target engagement. Here, we report the use of PARP1/2-targeted imaging to measure target engagement of PARP inhibitors in vivo. Using a panel of clinical PARP inhibitors, we show that PARP imaging can quantify target engagement of chemically diverse small molecule inhibitors in vitro and in vivo. We measure PARP1/2 inhibition over time to calculate effective doses for individual drugs. Using patient-derived xenografts, we demonstrate that different therapeutics achieve similar integrated inhibition efficiencies under different dosing regimens. This imaging approach to non-invasive, quantitative assessment of dynamic intratumoral target inhibition may improve patient care through real-time monitoring of drug delivery.

Effect of sequential chemoradiotherapy in patients with limited-disease small-cell lung cancer who were ineligible for concurrent therapy: a retrospective study at two institutions. Ohara S1,2, Kanda S1, Okuma H1, et al. Jpn J Clin Oncol. 2018 Jan 1;48(1):82-88. doi: 10.1093/jjco/hyx153. **BACKGROUND:** The standard treatment for limited-disease small-cell lung cancer (LD-SCLC) is a combination of chemotherapy and concurrent thoracic radiotherapy. In selected cases, sequential radiotherapy is preferred because of the need for a large irradiation field, patient age, comorbidities or performance status. Nevertheless, the efficacy of sequential chemoradiotherapy in patients in whom concurrent chemoradiotherapy is contraindicated is not well known. **METHODS:** We retrospectively analyzed 286 patients with LD-SCLC at two institutions in Japan between 2000 and 2014. We compared the clinical characteristics and treatment outcomes of patients undergoing sequential radiotherapy with those undergoing concurrent radiotherapy. **RESULTS:** One hundred and seventy-five patients received concurrent chemoradiotherapy, 33 received sequential chemoradiotherapy and 46 received chemotherapy only. The median patient age was 64 years (range, 18-82 years) for the concurrent group and 71 years (49-82 years) for the sequential group. Conventional radiotherapy was selected more frequently than accelerated hyperfractionated radiotherapy (27 patients [82%] with conventional radiotherapy, and six patients [18%] with hyperfractionated radiotherapy). The major reasons for the selection of sequential radiotherapy were advanced age (12 patients) and a large irradiation field (11 patients). The median overall survival time was 41.1 months for the sequential group and 38.1 months for the concurrent group. The 5-year survival rates were 36.0% for the sequential group and 41.6% for the concurrent group. **CONCLUSIONS:** In clinical situation, since the treatment outcomes for patients with sequential radiotherapy were comparable to those receiving concurrent radiotherapy, sequential chemoradiotherapy can be a choice for the treatment of patients who are not candidates for concurrent chemoradiotherapy.

Patients with advanced cancer and depression report a significantly higher symptom burden than non-depressed patients.
Grotmol KS1, Lie HC2, Loge JH1, Aass N3, Haugen DF4, Stone PC5, Kaasa S6, Hjermstad MJ1. Palliat Support Care. 2018 Jan 10:1-7. doi: 10.1017/S1478951517001183. [Epub ahead of print]
OBJECTIVE: Clinical observations indicate that patients with advanced cancer and depression report higher symptom burden than nondepressed patients. This is rarely examined empirically. Study aim was to investigate the association between self-reported depression disorder (DD) and symptoms in patients with advanced cancer controlled for prognostic factors. **METHOD:** The sample included 935 patients, mean age 62, 52% males, from an international multicentre observational study (European Palliative Care Research Collaborative - Computerised Symptom Assessment and Classification of Pain, Depression and Physical Function). DD was assessed by the Patient Health Questionnaire-9 and scored with Diagnostic and Statistical Manual of Mental Disorder-5 algorithm for major depressive disorder, excluding somatic symptoms. Symptom burden was assessed by summing scores on somatic Edmonton Symptom Assessment Scale (ESAS) symptoms, excluding depression, anxiety, and well-being. Item-by-item scores and symptom burden of those with and without DD were compared using nonparametric Mann-Whitney U tests. The relative importance of sociodemographic, medical, and prognostic factors and DD in predicting symptom burden was assessed by hierarchical, multiple regression analyses. **RESULT:** Patients with DD reported significantly higher scores on ESAS items and a twofold higher symptom burden compared with those without. Factors associated with higher symptom burden were as follows. **DIAGNOSIS:** lung ($\beta = 0.15$, $p < 0.001$) or breast cancer ($\beta = 0.08$, $p < 0.05$); poorer prognosis: high C-reactive protein ($\beta = 0.08$, $p < 0.05$), lower Karnofsky Performance Status ($\beta = -0.14$, $p < 0.001$), and greater weight loss ($\beta = -0.15$, $p < 0.001$); taking opioids ($\beta = 0.11$, $p < 0.01$); and having DD ($\beta = 0.23$, $p < 0.001$). The full model explained 18% of the variance in symptom burden. DD explained 4.4% over and above that explained by all the other variables. **SIGNIFICANCE OF RESULTS:** Depression in patients with advanced cancer is associated with higher symptom burden. These results encourage improved routines for identifying and treating those suffering from depression.

Differential effects of early palliative care based on the age and sex of patients with advanced cancer from a randomized controlled trial. Nipp RD1, El-Jawahri A1, Traeger L2, Jacobs JM2, Gallagher ER1, Park ER2, Jackson VA3, Pirl WF4, Temel JS1, Greer JA2. Palliat Med. 2018 Jan 1:269216317751893. doi: 10.1177/0269216317751893. [Epub ahead of print]
BACKGROUND: Early palliative care interventions enhance patient outcomes, including quality of life, mood, and coping, but it remains unclear whether certain subgroups of patients are more likely to benefit from early palliative care. We explored whether age and sex moderate the improved outcomes seen with early palliative care. **METHODS:** We performed a secondary analysis of data from a randomized trial of 350 patients with advanced lung and non-colorectal gastrointestinal cancer. Patients received an early palliative care intervention integrated with oncology care or usual oncology care alone. We used linear regression to determine if age (older or younger than 65) and sex moderated the effects of the intervention on quality of life (Functional Assessment of Cancer Therapy-General (FACT-G)), depression symptoms (Patient Health Questionnaire 9 (PHQ-9)), and coping (Brief COPE) within lung and gastrointestinal subgroups. **RESULTS:** At 24 weeks, younger patients with lung cancer receiving early palliative care reported increased use of active coping ($B = 1.74$; $p = 0.02$) and decreased use of avoidant coping ($B = -0.97$; $p = 0.02$), but the effects of early palliative care on these outcomes were not significant for older patients. Male patients with lung cancer assigned to early palliative care reported better quality of life (FACT-G: $B = 9.31$; $p = 0.01$) and lower depression scores (PHQ-9: $B = -2.82$; $p = 0.02$), but the effects of early palliative care on these outcomes were not significant for female patients. At 24 weeks, we found no

age or sex moderation effects within the gastrointestinal cancer subgroup. **CONCLUSION:** Age and sex moderate the effects of early palliative care for patients with advanced lung cancer. Early palliative care may need to be tailored to individuals' unique sociodemographic and clinical characteristics.

Supportive care in the era of immunotherapies for advanced non-small-cell lung cancer. Awada G1, Klastersky J2. Curr Opin Oncol. 2018 Jan 4. doi: 10.1097/CCO.0000000000000434. [Epub ahead of print]
PURPOSE OF REVIEW: The therapeutic armamentarium for advanced non-small-cell lung cancer has evolved considerably over the past years. Immune checkpoint inhibitors targeting programmed cell death-1 such as pembrolizumab and nivolumab or programmed cell death ligand 1 such as atezolizumab, durvalumab and avelumab have shown favorable efficacy results in this patient population in the first-line and second-line setting. These immunotherapies are associated with a distinct toxicity profile based on autoimmune organ toxicity which is a new challenge for supportive care during treatment with these drugs. **RECENT FINDINGS:** The differential diagnosis of events occurring during immune checkpoint inhibitor treatment is broad: they can be due to immune-related or nonimmune-related adverse events, atypical tumor responses (pseudoprogression or hyperprogression) or events related to comorbidities or other treatments. **SUMMARY:** The management of these patients includes a thorough baseline clinical, biological and radiologic evaluation, patient education, correct follow-up and management by a multidisciplinary team with a central role for the medical oncologist. Immune-related toxicities should be managed according to available guidelines.

Coping Skills Practice and Symptom Change: A Secondary Analysis of a Pilot Telephone Symptom Management Intervention for Lung Cancer Patients and their Family Caregivers. Winger JG1, Rand KL2, Hanna N3, et al. J Pain Symptom Manage. 2018 Jan 20. pii: S0885-3924(18)30012-5. doi: 10.1016/j.jpainsymman.2018.01.005. [Epub ahead of print]
CONTEXT: Little research has explored coping skills practice in relation to symptom outcomes in psychosocial interventions for cancer patients and their family caregivers. **OBJECTIVES:** To examine associations of coping skills practice to symptom change in a telephone symptom management (TSM) intervention delivered concurrently to lung cancer patients and their caregivers. **METHODS:** This study was a secondary analysis of a randomized pilot trial. Data were examined from patient-caregiver dyads (n=51 dyads) that were randomized to the TSM intervention. Guided by social cognitive theory, TSM involved four weekly sessions where dyads were taught coping skills including: a mindfulness exercise, guided imagery, pursed lips breathing, cognitive restructuring, problem solving, emotion-focused coping, and assertive communication. Symptoms were assessed, including patient and caregiver psychological distress and patient pain interference, fatigue interference, and distress related to breathlessness. Multiple regression analyses examined associations of coping skills practice during the intervention to symptoms at 6 weeks post-intervention. **RESULTS:** For patients, greater practice of assertive communication was associated with less pain interference (β=-0.45, p=0.02) and psychological distress (β=-0.36, p=0.047); for caregivers, greater practice of guided imagery was associated with less psychological distress (β=-0.30, p=0.01). Unexpectedly, for patients, greater practice of a mindfulness exercise was associated with higher pain (β=0.47, p=0.07) and fatigue interference (β=0.49, p=0.04); greater practice of problem solving was associated with higher distress related to breathlessness (β=0.56, p=0.01) and psychological distress (β=0.36, p=0.08). **CONCLUSION:** Findings suggest the effectiveness of TSM may have been reduced by competing effects of certain coping skills. Future interventions should consider focusing on assertive communication training for patients and guided imagery for caregivers.

Perspectives of newly diagnosed advanced cancer patients receiving dignity therapy during cancer treatment. Dose AM1, Rhudy LM2. Support Care Cancer. 2018 Jan;26(1):187-195. doi: 10.1007/s00520-017-3833-2. Epub 2017 Jul 21.

PURPOSE: Dignity therapy is a psychosocial intervention that has been used primarily at the end of life to improve quality of life and other patient outcomes, but many individuals are unable to complete it due to health decline and death. The purpose of this study was to identify what individuals with advanced pancreatic or lung cancer with limited life expectancy, undergoing active cancer treatment describe during the dignity therapy intervention as important to them when not immediately facing end of life.
METHODS: Twenty patients undergoing chemotherapy for advanced cancer participated in a dignity therapy intervention study. Initial interviews were analyzed using descriptive content analysis.
RESULTS: Family provided the overall context and background for emerging themes of defining events, accomplishments, and God's plan, which led to lessons learned, and resulted in messages of hope. Interviews were often autobiographical in nature and contained much reminiscence, consistent with dignity therapy's intent. Few participants spoke about their cancer diagnoses during the interview.
CONCLUSIONS: This study adds unique insight into the use of dignity therapy for those still receiving active cancer treatment, different from work by others in which it was offered only at end of life. As part of supportive care, clinicians need to validate the importance of family to those with advanced cancer and to provide opportunities for patients to share what they have learned throughout life and to impart messages of hope to those closest to them.

Intensity of Anxiety and Depression in Patients with Lung Cancer in Relation to Quality of Life. Polański J1, Chabowski M2,3, Chudiak A4, Uchmanowicz B4, Janczak D5, Rosińczuk J6, Mazur G7. Adv Exp Med Biol. 2018;1023:29-36. doi: 10.1007/5584_2017_50.

Psychological factors, such as the anxiety and depression, which often occur in patients with lung cancer might negatively influence their quality of life. The aim of the study was to evaluate the effect of anxiety and depression in lung cancer patients on quality of life. The study included 180 lung patients of the mean age of 62.7 ± 9.7 years. The following scales were employed in the study: Quality of Life Questionnaire QLQ-C30 and LC13 scale, and Hospital Anxiety and Depression scale (HADS). The overall score of quality of life measured by QLQ-C30 was 47.1 ± 23.4 points on a hundred-point scale. Anxiety was diagnosed in 67 patients (37.2%) and depression in 75 patients (41.7%) by HADS. Quality of life was significantly worse in case of anxiety and depression ($p < 0.05$), which negatively influenced both functional and symptom intensity scales measured with QLQ-C30 and QLQ-LC13. We conclude that early identification of anxiety and depression may help in therapeutic decision-making and may be a useful predictive factor in lung cancer patients.

Shared Attributes of Responsibility and Emotion in Patients With Lung Cancer and Family Caregivers O'Rourke DJ1, Lobchuk MM, Ahmed R2. Oncol Nurs Forum. 2018 Jan 1;45(1):33-44. doi: 10.1188/18.ONF.33-44.

OBJECTIVES: To compare the attributions and emotions held by patients with lung cancer (affected individuals) and family caregivers in their management of the disease. **SAMPLE & SETTING:** A secondary data analysis of 304 affected individuals and 304 family caregivers. Participants were selected from five oncology outpatient settings. **METHODS & AMP; VARIABLES:** Comparative analysis and regression modeling. Variables include responsibility, anger, and pride in managing lung cancer. **RESULTS:** Affected individuals reported higher self-oriented blame, fault, and anger than did family caregivers. Family caregivers reported more blame, fault, and anger toward the affected individual than toward themselves. Current smoking behavior of either the affected individual or family caregiver was associated with increased reports of self-oriented blame, fault, and anger. Additional research is needed to understand the attributional and emotional responses affected by the type of lung cancer, gender

differences, and characteristics of the caregiving dyad. **IMPLICATIONS FOR NURSING:** Nurses should be aware of the potential for affected individuals to experience internal (self) and external (family caregiver) sources of blame, fault, and anger. Knowledge of the reasons for current smoking behavior is important for understanding emotional responses and determining interventions.

Proxy and patient reports of health-related quality of life in a national cancer survey. Roydhouse JK1, Gutman R2, Keating NL3, Mor V4, Wilson IB4. Health Qual Life Outcomes. 2018 Jan 5;16(1):6. doi: 10.1186/s12955-017-0823-5.
BACKGROUND: Proxy respondents are frequently used in surveys, including those assessing health-related quality of life (HRQOL). In cancer, most research involving proxies has been undertaken with paired proxy-patient populations, where proxy responses are compared to patient responses for the same individual. In these populations, proxy-patient differences are small and suggest proxy underestimation of patient HRQOL. In practice, however, proxy responses will only be used when patient responses are not available. The difference between proxy and patient reports of patient HRQOL where patients are not able to report for themselves in cancer is not known. The objective of this study was to evaluate the difference between patient and proxy reports of patient HRQOL in a large national cancer survey, and determine if this difference could be mitigated by adjusting for clinical and sociodemographic information about patients. **METHODS:** Data were from the Cancer Care Outcomes Research and Surveillance (CanCORS) study. Patients or their proxies were recruited within 3-6 months of diagnosis with lung or colorectal cancer. HRQOL was measured using the SF-12 mental and physical composite scales. Differences of ½ SD (=5 points) were considered clinically significant. The primary independent variable was proxy status. Linear regression models were used to adjust for patient sociodemographic and clinical covariates, including cancer stage, patient age and education, and patient co-morbidities. **RESULTS:** Of 6471 respondents, 1011 (16%) were proxies. Before adjustment, average proxy-reported scores were lower for both physical (-6.7 points, 95% CI -7.4 to -5.9) and mental (-6 points, 95% CI -6.7 to -5.2) health. Proxy-reported scores remained lower after adjustment (physical: -5.8 points, -6.6 to -5; mental: -5.8 points, -6.6 to 5). Proxy-patient score differences remained clinically and statistically significant, even after adjustment for sociodemographic and clinical variables. **CONCLUSIONS:** Proxy-reported outcome scores for both physical and mental health were clinically and significantly lower than patient-reported scores for these outcomes. The size of the proxy-patient score differences was not affected by the health domain, and adjustment for sociodemographic and clinical variables had minimal impact.

Cancer-associated cachexia. Baracos VE1, Martin L2, Korc M3, Guttridge DC4, Fearon KCH5. Nat Rev Dis Primers. 2018 Jan 18;4:17105. doi: 10.1038/nrdp.2017.105.
Cancer-associated cachexia is a disorder characterized by loss of body weight with specific losses of skeletal muscle and adipose tissue. Cachexia is driven by a variable combination of reduced food intake and metabolic changes, including elevated energy expenditure, excess catabolism and inflammation. Cachexia is highly associated with cancers of the pancreas, oesophagus, stomach, lung, liver and bowel; this group of malignancies is responsible for half of all cancer deaths worldwide. Cachexia involves diverse mediators derived from the cancer cells and cells within the tumour microenvironment, including inflammatory and immune cells. In addition, endocrine, metabolic and central nervous system perturbations combine with these mediators to elicit catabolic changes in skeletal and cardiac muscle and adipose tissue. At the tissue level, mechanisms include activation of inflammation, proteolysis, autophagy and lipolysis. Cachexia associates with a multitude of morbidities encompassing functional, metabolic and immune disorders as well as aggravated toxicity and complications of cancer therapy. Patients experience impaired quality of life, reduced physical, emotional and social well-being and increased use of healthcare resources. To date, no effective medical intervention completely reverses cachexia and there are no approved drug therapies. Adequate nutritional support remains a mainstay of cachexia therapy,

whereas drugs that target overactivation of catabolic processes, cell injury and inflammation are currently under investigation.

Evidence, education and multi-disciplinary integration are needed to embed exercise into lung cancer clinical care: A qualitative study involving physiotherapists. Granger CL1,2,3, Parry SM1, Denehy L1,3, Remedios L1. Physiother Theory Pract. 2018 Jan 16:1-9. doi: 10.1080/09593985.2018.1425939. [Epub ahead of print]
AIMS: To explore physiotherapists perceptions regarding barriers and enablers to embedding exercise into routine lung cancer clinical care. **DESIGN:** Qualitative study (content analysis). Eight physiotherapists working in the area of lung cancer at five hospitals participated. The focus group was conducted, transcribed verbatim and independently crosschecked. Thematic analysis was utilized. **RESULTS:** The data generated four major themes: evidence justifying exercise; staffing and services; maximising the efficacy of interventions; and hospital culture. Physiotherapists perceived that barriers included lack of evidence, lack of physiotherapy time and funding, inconsistencies in patient access to outpatient exercise programs, lack of clear referral pathways, limited knowledge about exercise by the wider multi-disciplinary team, and poor culture of physical activity in the inpatient setting. Recommendations included developing a stronger evidence-base, establishing set patient pathways into exercise programs, re-allocating physiotherapy services to high-risk patients, and integrating/involving the multi-disciplinary team particularly through education and communication. **CONCLUSION:** This study has identified barriers to, and potential strategies for, the embedding of exercise into lung cancer clinical practice. Evidence, education and multi-disciplinary integration are viewed by physiotherapists as critical for success. A targeted gradual approach, by applying these strategies at defined stages across the lung cancer pathway, is recommended to facilitate future practice change.

COMPLEMENTARY & ALTERNATIVE THERAPY

Cinnamomum Cassia Extracts Suppress Human Lung Cancer Cells Invasion by Reducing u-PA/MMP Expression through the FAK to ERK Pathways. Wu HC1, Horng CT2,3, Lee YL1, et al. Int J Med Sci. 2018 Jan 1;15(2):115-123. doi: 10.7150/ijms.22293. eCollection 2018.
Cinnamomum cassia exhibits antioxidative, apoptotic, and cytostatic properties. These activities have been attributed to the modulation of several biological processes and are beneficial for possible pharmaceutical applications. However, the potential of C. cassia in retarding lung adenocarcinoma cells metastasis remains ambiguous. We determined whether C. cassia extract (CCE) reduces metastasis of human lung adenocarcinoma cells. The results showed that CCE treatment (up to 60 μg/mL) for 24 h exhibited no cytotoxicity on the A549 and H1299 cell lines but inhibited the motility, invasiveness, and migration of these cells by repressing matrix metalloproteinase (MMP)-2 and urokinase-type plasminogen activator (u-PA). CCE also impaired cell adhesion to collagen. CCE significantly reduced p-focal adhesion kinase (FAK) Tyr397, p-FAK Tyr925, p-extracellular signal-regulated kinases (ERK)1/2, and Ras homolog gene family (Rho)A expression. CCE showed anti-metastatic activity of A549 and H1299 cells by repressing u-PA/MMP-2 via FAK to ERK1/2 pathways. These findings may facilitate future clinical trials of lung adenocarcinoma chemotherapy to confirm the promising results.

MISCELLANEOUS WORKS

Smoking status and survival among a national cohort of lung and colorectal cancer patients. Japuntich SJ1, Kumar P2, Pendergast J3, et al. Nicotine Tob Res. 2018 Jan 17. doi: 10.1093/ntr/nty012. [Epub ahead of print]

INTRODUCTION: The purpose of this study was to explore the association of smoking status and clinically relevant duration of smoking cessation with long-term survival after lung cancer (LC) or colorectal cancer (CRC) diagnosis. We compared survival of patients with LC and CRC who were never-smokers, long-term, medium-term, and short-term quitters, and current smokers around diagnosis. **METHODS:** We studied 5,575 patients in Cancer Care Outcomes Research and Surveillance (CanCORS), a national, prospective observational cohort study, who provided smoking status information approximately 5 months after LC or CRC diagnosis. Smoking status was categorized as: never-smoker, quit > 5 years prior to diagnosis, quit between 1-5 years prior to diagnosis, quit less than 1 year before diagnosis, and current smoker. We examined the relationship between smoking status around diagnosis with mortality using Cox regression models. **RESULTS:** Among participants with LC, never-smokers had lower mortality risk compared with current smokers (HR 0.71 95% CI 0.57 to 0.89). Among participants with CRC, never smokers had a lower mortality risk as compared to current smokers (HR 0.79, 95% CI 0.64 to 0.99). **CONCLUSIONS:** Among both LC and CRC patients, current smokers at diagnosis have higher mortality than never-smokers. This effect should be further studied in the context of tumor biology. However, smoking cessation around the time of diagnosis did not affect survival in this sample. **IMPLICATIONS:** The results from our analysis of patients in the Cancer Care Outcomes Research and Surveillance (CanCORS) consortium, a large, geographically diverse cohort, show that both lung and colorectal cancer patients who were actively smoking at diagnosis have worse survival as compared to never smokers. While current smoking is detrimental to survival, cessation upon diagnosis may not mitigate this risk.

Health care disparities among octogenarians and nonagenarians with stage III lung cancer.
Cassidy RJ1, Zhang X2, Switchenko JM2, et al. Cancer. 2018 Jan 8. doi: 10.1002/cncr.31077. [Epub ahead of print]
BACKGROUND: To the authors' knowledge, the practice patterns for patients aged more than 80 years with stage III non-small cell lung cancer (NSCLC) is not well known. The purpose of the current study was to investigate factors predictive of and the impact on overall survival (OS) after concurrent chemoradiation (CRT) among patients aged ≥80 years with American Joint Committee on Cancer stage III NSCLC in the National Cancer Data Base (NCDB). **METHODS:** In the NCDB, patients aged ≥80 years who were diagnosed with stage III NSCLC from 2004 to 2013 with complete treatment records were identified. Multivariable logistic regression and Cox proportional hazard models were generated and propensity score-matched analysis was used. **RESULTS:** A total of 12,641 patients met the entry criteria: 6018 (47.6%) had stage IIIA disease and 6623 (52.4%) had stage IIIB disease. The median age at the time of diagnosis was 83.0 years (range, 80-91 years). A total of 7921 patients (62.7%) received no therapy. Black race (odds ratio [OR], 1.23; 95% confidence interval [95% CI], 1.06-1.43) and living in a lower educated census tract of residence (OR, 1.20; 95% CI, 1.03-1.40) were found to be associated with not receiving care, whereas treatment at an academic center (OR, 0.80; 95% CI, 0.70-0.92) was associated with receiving cancer-directed therapy. Receipt of no treatment (hazard ratio [HR], 2.69; 95% CI, 2.57-2.82) or definitive radiation alone (HR, 1.15; 95% CI, 1.07-1.24) compared with CRT was associated with worse OS. On propensity score matching, not receiving CRT was found to be associated with worse OS (HR, 1.58; 95% CI, 1.44-1.72). **CONCLUSIONS:** In this NCDB analysis, approximately 62.7% of patients aged ≥80 years with stage III NSCLC received no cancer-directed care. Black race and living in a lower educated census tract were associated with not receiving cancer-directed care. OS was found to be improved in patients receiving CRT.

Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. Lindeman NI1, Cagle PT1, Aisner DL1, et al. Arch Pathol Lab Med. 2018 Jan 22. doi: 10.5858/arpa.2017-0388-CP. [Epub ahead of print]

CONTEXT: In 2013, an evidence-based guideline was published by the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology to set standards for the molecular analysis of lung cancers to guide treatment decisions with targeted inhibitors. New evidence has prompted an evaluation of additional laboratory technologies, targetable genes, patient populations, and tumor types for testing. **OBJECTIVE:** To systematically review and update the 2013 guideline to affirm its validity; to assess the evidence of new genetic discoveries, technologies, and therapies; and to issue an evidence-based update. **DESIGN:** The College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology convened an expert panel to develop an evidence-based guideline to help define the key questions and literature search terms, review abstracts and full articles, and draft recommendations. **RESULTS:** Eighteen new recommendations were drafted. The panel also updated 3 recommendations from the 2013 guideline. **CONCLUSIONS:** The 2013 guideline was largely reaffirmed with updated recommendations to allow testing of cytology samples, require improved assay sensitivity, and recommend against the use of immunohistochemistry for EGFR testing. Key new recommendations include ROS1 testing for all adenocarcinoma patients; the inclusion of additional genes (ERBB2, MET, BRAF, KRAS, and RET) for laboratories that perform next-generation sequencing panels; immunohistochemistry as an alternative to fluorescence in situ hybridization for ALK and/or ROS1 testing; use of 5% sensitivity assays for EGFR T790M mutations in patients with secondary resistance to EGFR inhibitors; and the use of cell-free DNA to "rule in" targetable mutations when tissue is limited or hard to obtain.

Not a Death Sentence: Perspectives of African American Women Living With Lung Cancer Webb LA1, McDonnell KK1. Oncol Nurs Forum. 2018 Jan 1;45(1):46-54. doi: 10.1188/18.ONF.46-54.

PURPOSE: To conduct a descriptive, qualitative study to describe the experience of female African American lung cancer survivors, their perception of living with lung cancer, and their desire and ability to adopt positive health-related behaviors. **PARTICIPANTS & SETTING:** The sample consisted of 18 African American women with a history of stages I-IIIa lung cancer. Three focus groups were conducted in a private conference center in two community hospitals in the southeastern United States. **METHODOLOGIC APPROACH:** A 20-item questionnaire was used to collect demographic, health status, and behavior information. A trained moderator led the audio-recorded focus group discussions using a semistructured interview guide. **FINDINGS:** Thematic analysis of the professionally transcribed data resulted in identification of four major themes. In addition, participants experienced stigma that influenced their perspectives on living with lung cancer. **IMPLICATIONS FOR NURSING:** Healthcare professionals should provide culturally tailored communication and support for female African American lung cancer survivors. Additional research is needed to inform the development of interventions focused on health behavior change to enhance lung cancer survivorship in this vulnerable and understudied group.