Caring Ambassadors Lung Cancer Program
Literature Review, January 2018

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Emerging roles of circular RNA hsa_circ_0000064 in the proliferation and metastasis of lung cancer. Luo YH1, Zhu XZ1, Huang KW1, Zhang Q1, Fan YX1, Yan PW1, Wen J2. Biomed Pharmacother. 2017 Dec;96:892-898. doi: 10.1016/j.biopha.2017.12.015. Epub 2017 Dec 7.
Circular RNAs (circRNAs), a novel class of widespread and diverse endogenous RNAs, can regulate gene expression in mammals. CircRNAs have recently been identified as microRNA sponges and involved in the development of some human diseases. However, the role of circRNAs in the process of tumorigenesis and development of lung cancer remains vague. The purpose of this study is to investigate the role of circRNAs in the lung cancer. In this study, we chose hsa_circ_0000064 as a targeted circRNA to investigate its clinical significances in lung cancer patients. The result indicated that hsa_circ_0000064 was up-regulated in lung cancer tissues and lung cancer cell lines (A549 and H1229). Moreover, its aberrant expression was correlated with several clinical characteristics, including T stage, lymphatic metastasis, and TNM stage. Fluorescence in situ hybridization detected that hsa_circ_0000064 was mostly located in the cytoplasm in A549 and H1229 cells. In addition, knockdown of hsa_circ_0000064 with siRNA dramatically attenuated the proliferation, blocked cell cycle progression, and promoted cell apoptosis. Western blot analysis showed that the protein levels of caspase-3, caspase-9, bax, p21, CDK6 and cyclin D1 significantly restrained by si-hsa_circ_0000064, while the expression of bcl-2 notably increased in A549 and H1229 cells. Further, si-hsa_circ_0000064 also abated migration and invasion activities of A549 and H1229 cells, which may be associated with reduced expressions of MMP-2 and MMP-9. In general, our data suggest that hsa_circ_0000064 represents a novel potential biomarker and therapeutic target of lung cancer.

MEK inhibitors under development for treatment of non-small-cell lung cancer. Kim C1,2, Giaccone G2. Expert Opin Investig Drugs. 2017 Dec 13:1-14. doi: 10.1080/13543784.2018.1415324. [Epub ahead of print]
The mitogen-activated protein kinase (MAPK) pathway is intimately implicated in the molecular pathogenesis of non-small-cell lung cancer (NSCLC). Aberrant MAPK signaling resulting from the upstream activating mutations converges on mitogen-activated protein kinase kinase 1/2 (MEK1/2),

making MEK inhibition an attractive strategy for the treatment of NSCLC. Several MEK inhibitors have demonstrated anticancer activity in patients with NSCLC. Areas covered: In this article, we discuss the biological rationale for the use of MEK inhibitors and summarize the clinical experience with MEK1/2 inhibitors for the treatment of NSCLC, from initial phase I studies to phase II/III studies, both as monotherapy or in combination with other anticancer agents. Expert opinion: Trametinib in combination with the BRAF inhibitor dabrafenib represents the first MEK1/2 inhibitor containing regimen that is approved for advanced BRAFV600E-mutant NSCLC. Other MEK1/2 inhibitors that are also in advanced stages of clinical development include selumetinib, cobimetinib, and binimetinib. Several studies of MEK inhibitor combination therapies are underway, including trials using combined MEK inhibition and immune checkpoint blockade. Further research aimed at discovering biomarkers of response and resistance to MEK1/2 inhibitors will be needed to develop rational combination strategies for the treatment of NSCLC driven by aberrant MAPK signaling.

SCREENING, DIAGNOSIS AND STAGING

Blood-based biomarkers in lung cancer: prognosis and treatment decisions. Xu-Welliver M1, Carbone DP2. Transl Lung Cancer Res. 2017 Dec;6(6):708-712. doi: 10.21037/tlcr.2017.09.08.
Despite recent advances, non-small cell lung cancer (NSCLC) remains a devastating disease with overall poor prognosis. Major contributing factors include obstacles to diagnosing the disease early in its course during the asymptomatic stage as well as diversity and complexity of its biology underlying tumorigenesis and tumor progression. Advances in molecularly targeted therapies which drives the development of personalized cancer care require precise and comprehensive understanding of tumor biology, not only at the time of diagnosis but also during treatment course and surveillance. As lung tumor tissue can be difficult to obtain without invasive and potentially risky procedures, it is difficult to monitor treatment response with serial tissue biopsies. Development of non-invasive but reliable blood based tumor markers has become an important research area. In this review, we focus on the following circulating biomarkers that have been identified in recent years: circulating tumor cells (CTCs); circulating cell-free nucleic acids, such as circulating tumor DNA (ctDNA) and microRNA (miR); and other biomarkers such as genomic and proteomic features. These biomarkers not only have prognostic values, but also can help guild treatment decisions by monitoring tumor burden, detecting minimal residual disease and/or recurrent disease, as well as monitoring evolution of genetic alterations throughout the treatment course.

Blood-based tumor biomarkers in lung cancer for detection and treatment. Mamdani H1, Ahmed S2, Armstrong S3, Mok T4, Jalal SI2. Transl Lung Cancer Res. 2017 Dec;6(6):648-660. doi: 10.21037/tlcr.2017.09.03.
The therapeutic landscape of lung cancer has expanded significantly over the past decade. Advancements in molecularly targeted therapies, strategies to discover and treat resistance mutations, and development of personalized cancer treatments in the context of tumor heterogeneity and dynamic tumor biology have made it imperative to obtain tumor samples on several different occasions through the course of patient treatment. While this approach is critical to the delivery of optimal cancer treatment, it is fraught with a number of barriers including the need for invasive procedures with associated complications, access to limited amount of tissue, logistical delays in obtaining the biopsy, high healthcare cost, and in many cases inability to obtain tissue because of technically difficult location of the tumor. Given multiple limitations of obtaining tissue samples, the use of blood-based biomarkers ("liquid biopsies") may enable earlier diagnosis of cancer, lower costs by avoiding complex invasive procedures, tailoring molecular targeted treatments, improving patient convenience, and ultimately supplement clinical oncologic decision-making. In this paper, we review various blood-based biomarkers including circulating tumor cells

(CTCs), circulating tumor DNA (ctDNA), tumor derived exosomes, tumor educated platelets (TEPs), and microRNA; and highlight current evidence for their use in detection and treatment of lung cancer.

[Histologic Grade Is Predictive of Incidence of Epidermal Growth Factor Receptor Mutations in Metastatic Lung Adenocarcinoma.](#) Levy M1, Lyon L2, Barbero E3, Wong J4, Suga M5, Sam D6, Pan M7,8,9. Med Sci (Basel). 2017 Dec 11;5(4). pii: E34. doi: 10.3390/medsci5040034.

Activating epidermal growth factor receptor (EGFR) mutations in metastatic non-small cell lung cancer (NSCLC) are associated with a high response rate to EGFR tyrosine kinase inhibitor (TKI). The current guidelines recommend routine EGFR mutational analysis prior to initiating first line systemic therapy. The clinical characteristics including smoking status, histologic type, sex and ethnicity are known to be associated with the incidence of EGFR mutations. We retrospectively analyzed 277 patients with metastatic NSCLC within Kaiser Permanente Northern California (KPNC); among these patients, 83 were positive for EGFR mutations. We performed both univariate and multivariable logistic regressions to identify predictors of EGFR mutations. We found that histologic grade was significantly associated with the incidence of EGFR mutation, regardless of ethnicity, sex and smoking status. In grade I (well differentiated) and II (moderately differentiated), histology was associated with significantly higher incidence of EGFR mutations compared to grade II-III (moderate-to-poorly differentiated) and III (poorly differentiated). Ever-smokers with grade III lung adenocarcinoma had 1.8% incidence of EGFR mutations. This study indicates that histologic grade is a predictive factor for the incidence of EGFR mutations and suggests that for patients with grade II-III or III lung adenocarcinoma, prompt initiation of first-line chemotherapy or immunotherapy is appropriate while awaiting results of EGFR mutational analysis, particularly for patients with history of smoking.

[Automated image quality assessment for chest CT scans.](#) Reeves AP1, Xie Y1, Liu S1. Med Phys. 2017 Dec 14. doi: 10.1002/mp.12729. [Epub ahead of print]

PURPOSE: Medical image quality needs to be maintained at standards sufficient for effective clinical reading. Automated computer analytic methods may be applied to medical images for quality assessment. **METHODS:** For chest CT scans in a lung cancer screening context, an automated quality assessment method is presented that characterizes image noise and image intensity calibration. This is achieved by image measurements in three automatically segmented homogeneous regions of the scan: external air, trachea lumen air, and descending aorta blood. Profiles of CT scanner behavior are also computed. **RESULTS:** The method has been evaluated on both phantom and real low-dose chest CT scans and results show that repeatable noise and calibration measures may be realized by automated computer algorithms. Noise and calibration profiles show relevant differences between different scanners and protocols. **CONCLUSIONS:** Automated image quality assessment may be useful for quality control for lung cancer screening and may enable performance improvements to automated computer analysis methods. This article is protected by copyright. All rights reserved.

[Long-term outcomes after near-infrared sentinel lymph node mapping in non-small cell lung cancer.](#) Digesu CS1, Hachey KJ2, Gilmore DM3, Khullar OV4, Tsukada H1, Whang B1, Chirieac LR5, Padera RF5, Jaklitsch MT1, Colson YL6. J Thorac Cardiovasc Surg. 2017 Dec 13. pii: S0022-5223(17)32505-9. doi: 10.1016/j.jtcvs.2017.09.150. [Epub ahead of print]

OBJECTIVE: To report the first analysis of long-term outcomes using near-infrared (NIR) image-guided sentinel lymph node (SLN) mapping in non-small cell lung cancer (NSCLC). **METHODS:** Retrospective analysis of patients with NSCLC enrolled in 2 prospective phase 1 NIR-guided SLN mapping trials, including an indocyanine green (ICG) dose-escalation trial, was performed. All patients underwent NIR imaging for SLN identification followed by multistation mediastinal lymph node sampling (MLNS) and pathologic assessment. Disease-free (DFS) and overall survival (OS) were compared between patients

with NIR+ SLN (SLN group) and those without (non-SLN group). **RESULTS:** SLN detection, recurrence, DFS, and OS were assessed in 42 patients with NSCLC who underwent intraoperative peritumoral ICG injection, NIR imaging, and MLNS. NIR+ SLNs were identified in 23 patients (SLN group), whereas SLNs were not identified in 19 patients enrolled before ICG dose and camera optimization (non-SLN group). Median follow-up was 44.5 months. Pathology from NIR+ SLNs was concordant with overall nodal status in all 23 patients. Sixteen patients with SLN were deemed pN0 and no recurrences were, whereas 4 of 15 pN0 non-SLN patients developed nodal or distant recurrent disease. Comparing SLN versus non-SLN pN0 patients, the probability of 5-year OS is 100% versus 70.0% (P = .062) and 5-year DFS is statistically significantly improved at 100% versus 66.1% (P = .036), respectively. Among the 11 pN+ patients, 7 were in the SLN group, with >40% showing metastases in the SLN alone. **CONCLUSIONS:** Patients with pN0 SLNs showed favorable disease-free and overall survival. This preliminary review of NIR SLN mapping in NSCLC suggests that pN0 SLNs may better represent true N0 status. A larger clinical trial is planned to validate these findings.

[Influence of Ground-Glass Opacity and the Corresponding Pathological Findings on Survival in Patients with Clinical Stage I Non-Small Cell Lung Cancer.](#) Aokage K1, Miyoshi T2, Ishii G3, Kusumoto M4, Nomura S5, Katsumata S2, Sekihara K2, Tane K2, Tsuboi M2.
J Thorac Oncol. 2017 Dec 12. pii: S1556-0864(17)33080-0. doi: 10.1016/j.jtho.2017.11.129. [Epub ahead of print]
INTRODUCTION: The aim was to clarify the influence on patient prognosis of ground glass opacity (GGO) component in each new tumor-node-metastasis stage and propose grouping reflecting the prognosis more accurately. **METHODS:** We examined the data of 1290 patients who underwent lung cancer resection from 2003 to 2011. The demographics and overall survival of patients with adenocarcinoma with and without GGO, squamous cell carcinoma, and the others, were compared according to clinical stage (c-stage) from 0 to IB. In adenocarcinoma, we examined the distribution of histological subtypes of adenocarcinoma with and without GGO in each c-stage. **RESULTS:** Each c-stage differentiated overall survival well. However, prognosis of the patients with adenocarcinoma with GGO was considerably favorable compared to the others in c-stage IA2 and IA3, whereas not in IB. In c-stage 0 to IA3, patients showing adenocarcinoma in situ, minimally invasive adenocarcinoma, and invasive lepidic predominant adenocarcinoma accounted for about 50% of the total numbers of patients with adenocarcinoma with GGO (0: 16/21, IA1: 113/143, IA2: 80/157, IA3: 45/94). In c-stage IB, 20% of adenocarcinomas with GGO showed invasive solid predominant adenocarcinoma (IB: 7/38). Most of adenocarcinomas without GGO were in c-stage IA2 to IB, and the distribution of the histological subtype was similar at each c-stage. Invasive acinar and solid predominant adenocarcinomas were more common in adenocarcinoma without GGO. **CONCLUSIONS:** Clinical T classification considering GGO component may offer further accurate prognosis for patients with lung cancer less than 3cm in invasive diameter.

[Serial 4DCT/4DPET imaging to predict and monitor response for locally-advanced non-small cell lung cancer chemo-radiotherapy.](#) Bissonnette JP1, Yap ML2, Clarke K2, et al. Radiother Oncol. 2017 Dec 12. pii: S0167-8140(17)32743-3. doi: 10.1016/j.radonc.2017.11.023. [Epub ahead of print]
BACKGROUND AND PURPOSE: A FDG-PET/CT image feature with optimal prognostic potential for locally-advanced non-small cell lung cancer (LA-NSCLC) patients has yet to be identified, and neither has the optimal time for FDG-PET/CT response assessment; furthermore, nodal features have been largely ignored in the literature. We propose to identify image features or imaging time point with maximal prognostic power. **MATERIALS AND METHODS:** Consecutive consenting patients with LA-NSCLC receiving curative intent CRT were enrolled. 4DPET/4DCT scans were acquired 0, 2, 4, and

7 weeks during IMRT treatment. Eleven image features and their rates of change were recorded for each time point and tested for each of the possible outcome 2 years post CRT using the Kaplan-Meier method. **RESULTS:** 32 consecutive patients were recruited, 27 completing all scans. Restricting analysis to 4DPET/4DCT features and rates of change with $p < 0.005$, several volume-based features and their rates of change reached significance. Image features involving nodal disease were the only ones associated with overall survival. **CONCLUSIONS:** Several 4DPET/CT features and rates of change can reach significant association ($p < 0.005$) with outcomes, including overall survival, at many time points. The optimal time for adaptive CRT is therefore not constrained uniquely on imaging.

[The applications of liquid biopsy in resistance surveillance of anaplastic lymphoma kinase inhibitor.](#)

With the clinical promotion of precision medicine and individualized medical care, molecular targeted medicine has been used to treat non-small cell lung cancer (NSCLC) patients and proved to be significantly effective. Anaplastic lymphoma kinase (ALK) inhibitor is one of the most important specific therapeutic agents for patients with ALK-positive NSCLC. It can extend the survival of patients. However, resistance to the ALK inhibitor inevitably develops in the application process. So, the real-time resistance surveillance is particularly important, and liquid biopsy is one of the most potential inspection methods. Circulating tumor cells, circulating free tumor DNA and exosome in body fluid are used as the main detection biomarkers to reflect the occurrence of resistance in real time through sequencing or counting and then to guide the follow-up treatment.

[Characteristics of percutaneous core biopsies adequate for next generation genomic sequencing.](#)

PURPOSE: Determine the characteristics of percutaneous core biopsies that are adequate for a next generation sequencing (NGS) genomic panel. **MATERIALS AND METHODS:** All patients undergoing percutaneous core biopsies in interventional radiology (IR) with samples evaluated for a 46-gene NGS panel during 1-year were included in this retrospective study. Patient and procedure variables were collected. An imaging-based likelihood of adequacy score incorporating targeting and sampling factors was assigned to each biopsied lesion. Univariate and multivariate logistic regression was performed. **RESULTS:** 153 patients were included (58.2% female, average age 59.5 years). The most common malignancy was lung cancer (40.5%), most common biopsied site was lung (36%), and average size of biopsied lesions was 3.8 cm (+/- 2.7). Adequacy for NGS was 69.9%. Univariate analysis showed higher likelihood of adequacy score ($p = 0.004$), primary malignancy type ($p = 0.03$), and absence of prior systemic therapy ($p = 0.018$) were associated with adequacy for NGS. Multivariate analysis showed higher adequacy for lesions with likelihood of adequacy scored 3 (high) versus lesions scored 1 (low) (OR, 7.82; $p = 0.002$). Melanoma lesions had higher adequacy for NGS versus breast cancer lesions (OR 9.5; $p = 0.01$). Absence of prior systemic therapy (OR, 6.1; $p = 0.02$) and systemic therapy $</ = 3$ months (OR 3.24; $p = 0.01$) compared to systemic therapy >3 months before biopsy yielded greater adequacy for NGS. Lesions <3 cm had greater adequacy for NGS than larger lesions (OR 2.72, $p = 0.02$). **CONCLUSION:** As targeted therapy becomes standard for more cancers, percutaneous biopsy specimens adequate for NGS genomic testing will be needed. An imaging-based likelihood of adequacy score assigned by IR physicians and other pre-procedure variables can help predict the likelihood of biopsy adequacy for NGS.

[Determining the Optimal Number of Core Needle Biopsy Passes for Molecular Diagnostics.](#)

Hoang NS1, Ge BH1, Pan LY1, Ozawa MG1, Kong CS1, Louie JD1, Shah RP2,3,4. Cardiovasc Intervent Radiol. 2017 Dec 26. doi: 10.1007/s00270-017-1861-4. [Epub ahead of print]

PURPOSE: The number of core biopsy passes required for adequate next-generation sequencing is impacted by needle cut, needle gauge, and the type of tissue involved. This study evaluates diagnostic adequacy of core needle lung biopsies based on number of passes and provides guidelines for other tissues based on simulated biopsies in ex vivo porcine organ tissues. **METHODS:** The rate of diagnostic adequacy for pathology and molecular testing from lung biopsy procedures was measured for eight operators pre-implementation (September 2012-October 2013) and post-implementation (December 2013-April 2014) of a standard protocol using 20-gauge side-cut needles for ten core biopsy passes at a single academic hospital. Biopsy pass volume was then estimated in ex vivo porcine muscle, liver, and kidney using side-cut devices at 16, 18, and 20 gauge and end-cut devices at 16 and 18 gauge to estimate minimum number of passes required for adequate molecular testing. **RESULTS:** Molecular diagnostic adequacy increased from 69% (pre-implementation period) to 92% (post-implementation period) (p < 0.001) for lung biopsies. In porcine models, both 16-gauge end-cut and side-cut devices require one pass to reach the validated volume threshold to ensure 99% adequacy for molecular characterization, while 18- and 20-gauge devices require 2-5 passes depending on needle cut and tissue type. **CONCLUSION:** Use of 20-gauge side-cut core biopsy needles requires a significant number of passes to ensure diagnostic adequacy for molecular testing across all tissue types. To ensure diagnostic adequacy for molecular testing, 16- and 18-gauge needles require markedly fewer passes.

[The Impact of Smoking and TP53 mutations in lung adenocarcinoma patients with targetable mutations - the Lung Cancer Mutation Consortium (LCMC2).](#)

Aisner DL1, Sholl LM2, Berry L3, et al. Clin Cancer Res. 2017 Dec 7. pii: clincanres.2289.2017. doi: 10.1158/1078-0432.CCR-17-2289. [Epub ahead of print]

PURPOSE: Multiplex genomic profiling is standard of care for patients with advanced lung adenocarcinomas. The Lung Cancer Mutation Consortium (LCMC) is a multi-institutional effort to identify and treat oncogenic driver events in patients with lung adenocarcinomas. PATIENTS AND **METHODS:** Sixteen U.S. institutions enrolled 1367 lung cancer patients in LCMC2; 904 were deemed eligible and had at least one of 14 cancer-related genes profiled using validated methods including genotyping, massively parallel sequencing, and immunohistochemistry. **RESULTS:** The use of targeted therapies in patients with EGFR, ERBB2, or BRAF p.V600E mutations, ALK, ROS1 or RET rearrangements, or MET amplification was associated with a survival increment of 1.5 years compared to those with such mutations not receiving targeted therapy; and 1.0 year compared to those lacking a targetable driver. Importantly, 60 patients with a history of smoking derived similar survival benefit from targeted therapy for alterations in EGFR ALK/ROS1, when compared to 75 never smokers with the same alterations. In addition, co-existing TP53 mutations were associated with shorter survival among patients with EGFR, ALK, or ROS1 alterations. **CONCLUSION:** Patients with adenocarcinoma of the lung and an oncogenic driver mutation treated with effective targeted therapy have a longer survival, regardless of prior smoking history. Molecular testing should be performed on all individuals with lung adenocarcinomas irrespective of clinical characteristics. Routine use of massively parallel sequencing enables detection of both targetable driver alterations and tumor suppressor gene and other alterations that have potential significance for therapy selection and as predictive markers for the efficacy of treatment.

NSCLC - SURGERY

Thoracic surgeon and patient focus groups on decision-making in early-stage lung cancer surgery.

Schwartz RM1,2, Gorbenko K3, Kerath SM4, Flores R5, Ross S6, Taylor TN7, Taioli E2,5, Henschke C8. Future Oncol. 2018 Jan;14(2):151-163. doi: 10.2217/fon-2017-0254. Epub 2017 Dec 12.
AIM: To investigate medical decision-making from the thoracic surgeons' and patients' perspectives in early-stage lung cancer. **PATIENTS & METHODS:** We conducted one focus group with thoracic surgeons (n = 15) and one with a group of early-stage lung cancer patients treated with surgery (n = 7). Focus groups were recorded, transcribed and coded for themes. **RESULTS:** For surgeons, surgical procedure choice was a primary concern, followed by the surgical treatment plan decision-making process. Survivors focused primarily on the physical and mental health-related postsurgical burden for which they felt they were not well prepared and placed less emphasis on surgical decision-making. **CONCLUSION:** As early-stage lung cancer mortality rates are improving, surgeons and patients can prioritize surgical approaches and postsurgical care that enhance quality of life.

Surgical Outcomes After Neoadjuvant Chemotherapy and Ipilimumab for Non-Small-Cell Lung Cancer.

Yang CJ1, McSherry F1, Mayne NR1, et al. Ann Thorac Surg. 2017 Dec 16. pii: S0003-4975(17)31276-6. doi: 10.1016/j.athoracsur.2017.09.030. [Epub ahead of print]
BACKGROUND: The objective of this study was to evaluate the safety and feasibility of using neoadjuvant chemotherapy plus ipilimumab followed by surgery as a treatment strategy for stage II-IIIA non-small-cell lung cancer. **METHODS:** From 2013 to 2017, postoperative data from patients who underwent surgery after neoadjuvant chemotherapy plus ipilimumab in the TOP1201 trial, an open label phase II trial (NCT01820754), were prospectively collected. The surgical outcomes from TOP1201 were compared with outcomes in a historical cohort of patients receiving standard preoperative chemotherapy followed by surgery identified from our institution's prospectively collected thoracic surgery database. **RESULTS:** In the TOP1201 trial, 13 patients were treated with preoperative chemotherapy and ipilimumab followed by surgery. In the historical cohort, 42 patients received preoperative chemotherapy by a platinum doublet regimen preoperative chemotherapy by a platinum doublet regimen without ipilimumab followed by lobectomy or pneumonectomy. The 30-day mortality in both groups was 0%. The most frequently occurring perioperative complications in the TOP1201 group were prolonged air leak (n = 2, 15%) and urinary tract infection (n = 2, 15%). The most common perioperative complication in the preoperative chemotherapy alone group was atrial fibrillation (n = 6, 14%). One patient (8%) had atrial fibrillation in the TOP1201 group. There was no apparent increased occurrence of adverse surgical outcomes for patients in the TOP1201 group compared with patients receiving standard of care neoadjuvant chemotherapy alone before surgery for stage II-IIIA non-small cell lung cancer. **CONCLUSIONS:** This report is the first to demonstrate the safety and feasibility of surgical resection after treatment with ipilimumab and chemotherapy in stage II-IIIA non-small-cell lung cancer.

Thoracoscopic Surgery Versus Thoracotomy for Lung Cancer: Short-Term Outcomes of a Randomized Trial.

Long H1, Tan Q2, Luo Q3, Wang Z4, Jiang G5, Situ D6, Lin Y6, Su X6, Liu Q7, Rong T6. Ann Thorac Surg. 2017 Dec 1. pii: S0003-4975(17)31191-8. doi: 10.1016/j.athoracsur.2017.08.045. [Epub ahead of print]
BACKGROUND: Safety and short-term efficacy of video-assisted thoracoscopic surgery (VATS) for early-stage non-small lung cancer (NSCLC) has been demonstrated by observational studies previously. However, these outcomes have never been verified by a large randomized controlled trial (RCT). The aim

of our RCT was to confirm that VATS is not inferior or even superior to open operation for early-stage NSCLC in terms of short-term and oncologic efficacy. **METHODS:** The trial was undertaken at five tertiary hospitals. Patients aged between 18 and 75 years with clinically early-stage NSCLC were randomly assigned to the VATS and axillary thoracotomy groups. Lobectomy plus mediastinal lymph node dissection was standard surgical intervention. Because patients continue to be followed up for oncologic outcome, the short-term perioperative outcomes would be reported here. **RESULTS:** Between 2008 and 2014, 508 patients were recruited and 425 were eligible for analyses (215 VATS and 210 axillary thoracotomy). Eight VATS procedures were converted to open operation intraoperatively (3.72%). Median operation time with VATS was significantly less than axillary thoracotomy (150 versus 166 minutes, p = 0.009). In addition, VATS was associated with less intraoperative blood loss (p = 0.001). There was no difference for postoperative pleural drainage, length of hospitalization, and rates of morbidity and mortality. Cancer residual margins were found in 1 patient with VATS and 5 with axillary thoracotomy (p = 0.128). The yield of lymph nodes from either surgical approach was similar (p = 0.389). **CONCLUSIONS:** Our study demonstrates that VATS lobectomy is safe and reliable to treat NSCLCs, and it may be superior to axillary thoracotomy for operation time and intraoperative blood loss.

[Risk and benefit of neoadjuvant therapy among patients undergoing resection for non-small-cell lung cancer.](#) Yendamuri S1,2, Groman A3, Miller A3, Demmy T1,2, Hennon M1,2, Dexter E1,2, Picone A1,2, Nwogu C1,2, Dy GK4. Eur J Cardiothorac Surg. 2017 Dec 13. doi: 10.1093/ejcts/ezx406. [Epub ahead of print]
OBJECTIVES: Neoadjuvant therapy has emerged as a favoured treatment paradigm for patients with clinical N2 disease undergoing surgical resection for non-small-cell lung cancer. It is unclear whether such a treatment paradigm affects perioperative outcomes. We sought to examine the National Cancer Database (NCDB) to assess the impact of neoadjuvant therapy on perioperative outcomes and long-term survival in these patients. **METHODS:** All patients with a history of non-small-cell lung cancer undergoing anatomical resection between 2004 and 2014 were included. Thirty-day and 90-day mortality of all patients having neoadjuvant therapy versus those who did not were compared. In addition, the impact of neoadjuvant therapy on the overall survival of patients with clinical N2 disease was examined. **RESULTS:** Of the 134 428 selected patients, 9896 (7.4%) patients had neoadjuvant chemotherapy. Patients undergoing neoadjuvant therapy had a higher 30-day (3% vs 2.6%; P < 0.01) and 90-day mortality (6.5% vs 4.9%; P < 0.01). This association remained after adjusting for covariates. Among patients with clinical N2 disease (n = 10 139), 42.3%, 35.3% and 22.4% of patients had neoadjuvant, adjuvant and no chemotherapy, respectively. Univariable, multivariable and propensity score-weighted analyses indicated no difference in survival between patients receiving neoadjuvant and adjuvant chemotherapy. **CONCLUSIONS:** Neoadjuvant therapy may adversely affect perioperative outcomes without providing a survival advantage compared with adjuvant therapy in clinical N2 stage patients. Randomized controlled trials need to be conducted to examine this issue further.

[Feasibility of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration Cytology Specimens for Next Generation Sequencing in Non-small-cell Lung Cancer.](#) Stoy SP1, Segal JP2, Mueller J2, Furtado LV3, Vokes EE1, Patel JD1, Murgu S4. Clin Lung Cancer. 2017 Dec 5. pii: S1525-7304(17)30322-4. doi: 10.1016/j.cllc.2017.11.010. [Epub ahead of print]
INTRODUCTION: Next generation sequencing (NGS) testing of lung cancer is recommended by guidelines, and endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) often provides the only material available for testing. Previous studies have demonstrated successful NGS testing on cell block samples obtained by EBUS; however, cytology smears provide a more reliable sample with better DNA quality for testing. In this study, we aimed to determine the success rate of OncoScreen (50 gene) and OncoPlus (1213 gene) panel NGS testing of cytology samples obtained by

EBUS utilizing 22- and 25-gauge needles. **METHODS:** Fifty-four patients underwent EBUS-TBNA of lung cancer for which NGS testing was requested. Data was analyzed for needle gauge, cytologic assessment, NGS test success, and sample type (cytology smear or cell block) used for testing. **RESULTS:** Eighty-five NGS tests were ordered on 54 samples. Overall, 95.3% of samples had successful testing. OncoScreen and OncoPlus panels were successful 98.0% and 91.4% of the time, respectively. Cytology smears provided testing material for 85% of the tests. OncoScreen testing was successful in 97.5% and 100% of the 22- and 25-gauge samples, respectively (P = 1.00). OncoPlus testing was successful in 91.3% and 100% of the 22- and 25-gauge samples, respectively (P = 1.00). **CONCLUSIONS:** NGS can be reliably performed on cytology smears obtained from EBUS-TBNA. The size of the needle does not seem to affect the success rate of small or large panel NGS tests.

[Indication of Cognitive Change and Associated Risk Factor after Thoracic Surgery in the Elderly: A Pilot Study.](#) Kulason K1, Nouchi R1,2,3, Hoshikawa Y4,5, Noda M5, Okada Y5, Kawashima R1,6. Front Aging Neurosci. 2017 Dec 5;9:396. doi: 10.3389/fnagi.2017.00396. eCollection 2017.

BACKGROUND: This pilot study investigated the effects of partial pulmonary lobectomy lung surgery on cognitive functions of elderly Japanese patients. It is recognized that elderly patients undergoing surgery have increased risk of Postoperative Cognitive Decline (POCD), a condition in which learning, memory, and processing speed is greatly reduced after surgery. Since elderly patients are more likely to exhibit symptoms of POCD, the incidence is increasing as the population receiving surgery is aging. **METHODS:** Cognitive function was measured for all subjects (n = 12) before and after surgery using three different cognitive tests: Mini-Mental Status Exam-Japanese (MMSE-J), Frontal Assessment Battery (FAB), and a computerized Cogstate Brief Battery (CBB). Changes in these measures indicate changes in cognitive function. In addition, the 12-item General Health Questionnaire (GHQ-12), the Geriatric Depression Scale (GDS), and the 5-item Quality of Life questionnaire (QOL-5) were administered at each time point to measure mental and emotional state. Changes in outcome measures were analyzed via Wilcoxon signed-rank test. Exploratory correlation analysis was conducted using Spearman's rho. **RESULTS:** Data show a decline in detection (DET; p = 0.045) and identification (IDN; p = 0.038). Spearman's correlation coefficient show a significant correlation between postoperative DET scores and postoperative IDN scores (ρ = 0.78, p = 0.005), a significant correlation between change in IDN and baseline GHQ-12 scores (ρ = -0.595, p = 0.027), and a significant correlation between change in one-back (OBK) scores and duration of anesthesia (ρ = -0.72, p = 0.012). **DISCUSSION:** This was the first report to examine cognitive decline after major thoracic surgery in Japanese patients. Previous studies have evidenced that POCD is a common phenomenon after surgery, and that age is a major risk factor. The CCB measured significant change in two cognitive domains: attention and psycomotor function. This study clarified that decline in cognition is detectable in certain measures after thoracic surgery in the elderly Japanese patient population. Additionally, longer anesthetic exposure may negatively impact attention and working memory, and preoperative mental wellbeing is a possible predictor of POCD. These preliminary results have important implications and support the need for future studies.

[Early and Long-Term Results of Tracheal Sleeve Pneumonectomy for Lung Cancer After Induction Therapy.](#) Galetta D1, Spaggiari L2. Ann Thorac Surg. 2017 Dec 22. pii: S0003-4975(17)31630-2. doi: 10.1016/j.athoracsur.2017.11.052. [Epub ahead of print]

BACKGROUND: The role of induction therapy (IT) and its effects on morbidity and mortality of patients receiving tracheal sleeve pneumonectomy (TSP) are unclear. We evaluated early and long-term outcomes of patients who underwent TSP after IT. **METHODS:** From 1998 to 2015, 32 patients (26 men; median age, 63 years) underwent TSP. Twenty-two patients (69%) received IT (cisplatin based chemotherapy). TSPs were all right sided and included 3 completion pneumonectomies. Superior vena

cava resection was combined with TSP in 15 cases. Diaphragmatic and vertebral resection was also associated in one case each. **RESULTS:** Operative mortality was nil. Thirty-day mortality was 9% (n=3). Major complications occurred in 7 patients (21.8%): 3 broncho-pleural fistulas, 2 ARDS, 1 cardiac hernia, and 1 empyema. IT had no significant effects on morbidity and mortality. Resection was complete in 31 patients (97%). Pathological N status was N0 in two cases, N1 in 17, and N2 in 13. Nodal downstaging was diagnosed in 13/22 (59.1%) patients who received IT (11 passed from N2 to N1, and 2 to N0). Mean survival was 36 months (range, 1 to 181 months). Overall 5-year survival and disease free survival were 30.3% and 27.7%, respectively. Patients receiving IT had a poor survival (p=.03). At multivariate analysis, nodal downstaging and adjuvant treatment, significantly affected survival (p=.035 and p=.007, respectively). **CONCLUSIONS:** TSP is a feasible but technically challenging surgical procedure and provides acceptable results in terms of early and long-term outcomes. IT did not significantly affect morbidity and mortality.

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

Epidemiology, Treatment, and Complications of Central Nervous System Metastases.
Pruitt AA. Continuum (Minneap Minn). 2017 Dec;23(6, Neuro-oncology):1580-1600. doi: 10.1212/CON.0000000000000551.
PURPOSE OF REVIEW: Neurologic problems resulting from systemic cancer metastases to brain parenchyma, dura, spinal cord, and leptomeninges are among the most common types of consultations addressed by neurologists. With patients surviving longer from systemic cancer, along with the rapidly evolving therapeutic options, the treatment of these devastating complications has become both more effective and more complicated. This article reviews current patterns of metastatic disease and the increasingly nuanced landscape of evolving therapies, their complications, and their impact on quality of survival. **RECENT FINDINGS:** Targeted therapies with tyrosine kinase inhibitors and immune checkpoint inhibitors and cytotoxic therapies directed at disease-specific chemosensitivity patterns have dramatically improved the prognosis of non-small cell lung cancer, melanoma, and breast cancer, but have led to some novel complications and altered recurrence patterns. Clinical trials suggest the superiority of hippocampal-avoidance radiation fields and the use of stereotactic radiosurgery over whole-brain radiation therapy to minimize long-term cognitive consequences of radiation therapy. Emerging data document tolerable safety when brain radiation is combined with immunotherapy. Chemotherapy can be a first-line treatment for some inoperable brain metastases, eliminating or deferring whole-brain radiation therapy. Stereotactic body radiation therapy is a new technique of radiation used for spinal and epidural metastases that spares spinal cord tissue while ablating tumors. **SUMMARY:** Metastases to the nervous system remain devastating, but their prognosis and therapies are more heterogeneous than previously appreciated. Neurologists now can offer more personalized prognostic information based on new stratification criteria, can predict drug complications relevant to the nervous system, and can provide critical partnership in the multidisciplinary effort to balance effective longer-term disease control with treatment-related adverse consequences.

Immunotherapy (excluding checkpoint inhibitors) for stage I to III non-small cell lung cancer treated with surgery or radiotherapy with curative intent. Zhu J1, Li R, Tiselius E, Roudi R, Teghararian O, Suo C, Song H. Cochrane Database Syst Rev. 2017 Dec 16;12:CD011300. doi: 10.1002/14651858.CD011300.pub2.
BACKGROUND: Non-small cell lung cancer (NSCLC) is the most common lung cancer, accounting for approximately 80% to 85% of all cases. For patients with localised NSCLC (stages I to III), it has been speculated that immunotherapy may be helpful for reducing postoperative recurrence rates, or improving the clinical outcomes of current treatment for unresectable tumours. While several new agents have now

entered phase III clinical trials, we felt a systematic review was needed to address the question of the effectiveness and safety of immunotherapy in patients with stages I to III NSCLC.
OBJECTIVES: To evaluate the effectiveness and safety of immunotherapy (excluding checkpoint inhibitors) in patients with localised NSCLC (stages I to III) who received surgery or radiotherapy with curative intent. **SEARCH METHODS:** We searched the following databases (from inception to 20 January 2017): CENTRAL, MEDLINE, Embase, and CINAHL, and five trial registers. We also manually checked abstracts or reports from relevant conference proceedings and the reference lists of included trials. **SELECTION CRITERIA:** We searched for randomised controlled trials (RCTs) in adults ($\geq$ 18 years) with histologically-confirmed early-stage (stages I to III) NSCLC after surgical resection, and those with unresectable locally advanced stage III NSCLC who had received radiotherapy with curative intent. For patients who had received primary surgical treatment, postoperative radiotherapy or chemo-radiotherapy was allowed if it was used for both experimental and control groups. **DATA COLLECTION AND ANALYSIS:** Two review authors independently selected eligible trials, assessed risk of bias, and extracted data. We used survival analysis to pool time-to-event data, expressing the intervention effect as a hazard ratio (HR). We calculated risk ratios (RR) for dichotomous data, and mean differences for continuous data, with 95% confidence intervals (CI). Due to clinical heterogeneity (immunotherapeutic agents with different underlying mechanisms), we used random-effects models for our meta-analyses. **MAIN RESULTS:** We identified nine eligible trials that randomised 4940 participants, who had received surgical resection or curative radiotherapy, to either an immunotherapy group or a control group. Included immunological interventions were active immunotherapy (i.e. Bacillus Calmette-Guérin (BCG)), adoptive cell transfer (i.e. transfer factor (TF), tumour-infiltrating lymphocytes (TIL), dendritic cell-cytokine induced killer (DC-CIK), and antigen-specific cancer vaccines (melanoma-associated antigen 3 (MAGE-A3) and L-BLP25). Except for one small trial, which provided insufficient information for risk assessment, we assessed five studies at high risk of bias for at least one of the seven biases studied; we considered the risk of bias in the other three trials to be low. We included data from seven of the nine trials in the meta-analyses (4695 participants). We pooled data from 3693 participants from the three high quality RCTs to evaluate overall survival (OS) and progression-free survival (PFS). We found a small, but not statistically significant, improvement in OS (HR 0.94, 95% CI 0.83 to 1.06; P = 0.35), and PFS (HR 0.93, 95% CI 0.81 to 1.07; P = 0.19; high-quality evidence). The addition of immunotherapy resulted in a small, but not statistically significant, increased risk of having any adverse event (RR 1.15, 95% CI 0.97 to 1.37; P = 0.11, three trials, 3955 evaluated participants, moderate-quality evidence), or severe adverse events (RR 1.10, 95% CI 0.88 to 1.39; four trials, 4362 evaluated participants; low-quality evidence).We analysed data from six studies for one-, two-, and three-year survival rates (4265 participants), and from six studies for five-year survival rates (4234 participants). We observed no clear between-group differences (low-quality evidence for one- and two-year survival rates, and moderate-quality evidence for three- and five-year survival rate).No trial reported the overall response rates; only one trial provided health-related quality of life results. **AUTHORS' CONCLUSIONS:** The current literature does not provide evidence that suggests a survival benefit from adding immunotherapy (excluding checkpoint inhibitors) to conventional curative surgery or radiotherapy, for patients with localised NSCLC (stages I to III). The addition of vaccine-based immunotherapy might increase the risk of adverse events. Several ongoing trials with immune checkpoints inhibitors (PD-1/PD-L1) might bring new insights for role of immunotherapy for patients with stages I to III NSCLC.

[Induction Cisplatin Docetaxel Followed by Surgery and Erlotinib in Non-Small Cell Lung Cancer.](#)
Cascone T1, Gold KA2, Swisher SG3, et al. Ann Thorac Surg. 2017 Dec 4. pii: S0003-4975(17)31202-X. doi: 10.1016/j.athoracsur.2017.08.052. [Epub ahead of print]
BACKGROUND: Data from meta-analyses support the use of induction or adjuvant platinum-based chemotherapy for locally advanced non-small cell lung cancers (NSCLCs). This phase 2 study assessed

the role of induction cisplatin and docetaxel followed by surgery in patients with resectable stage I to III NSCLCs, followed by 12 months of adjuvant erlotinib. **METHODS:** Patients with resectable stage I to III NSCLCs received cisplatin 80 mg/m2, docetaxel 75 mg/m2 every 21 days for 3 cycles, followed by surgery, followed by adjuvant erlotinib for 12 months. The primary endpoint included safety. Long-term efficacy outcomes and exploratory analysis of intermediary endpoints are also reported (NCT00254384). **RESULTS:** Forty-seven eligible patients received a median of 3 cycles of induction treatment, 37 underwent surgical resection, and only 21 received adjuvant erlotinib. Two patients died in the perioperative period (1 sepsis during chemotherapy, 1 acute respiratory distress syndrome postoperatively). Most common grade 3 to 5 toxicities during chemotherapy included hypokalemia (8%), infection (7%), and granulocytopenia (25%). During adjuvant erlotinib, 14% of patients experienced grade 2 rash. Median overall survival was 3.4 years. Major pathologic responses in the primary tumor were observed in 19% (7 of 37) of patients and correlated with improved long-term overall survival. Complete pathologic response in mediastinal/hilar nodes also correlated with superior survival. **CONCLUSIONS:** Induction cisplatin and docetaxel was well tolerated. Adjuvant erlotinib did not improve outcomes compared with historical controls. Major pathologic response predicted for improved long-term survival and is a suitable intermediary endpoint for future phase 2 studies.

Bevacizumab in the treatment of NSCLC: patient selection and perspectives. Russo AE1, Priolo D1, Antonelli G1, Libra M2, McCubrey JA3, Ferraù F1. Lung Cancer (Auckl). 2017 Dec 14;8:259-269. doi: 10.2147/LCTT.S110306. eCollection 2017.
Non-small-cell lung cancer (NSCLC) represents about 85% of all lung cancers, and more than half of NSCLCs are diagnosed at an advanced stage. Chemotherapy has reached a plateau in the overall survival curve of about 10 months. Therefore, in last decade novel targeted approaches have been developed to extend survival of these patients, including antiangiogenic treatment. Vascular endothelial growth factor (VEGF) signaling pathway plays a dominant role in stimulating angiogenesis, which is the main process promoting tumor growth and metastasis. Bevacizumab (bev; Avastin®) is a recombinant humanized monoclonal antibody that neutralizes VEGF's biologic activity through a steric blocking of its binding with VEGF receptor. Currently, bev is the only antiangiogenic agent approved for the first-line treatment of advanced or recurrent nonsquamous NSCLC in "bev-eligible" patients. The ineligibility to receive bev is related to its toxicity. In the pivotal trials of bev in NSCLC, fatal bleeding events including pulmonary hemorrhage were observed with rates higher in the chemotherapy-plus-bev group. Therefore, in order to reduce the incidence of severe pulmonary hemorrhage, numerous exclusion criteria have been characteristically applied for bev such as central tumor localization or tumor cavitation, use of anticoagulant therapy, presence of brain metastases, age of patients (elderly). Subsequent studies designed to evaluate the safety of bev have demonstrated that this agent is safe and well tolerated even in those patients subpopulations excluded from pivotal trials. This review outlines the current state-of-the-art on bev use in advanced NSCLC. It also describes patient selection and future perspectives on this antiangiogenic agent.

FDA Benefit-Risk Assessment of Osimertinib for the Treatment of Metastatic Non-Small Cell Lung Cancer Harboring Epidermal Growth Factor Receptor T790M Mutation. Odogwu L1, Mathieu L2, Goldberg KB2, et al. Oncologist. 2017 Dec 14. pii: theoncologist.2017-0425. doi: 10.1634/theoncologist.2017-0425. [Epub ahead of print]
On March 30, 2017, the U.S. Food and Drug Administration (FDA) approved osimertinib for the treatment of patients with metastatic, epidermal growth factor receptor (EGFR) T790M mutation-positive, non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, whose disease has progressed following EGFR tyrosine kinase inhibitor (TKI) therapy. Approval was based on demonstration of a statistically significant difference in the primary endpoint of progression-free survival (PFS) when

comparing osimertinib with chemotherapy in an international, multicenter, open-label, randomized trial (AURA3). In this confirmatory trial, which enrolled 419 patients, the PFS hazard ratio for osimertinib compared with chemotherapy per investigator assessment was 0.30 (95% confidence interval 0.23-0.41), p < .001, with median PFS of 10.1 months in the osimertinib arm and 4.4 months in the chemotherapy arm. Supportive efficacy data included PFS per blinded independent review committee demonstrating similar PFS results and an improved confirmed objective response rate per investigator assessment of 65% and 29%, with estimated median durations of response of 11.0 months and 4.2 months, in the osimertinib and chemotherapy arms, respectively. Patients received osimertinib 80 mg once daily and had a median duration of exposure of 8 months. The toxicity profile of osimertinib compared favorably with the profile of other approved EGFR TKIs and chemotherapy. The most common adverse drug reactions (>20%) in patients treated with osimertinib were diarrhea, rash, dry skin, nail toxicity, and fatigue. Herein, we review the benefit-risk assessment of osimertinib that led to regular approval, for patients with metastatic NSCLC harboring EGFR TKI whose disease has progressed on or after EGFR TKI therapy. **IMPLICATIONS FOR PRACTICE:** Osimertinib administered to metastatic non-small cell lung cancer (NSCLC) patients harboring an EGFR T790M mutation, who have progressed on or following EGFR TKI therapy, demonstrated a substantial improvement over platinum-based doublet chemotherapy as well as durable intracranial responses. The ability to test for the T790M mutation in plasma using the FDA-approved cobas EGFR Mutation Test v2 (Roche, Basel, Switzerland) identifies patients with NSCLC tumors not amenable to biopsy. Since a 40% false-negative rate has been observed with the circulating tumor DNA test, re-evaluation of the feasibility of tissue biopsy is recommended to identify patients with a false-negative plasma test result who may benefit from osimertinib.

Impact of mild to moderate COPD on feasibility and prognosis in non-small cell lung cancer patients who received chemotherapy.

Omote N1, Hashimoto N1, Morise M1, Sakamoto K1, Miyazaki S1, Ando A1, Nakahara Y1, Hasegawa Y1.

BACKGROUND: Non-small cell lung cancer (NSCLC) is the predominant cause of death in patients with COPD, and the severity of COPD in NSCLC patients is classified mainly as mild to moderate. Most advanced NSCLC patients with mild to moderate COPD are treated with chemotherapy; however, the feasibility for and prognosis after chemotherapy of these patients are not well understood. The aim of this study was to elucidate the impact of mild to moderate COPD on the feasibility for and prognosis after chemotherapy in NSCLC patients. **PATIENTS AND METHODS:** A retrospective review was performed on 268 NSCLC patients who received first-line chemotherapy from 2009 to 2014 in our institution. Finally, 85 evaluable patients were included in this study. The clinical characteristics, toxicity profile, objective response rate, and prognosis were analyzed a d compared between patients with mild to moderate COPD and those without COPD (non-COPD). **RESULTS:** Forty-three patients were classified as COPD (27 cases mild and 16 cases moderate) and 42 patients as non-COPD. The COPD group were older and had fewer never-smokers than the non-COPD group. The objective response rate did not differ between groups (p=0.14). There was no significant difference in overall survival between COPD and non-COPD groups (15.0 and 17.0 months, log-rank test p=0.57). In the multivariate Cox's proportional hazard model, the adjusted hazard ratio (HRadj) was statistically significant for male sex (HRadj =5.382, 95% CI: 1.496-19.359; p=0.010), pathological diagnosis of adenocarcinoma (HRadj =0.460, 95% CI: 0.223-0.948; p=0.035), and epithelial growth factor receptor negative mutation (HRadj =6.040, 95% CI: 1.158-31.497; p=0.033), but not for the presence of COPD (HRadj =0.661, 95% CI: 0.330-1.325; p=0.24). Toxicity profile in COPD group was favorable, as in the non-COPD group. **CONCLUSION:** Mild to moderate COPD did not have a significant deleterious impact on toxicity and prognosis in NSCLC patients.

[Effects of Chemotherapy Regimen and Radiation Modality on Hematologic Toxicities in Patients Receiving Definitive Platinum-based Doublet Chemoradiation for Non-Small Cell Lung Cancer.](#)

Tang C1, Lee MS2, Gomez D1, Levy LB1, Zhuang Y1, Lu C3, Liao Z1, Komaki R1. Am J Clin Oncol. 2017 Dec;40(6):625-630. doi: 10.1097/COC.0000000000000206.

OBJECTIVES: Predictors of acute hematologic toxicities during definitive chemoradiation for non-small cell lung cancer (NSCLC) are incompletely defined.

MATERIALS AND METHODS: We retrospectively analyzed 604 patients treated with definitive platinum-based doublet chemoradiation therapy for stage III NSCLC. The outcome of interest was grade ≥3 acute hematologic toxicities, specifically white blood cell, hemoglobin, platelet, neutrophil, and lymphocyte decrease during chemoradiation therapy. We assessed the association between any grade ≥3 acute hematologic toxicity with patient demographic, disease, radiation factors (specifically modality and dose), and chemotherapy agents via stepwise multivariate logistic regression. Survival was compared via log-rank and univariate Cox regression analyses. **RESULTS:** There was no significant association between radiation modality and any hematologic toxicity on multivariate analysis. However, use of etoposide was found to be significantly associated with white blood cell, platelet, and neutrophil decrease compared with paclitaxel and docetaxel (all P<0.05). No differences were found between platinum agents. Overall survival (OS) and event-free survival (EFS) were significantly worse in patients who experienced grade ≥3 hemoglobin (OS: hazard ratio [HR]=1.5; 95% confidence interval [CI], 1.05-2.26; P=0.03, EFS: HR=1.7; 95% CI, 1.2-2.4; P=0.0032) and lymphocyte (OS: HR=1.5; 95% CI, 1.1-2.1; P=0.01, EFS: HR=1.4; 95% CI, 1.1-1.9; P=0.02) decreases. **CONCLUSIONS:** Chemotherapy identity, specifically the nonplatinum agent, was significantly associated with grade ≥3 hematologic toxicities, whereas radiation modality was not.

[Brief Report: Tivantinib in Combination with Erlotinib Versus Erlotinib Alone for EGFR Mutant NSCLC: An Exploratory Analysis of the Phase 3 MARQUEE Study.](#)

Scagliotti GV1, Shuster D2, Orlov S3, von Pawel J4, Shepherd FA5, Ross JS6, Wang Q7, Schwartz B8, Akerley W9. J Thorac Oncol. 2017 Dec 27. pii: S1556-0864(17)33112-X. doi: 10.1016/j.jtho.2017.12.009. [Epub ahead of print]

INTRODUCTION: This exploratory subgroup analysis of the MARQUEE study evaluated the efficacy and safety of erlotinib plus tivantinib in patients with epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC). **METHODS:** Patients with advanced, non-squamous, EGFR and mesenchymal-epithelial transition (MET) inhibitor-naive NSCLC, previously treated with 1 to 2 lines of systemic therapy, were randomized to oral erlotinib (150 mg once daily) plus tivantinib (360 mg twice daily) or to erlotinib plus placebo. The primary endpoint was overall survival. **RESULTS:** Among 1,048 patients enrolled, 109 (10.4%) had EGFR-mutant disease. Erlotinib plus tivantinib improved progression-free survival (PFS) in this subpopulation; median PFS was 13.0 months for erlotinib plus tivantinib (n=56) and 7.5 months for erlotinib plus placebo (n=53) (hazard ratio [HR]=0.49, 95% confidence interval [CI]: 0.31-0.77). Deaths occurred in 73 (67%) patients, and median overall survival was 25.5 months in the erlotinib plus tivantinib arm versus 20.3 months in the erlotinib plus placebo arm (HR=0.68, 95% CI: 0.43-1.08). Common adverse events included diarrhea, rash, and asthenia. Neutropenia and febrile neutropenia were more common with erlotinib plus tivantinib. **CONCLUSIONS:** Erlotinib plus tivantinib was tolerable and showed improved efficacy over erlotinib monotherapy in previously treated EGFR-mutant NSCLC.

Magnetic resonance imaging in precision radiation therapy for lung cancer. Bainbridge H1, Salem A2, Tijssen RHN3, et al. Transl Lung Cancer Res. 2017 Dec;6(6):689-707. doi: 10.21037/tlcr.2017.09.02. Radiotherapy remains the cornerstone of curative treatment for inoperable locally advanced lung cancer, given concomitantly with platinum-based chemotherapy. With poor overall survival, research efforts continue to explore whether integration of advanced radiation techniques will assist safe treatment intensification with the potential for improving outcomes. One advance is the integration of magnetic resonance imaging (MRI) in the treatment pathway, providing anatomical and functional information with excellent soft tissue contrast without exposure of the patient to radiation. MRI may complement or improve the diagnostic staging accuracy of F-18 fluorodeoxyglucose position emission tomography and computerized tomography imaging, particularly in assessing local tumour invasion and is also effective for identification of nodal and distant metastatic disease. Incorporating anatomical MRI sequences into lung radiotherapy treatment planning is a novel application and may improve target volume and organs at risk delineation reproducibility. Furthermore, functional MRI may facilitate dose painting for heterogeneous target volumes and prediction of normal tissue toxicity to guide adaptive strategies. MRI sequences are rapidly developing and although the issue of intra-thoracic motion has historically hindered the quality of MRI due to the effect of motion, progress is being made in this field. Four-dimensional MRI has the potential to complement or supersede 4D CT and 4D F-18-FDG PET, by providing superior spatial resolution. A number of MR-guided radiotherapy delivery units are now available, combining a radiotherapy delivery machine (linear accelerator or cobalt-60 unit) with MRI at varying magnetic field strengths. This novel hybrid technology is evolving with many technical challenges to overcome. It is anticipated that the clinical benefits of MR-guided radiotherapy will be derived from the ability to adapt treatment on the fly for each fraction and in real-time, using 'beam-on' imaging. The lung tumour site group of the Atlantic MR-Linac consortium is working to generate a challenging MR-guided adaptive workflow for multi-institution treatment intensification trials in this patient group.

Simultaneous tumor and surrogate motion tracking with dynamic MRI for radiation therapy planning. Park S1, Farah R2, Shea SM3, Tryggestad EJ4, Hales R5, Lee J6. Phys Med Biol. 2017 Dec 15. doi: 10.1088/1361-6560/aaa20b. [Epub ahead of print]
Respiration-induced tumor motion is a major obstacle for achieving high-precision radiotherapy of cancers in the thoracic and abdominal regions. Surrogate-based estimation and tracking methods are commonly used in radiotherapy, but with limited understanding of quantified correlation to tumor motion. In this study, we propose a method to simultaneously track the lung tumor and external surrogates to evaluate their spatial correlation in a quantitative way using dynamic MRI, which allows real-time acquisition without ionizing radiation exposure. To capture the lung and whole tumor, four MRI-compatible fiducials are placed on the patient's chest and upper abdomen. Two different types of acquisitions are performed in the sagittal orientation including multi-slice 2D cine MRIs to reconstruct 4D-MRI and two-slice 2D cine MRIs to simultaneously track the tumor and fiducials. A phase-binned 4D-MRI is first reconstructed from multi-slice MR images using body area as a respiratory surrogate and groupwise registration. The 4D-MRI provides 3D template volumes for different breathing phases. 3D tumor position is calculated by 3D-2D template matching in which 3D tumor templates in the 4D-MRI reconstruction and the 2D cine MRIs from the two-slice tracking dataset are registered. 3D trajectories of the external surrogates are derived via matching a 3D geometrical model of the fiducials to their segmentations on the 2D cine MRIs. We tested our method on ten lung cancer patients. Using a correlation analysis, the 3D tumor trajectory demonstrates a noticeable phase mismatch and significant cycle-to-cycle motion variation, while the external surrogate was not sensitive enough to capture such

variations. Additionally, there was significant phase mismatch between surrogate signals obtained from the fiducials at different locations.

Choice of postoperative radiation for stage IIIA pathologic N2 non-small cell lung cancer: impact of metastatic lymph node number.
Wang S1,2, Ma Z1,2, Yang X3, et al. Radiat Oncol. 2017 Dec 29;12(1):207. doi: 10.1186/s13014-017-0946-1.
BACKGROUND: Postoperative radiation (PORT) is an option for non-small cell lung cancer (NSCLC) patients with resectable stage IIIA pathological N2 status (pN2). For patients with PORT, this study aims to investigate the impact of the exact number of positive lymph nodes (LNs) on overall survival (OS) and lung cancer-specific survival (LCSS). **METHODS:** Within the Surveillance, Epidemiology, and End Results database, we identified 3373 patients with stage IIIA pathological N2 status (pN2) NSCLC who underwent a lobectomy or pneumonectomy from 2004 to 2013. OS and LCSS were compared among patients coded as receiving PORT or observation. The proportional hazards model was applied for investigation. **RESULTS:** OS and LCSS favored PORT for patients with stage IIIA (pN2) NSCLC. Multivariable analyses showed that PORT and the exact number of positive LNs ($n \leq 3$) were independently associated with better OS and LCSS. Both better OS and LCSS emerged for positive LNs ($n > 3$) after the use of PORT in survival analyses, whereas the benefits of OS and LCSS were not observed anymore for positive LNs ($n \leq 3$) group. More importantly, multivariable analyses showed that the use of PORT is an independent risk factor of survival for positive LNs ($n > 3$) but not for positive LNs ($n \leq 3$). **CONCLUSIONS:** In Stage IIIA (pN2) NSCLC, the use of PORT demonstrated better survival results than no PORT for patients with positive LNs ($n > 3$), but not for patients with positive LNs ($n \leq 3$).

Single Fraction Stereotactic Ablative Body Radiotherapy for Oligometastasis: Outcomes from 132 Consecutive Patients. Gandhidasan S1, Ball D1, Kron T1, et al. Clin Oncol (R Coll Radiol). 2017 Dec 7. pii: S0936-6555(17)30487-9. doi: 10.1016/j.clon.2017.11.010. [Epub ahead of print]
AIMS: Stereotactic ablative body radiotherapy (SABR) is currently used to treat oligometastases, but the optimum dose/fractionation schedule is unknown. In this study, we evaluated outcomes after single fraction SABR in patients with oligometastatic disease. **MATERIALS AND METHODS:** Single institutional retrospective review of patients treated with single fraction SABR for one to three oligometastases between 2010 and 2015. The primary outcome was freedom from widespread disease defined as distant recurrence not amenable to surgery or SABR; or recurrence with four or more metastases. **RESULTS:** In total, 186 treatments were delivered in 132 patients. The two most common target sites were lung (51%) and bone (40%). The most frequent single fraction prescription dose was 26 Gy (47%). The most common primary malignancy was genitourinary (n = 46 patients). Freedom from widespread disease was 75% at 1 year (95% confidence interval 67-83%) and 52% at 2 years (95% confidence interval 42-63%). Freedom from local progression at 1 year was 90% (95% confidence interval 85-95%) and at 2 years was 84% (95% confidence interval 77-91%). A compression fracture of the lumbar vertebra was the only grade 3+ treatment-related toxicity. **CONCLUSIONS:** Single fraction SABR is associated with a high rate of freedom from widespread disease, favourable local control and low toxicity comparable with historic multi-fraction SABR reports.

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. 2017 Dec 14. doi: 10.1097/RCT.0000000000000653. [Epub ahead of print]

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.

SMALL CELL LUNG CANCER - SCLC

Combination treatment of RAD001 and BEZ235 exhibits synergistic antitumor activity via down-regulation of p-4E-BP1/Mcl-1 in small cell lung cancer. Hong B1, Wang H1, Deng K1, Wang W1, Dai H2, Yan Lui VW3, Lin W1. Oncotarget. 2017 Jul 4;8(63):106486-106498. doi: 10.18632/oncotarget.18984. eCollection 2017 Dec 5.

Small cell lung cancer (SCLC) is a highly malignant cancer with few targeted therapies. In the study, by mining the Cancer Cell Line Encyclopedia (CCLE) database, we found that PI3K/AKT/mTOR pathway was aberrant in 92% of SCLC cell lines. Moreover, we found that the phosphorylation level of 4E-BP1 was significantly correlated with SCLC sensitivity to RAD001 (mTOR inhibitor) and BEZ235 (PI3K/mTOR dual inhibitor). Combination of RAD001 and BEZ235 synergistically inhibited the growth of SCLC cells, which was accompanied by enhanced induction of cell cycle arrest and apoptosis. Such a combination dramatically inhibited the activation of AKT, and strongly reduced the phosphorylation of 4E-BP1 and its downstream target Mcl-1. Knock-down of Mcl-1 enhanced the growth inhibition of SCLC cells induced by RAD001 and BEZ235 co-treatment, whereas over-expression of Mcl-1 reduced the growth inhibitory effect. Furthermore, in vivo study demonstrated that the combination treatment suppressed tumor growth more effectively than RAD001 or BEZ235 treatment alone. In summary, our study suggests that combination of BEZ235 and RAD001 may be an effective regimen for SCLC treatment, and p-4E-BP1 may serve as a predictive biomarker for SCLC response to mTOR inhibitor.

A phase II trial of Ifosfamide combination with recommended supportive therapy for recurrent SCLC in second-line and heavily treated setting. Tanaka I1, Kawada K2, Morise M3, et al. Cancer Chemother Pharmacol. 2017 Dec 12. doi: 10.1007/s00280-017-3497-0. [Epub ahead of print]
PURPOSE: The response rate of ifosfamide (IFM) monotherapy for small-cell lung cancer (SCLC) is reported as 42.4% in Japanese package insert. However, these efficacy data are based on clinical studies conducted in 1970s. This phase II study evaluated the efficacy and safety of IFM combination with recommended current supportive therapy for recurrent SCLC in second-line and heavily treated setting. **METHODS:** Recurrent SCLC patients pretreated with one to three prior regimens received IFM monotherapy (1.5 g/m2 for 3 days every 3 weeks). Treatment was continued until disease progression or unacceptable toxicity. The primary end point was objective response rate. **RESULTS:** Twelve patients were enrolled in the study from June 2009 to January 2013. The study was early terminated at interim analysis due to futility stop. Patient characteristics were as follows: median age was 65 years, 11 were males (91.7%) and eight (66.7%) and four (33.3%) were Performance Status 0 and 1, respectively. Four

patients (33.3%) enrolled in second-line setting were all refractory relapse SCLC and 8 (66.7%) were heavily treated patients. No patient showed objective response. Stable disease was observed in 3 patients. Median progression-free survival and overall survival were 0.9 months (95% CI, 0.3-1.5) and 4.8 months (95% CI, 1.6-9.9), respectively. Although one grade 4 amylase increase possibly related to IFM was observed, toxicity profile was totally favorable. **CONCLUSIONS:** IFM monotherapy should not be used for refractory relapse or heavily treated SCLC, and no further investigation is required in these populations.

[A phase IIa study of HA-irinotecan, formulation of hyaluronic acid and irinotecan targeting CD44 in extensive-stage small cell lung cancer.](#) Alamgeer M1,2,3, Neil Watkins D4, Banakh I5, Kumar B6, Gough DJ7, Markman B8, Ganju V7,5,9. Invest New Drugs. 2017 Dec 26. doi: 10.1007/s10637-017-0555-8. [Epub ahead of print]

Preclinical studies in small cell lung cancer (SCLC) have shown that hyaluronic acid (HA) can be effectively used to deliver chemotherapy and selectively decrease CD44 expressing (stem cell-like) tumour cells. The current study aimed to replicate these findings and obtain data on safety and activity of HA-irinotecan (HA-IR). Eligible patients with extensive stage SCLC were consented. A safety cohort (n = 5) was treated with HA-IR and Carboplatin (C). Subsequently, the patients were randomised 1:1 to receive experimental (HA-IR + C) or standard (IR + C) treatment, to a maximum of 6 cycles. The second line patients were added to the study and treated with open label HA-IR + C. Tumour response was measured after every 2 cycles. Baseline tumour specimens were stained for CD44s and CD44v6 expression. Circulating tumour cells (CTCs) were enumerated before each treatment cycle. Out of 39 patients screened, 34 were evaluable for the study. The median age was 66 (range 39-83). The overall response rates were 69% and 75% for experimental and standard arms respectively. Median progression free survival was 42 and 28 weeks, respectively (p = 0.892). The treatments were well tolerated. The incidence of grade III/IV diarrhea was more common in the standard arm, while anaemia was more common in the experimental arm. IHC analysis suggested that the patients with CD44s positive tumours may gain survival benefit from HA-IR. HA-IR is well tolerated and active in ES-SCLC. The effect of HA-IR on CD44s + cancer stem-like cells provide an early hint towards a potential novel target.

PALLIATIVE AND SUPPORTIVE CARE

[Patient-clinician communication among patients with stage I lung cancer.](#) Nugent SM1,2, Golden SE3, Thomas CR Jr4, et al. Support Care Cancer. 2017 Dec 5. doi: 10.1007/s00520-017-3992-1. [Epub ahead of print]

PURPOSE: Limited data exist about patient-centered communication (PCC) and patient-centered outcomes among patients who undergo surgery or stereotactic body radiation therapy (SBRT) for stage I non-small cell lung cancer (NSCLC). We aimed to examine the relationship between PCC and decision-making processes among NSCLC patients, using baseline data from a prospective, multicenter study. **METHODS:** Patients with stage 1 NSCLC completed a survey prior to treatment initiation. The survey assessed sociodemographic characteristics, treatment decision variables, and patient psychosocial outcomes: health-related quality of life (HRQOL), treatment self-efficacy, decisional conflict, and PCC. **RESULTS:** Fifty-two percent (n = 85) of 165 individuals planned to receive SBRT. There were no baseline differences detected on patient psychosocial outcomes between those who planned to receive SBRT or surgery. All participants reported high HRQOL (M = 72.5, SD = 21.3) out of 100, where higher scores indicate better functioning; high self-efficacy (M = 1.5, SD = 0.5) out of 6, where lower numbers indicate higher self-efficacy; minimal decisional conflict (M = 15.2, SD = 12.7) out of 100, where higher scores indicate higher decisional conflict; and high levels of patient-centered communication (M = 2.4, SD = 0.8) out of 7 where higher scores indicate worse communication. Linear regression analyses

adjusting for sociodemographic and clinical variables showed that higher quality PCC was associated with higher self-efficacy ($\beta = 0.17$, $p = 0.03$) and lower decisional conflict ($\beta = 0.42$, $p < 0.001$).
CONCLUSIONS: Higher quality PCC was associated with higher self-efficacy and lower decisional conflict. Self-efficacy and decisional conflict may influence subsequent health outcomes. Therefore, our findings may inform future research and clinical programs that focus on communication strategies to improve these outcomes.

Anamorelin (ONO-7643) for the treatment of patients with non-small cell lung cancer and cachexia: Results from a randomized, double-blind, placebo-controlled, multicenter study of Japanese patients (ONO-7643-04). Katakami N1, Uchino J2,3, Yokoyama T4, et al. Cancer. 2017 Dec 4. doi: 10.1002/cncr.31128. [Epub ahead of print]
BACKGROUND: Cachexia, described as weight loss (mainly in lean body mass [LBM]) and anorexia, is common in patients with advanced cancer. This study examined the efficacy and safety of anamorelin (ONO-7643), a novel selective ghrelin receptor agonist, in Japanese cancer patients with cachexia.
METHODS: This double-blind clinical trial (ONO-7643-04) enrolled 174 patients with unresectable stage III/IV non-small cell lung cancer (NSCLC) and cachexia in Japan. Patients were randomized to daily oral anamorelin (100 mg) or a placebo for 12 weeks. The primary endpoint was the change from the baseline LBM (measured with dual-energy x-ray absorptiometry) over 12 weeks. The secondary endpoints were changes in appetite, body weight, quality of life, handgrip strength (HGS), and 6-minute walk test (6MWT) results. **RESULTS:** The least squares mean change (plus or minus the standard error) in LBM from the baseline over 12 weeks was 1.38 ± 0.18 and -0.17 ± 0.17 kg in the anamorelin and placebo groups, respectively ($P < .0001$). Changes from the baseline in LBM, body weight, and anorexia symptoms showed significant differences between the 2 treatment groups at all time points. Anamorelin increased prealbumin at weeks 3 and 9. No changes in HGS or 6MWT were detected between the groups. Twelve weeks' treatment with anamorelin was safe and well tolerated in NSCLC patients.
CONCLUSIONS: Anamorelin significantly increased LBM and improved anorexia symptoms and the nutritional state, but not motor function, in Japanese patients with advanced NSCLC. Because no effective treatment for cancer cachexia is currently available, anamorelin can be a beneficial treatment option. Cancer 2017. © 2017 American Cancer Society.
© 2017 American Cancer Society.

Risk of thromboembolism in cisplatin versus carboplatin-treated patients with lung cancer. Kim ES1, Baran AM2, Mondo EL1, Rodgers TD1, Nielsen GC1, Dougherty DW1, Pandya KJ1, Rich DQ3, Wijngaarden EV3. PLoS One. 2017 Dec 11;12(12):e0189410. doi: 10.1371/journal.pone.0189410. eCollection 2017.
INTRODUCTION: Carboplatin is widely used to treat lung cancer in the United States as an alternative to cisplatin. Several studies have demonstrated that cisplatin-based regimen is associated with a high frequency of thromboembolic complications. However, there has been limited investigation directly comparing the risk of thromboembolic events (TEEs) between cisplatin- and carboplatin-treated patients with lung cancer. **METHODS:** All lung cancer patients treated with cisplatin or carboplatin at Wilmot Cancer Center, University of Rochester between 2011 and 2014 were included. Patient characteristics including exposure (cisplatin vs. carboplatin) and outcome (TEEs between the time of the first dose of cisplatin or carboplatin and 4 weeks after the last dose) were collected by reviewing electronic medical records. A Fisher's exact test was used to compare the proportion of incident TEEs between cisplatin and carboplatin groups. The risk of TEE associated with carboplatin compared to cisplatin was assessed using multiple logistic regression. **RESULTS:** Among 415 subjects, 317 patients (76.4%) received carboplatin and 98 (23.6%) patients received cisplatin. In the carboplatin group, 10.9% (33/302) of evaluable patients developed treatment-related TEEs vs. 14.7% (14/95) in the cisplatin group. There was no significant

difference in the risk of developing TEEs between the two groups (P = 0.32). However, 15.2% of carboplatin-related TEEs were arterial thromboses compared to none in the cisplatin group. **CONCLUSIONS:** The incidence of carboplatin-related TEEs was high in lung cancer patients without significant difference in the risk of developing TEEs between cisplatin and carboplatin groups. Potential use of prophylactic anticoagulation in all platinum-treated patients should be further investigated.

[Participation and interest in support services among family caregivers of older adults with cancer.](#)
Dionne-Odom JN1, Applebaum AJ2, Ornstein KA3, et al. Psychooncology. 2017 Dec 11. doi: 10.1002/pon.4603. [Epub ahead of print]
OBJECTIVE: The purpose of this study was to describe distressed and underprepared family caregiver's use of and interest in formal support services (eg, professional counseling, education, organizational assistance). **METHOD:** Cross-sectional mail survey conducted in communities of 8 cancer centers in Tennessee, Alabama, and Florida (response rate: 42%). Family caregivers of Medicare beneficiaries with pancreatic, lung, brain, ovarian, head and neck, hematologic, and stage IV cancers reported support service use and completed validated measures of depression, anxiety, burden, preparedness, and health. **RESULTS:** Caregivers (n = 294) were on average age 65 years and mostly female (73%), White (91%), and care recipients' spouse/partner (60%); patients averaged 75 years were majority male (54%) with lung cancer (39%). Thirty-two percent of caregivers reported accessing services while 28% were "mostly" or "extremely" interested. Thirty-five percent of caregivers with high depressive symptoms (n = 122), 33% with high anxiety symptoms (n = 100), and 25% of those in the lowest quartile of preparedness (n = 77) accessed services. Thirty-eight percent of those with high depressive symptoms, 47% with high anxiety symptoms, and 36% in the lowest quartile of preparedness were "mostly" or "extremely" interested in receiving services. Being interested in support services was significantly associated with being a minority, shorter durations of caregiving, and with higher stress burden. **CONCLUSIONS:** A large proportion of family caregivers, including those experiencing depression and anxiety symptoms and who were underprepared, are not using formal support services but have a strong interest in services. Strategies to increase service use may include targeting distressed caregivers early in their caregiving experience.

[Tai Chi and Qigong for cancer-related symptoms and quality of life: a systematic review and meta-analysis.](#) Wayne PM1, Lee MS2, Novakowski J3, Osypiuk K3, Ligibel J4, Carlson LE5, Song R6. J Cancer Surviv. 2017 Dec 8. doi: 10.1007/s11764-017-0665-5. [Epub ahead of print]
PURPOSE: This study aims to summarize and critically evaluate the effects of Tai Chi and Qigong (TCQ) mind-body exercises on symptoms and quality of life (QOL) in cancer survivors. **METHODS:** A systematic search in four electronic databases targeted randomized and non-randomized clinical studies evaluating TCQ for fatigue, sleep difficulty, depression, pain, and QOL in cancer patients, published through August 2016. Meta-analysis was used to estimate effect sizes (ES, Hedges' g) and publication bias for randomized controlled trials (RCTs). Methodological bias in RCTs was assessed. **RESULTS:** Our search identified 22 studies, including 15 RCTs that evaluated 1283 participants in total, 75% women. RCTs evaluated breast (n = 7), prostate (n = 2), lymphoma (n = 1), lung (n = 1), or combined (n = 4) cancers. RCT comparison groups included active intervention (n = 7), usual care (n = 5), or both (n = 3). Duration of TCQ training ranged from 3 to 12 weeks. Methodological bias was low in 12 studies and high in 3 studies. TCQ was associated with significant improvement in fatigue (ES = - 0.53, p < 0.001), sleep difficulty (ES = - 0.49, p = 0.018), depression (ES = - 0.27, p = 0.001), and overall QOL (ES = 0.33, p = 0.004); a statistically non-significant trend was observed for pain (ES = - 0.38, p = 0.136). Random effects models were used for meta-analysis based on Q test and I 2 criteria. Funnel plots suggest some degree of publication bias. Findings in non-randomized studies largely paralleled meta-analysis results. **CONCLUSIONS:** Larger and methodologically sound trials with longer follow-up periods and appropriate comparison groups are needed before definitive conclusions can be drawn, and cancer- and

symptom-specific recommendations can be made. **IMPLICATIONS FOR CANCER SURVIVORS:**
TCQ shows promise in addressing cancer-related symptoms and QOL in cancer survivors.

Post-diagnosis weight loss as a prognostic factor in non-small cell lung cancer. Mytelka DS1, Li L1,
Benoit K1. J Cachexia Sarcopenia Muscle. 2017 Dec 4. doi: 10.1002/jcsm.12253. [Epub ahead of print]
BACKGROUND: Cachexia and its most visible manifestation, weight loss, represent important poor
prognostic factors for patients with non-small cell lung cancer. This work examines how severity of
weight loss as an indicator of cachexia affects outcomes. **METHODS:** In a retrospective observational
study of electronic medical records, patients with non-small cell lung cancer were monitored for weight
loss from an initial assessment (within 2 months of index diagnosis) to a landmark at 5 months (at least 3
months after initial assessment). Patients who survived to the landmark were then followed to determine
the association of baseline body mass index (BMI) and weight loss during the assessment period with
outcomes. Patients were clustered to determine how BMI and weight loss related to survival as
approximated by time of last appearance in the database, a strong proxy for time of death. **RESULTS:**
Twelve thousand one hundred and one patients were divided into 5 cachexia risk groups based on a
combination of weight loss and initial BMI. More severe groups demonstrated progressively worse
outcomes, with the most severe group surviving for a median of 263 days (95% CI 254-274) from index
and having a 1-year survival rate of 31%. The least severe group survived for a median of 825 days from
index (95% CI 768-908) and had a 1-year survival rate of 78%. Cachexia risk group was a stronger
predictor of survival than any baseline variable, including disease stage, performance status, or age.
CONCLUSIONS: In this study, we showed that increasing weight loss and, to a lesser extent, decreasing
BMI, led to substantially worse outcomes for non-small cell lung cancer patients independent of other
variables. We suggest risk score groups that provide an improved approach for identifying poor prognosis
patients with the greatest need.

Pilot Testing of a Brief Couple-Based Mind-Body Intervention for Patients with Metastatic Non-Small Cell Lung Cancer and Their Partners. Milbury K1, Engle R2, Tsao A3, Liao Z4, Owens A2,
Chaoul A2, Bruera E2, Cohen L2. J Pain Symptom Manage. 2017 Dec 2. pii: S0885-3924(17)30692-9.
doi: 10.1016/j.jpainsymman.2017.11.027. [Epub ahead of print]
CONTEXT: Given the generally incurable nature of metastatic lung cancer, patients and their
spouses/partners are at risk for psychological and spiritual distress. To address this concern, we developed
a couple-based mind-body (CBMB) intervention. **OBJECTIVES:** This formative research was aimed at
examining the intervention's acceptability and initial efficacy in patients with metastatic lung cancer
undergoing treatment and their spouses. **METHODS:** Intervention content evaluation sessions and an
ensuing single-arm trial were conducted. To evaluate intervention content, participants performed
intervention exercises and then participated in semi-structured interviews and completed written
evaluations. In the single-arm trial, four intervention sessions were delivered over 2 weeks, focusing on
cultivating mindfulness, interpersonal connection, gratitude, and purpose. Newly recruited couples
completed measures of depressive symptoms, cancer distress, spiritual well-being, and sleep disturbances
before and after the intervention. **RESULTS:** Content evaluations by seven dyads of patients and their
partners revealed high acceptability ratings for the CBMB intervention (e.g., all participants would
recommend the intervention). Consent and adherence rates (54% and 67%, respectively) were acceptable
in the single-arm trial. All patients (n= 7 dyads; 67% male; mean age, 55 years) and partners (33% male;
mean age, 59 years) rated the intervention as useful. Paired t-test analyses revealed large effect sizes for
reduced sleep disturbances (d = 1.83) and medium effect sizes for cancer-specific distress (d = 0.61) for
patients and large effect sizes for depressive symptoms (d = 0.90) for partners. **CONCLUSION:** Based
on these results the CBMB intervention appears to be acceptable and subjectively useful. Also, we
observed preliminary evidence of quality of life gains in both patients and their partners.

Tai Chi and Qigong for cancer-related symptoms and quality of life: a systematic review and meta-analysis. Wayne PM1, Lee MS2, Novakowski J3, Osypiuk K3, Ligibel J4, Carlson LE5, Song R6. J Cancer Surviv. 2017 Dec 8. doi: 10.1007/s11764-017-0665-5. [Epub ahead of print]

PURPOSE: This study aims to summarize and critically evaluate the effects of Tai Chi and Qigong (TCQ) mind-body exercises on symptoms and quality of life (QOL) in cancer survivors. **METHODS:** A systematic search in four electronic databases targeted randomized and non-randomized clinical studies evaluating TCQ for fatigue, sleep difficulty, depression, pain, and QOL in cancer patients, published through August 2016. Meta-analysis was used to estimate effect sizes (ES, Hedges' g) and publication bias for randomized controlled trials (RCTs). Methodological bias in RCTs was assessed. **RESULTS:** Our search identified 22 studies, including 15 RCTs that evaluated 1283 participants in total, 75% women. RCTs evaluated breast (n = 7), prostate (n = 2), lymphoma (n = 1), lung (n = 1), or combined (n = 4) cancers. RCT comparison groups included active intervention (n = 7), usual care (n = 5), or both (n = 3). Duration of TCQ training ranged from 3 to 12 weeks. Methodological bias was low in 12 studies and high in 3 studies. TCQ was associated with significant improvement in fatigue (ES = - 0.53, p < 0.001), sleep difficulty (ES = - 0.49, p = 0.018), depression (ES = - 0.27, p = 0.001), and overall QOL (ES = 0.33, p = 0.004); a statistically non-significant trend was observed for pain (ES = - 0.38, p = 0.136). Random effects models were used for meta-analysis based on Q test and I 2 criteria. Funnel plots suggest some degree of publication bias. Findings in non-randomized studies largely paralleled meta-analysis results. **CONCLUSIONS:** Larger and methodologically sound trials with longer follow-up periods and appropriate comparison groups are needed before definitive conclusions can be drawn, and cancer- and symptom-specific recommendations can be made. **IMPLICATIONS FOR CANCER SURVIVORS:** TCQ shows promise in addressing cancer-related symptoms and QOL in cancer survivors.

Anticancer activity of Astragalus polysaccharide in human non-small cell lung cancer cells. Wu CY1, Ke Y2, Zeng YF2, Zhang YW1, Yu HJ2. Cancer Cell Int. 2017 Dec 4;17:115. doi: 10.1186/s12935-017-0487-6. eCollection 2017.

BACKGROUND: We have reported that Chinese herbs Astragalus polysaccharide (APS) can inhibit nuclear factor kappaB (NF-κB) activity during the development of diabetic nephropathy in mice. NF-κB plays important roles in genesis, growth, development and metastasis of cancer. NF-κB is also involved in the development of treatment resistance in tumors. Here we investigated the antitumor activity of APS in human non-small cell lung cells (A549 and NCI-H358) and the related mechanisms of action.
METHODS: The dose-effect and time-effect of antitumor of APS were determined in human lung cancer cell line A549 and NCI-H358. The inhibition effect of APS on the P65 mRNA and protein was detected by reverse transcriptase-PCR (RT-PCR) and Western blot in A549 cells respectively. The inhibition effect of APS on the p50, CyclinD1 and Bcl-xL protein was detected by Western blot in A549 cells respectively. The effect of APS on NF-κB transcription activity was measured with NF-κB luciferase detection. Finally, the nude mice A549 xenograft was introduced to confirm the antitumor activity of APS in vivo.
RESULTS: Cell viability detection results indicated that APS can inhibit the proliferation of human lung cancer cell line A549 and NCI-H358 in the concentration of 20 and 40 mg/mL. NF-κB activator Phorbol 12-myristate13-acetate (PMA) can attenuate the antitumor activity of APS in both cell lines, but NF-κB inhibitor BAY 11-7082 (Bay) can enhance the effect of APS in both cell lines. In vivo APS can delay the growth of A549 xenograft in BALB/C nude mice. APS can down-regulate the expression of P65 mRNA and protein of A549 cells and decrease the expression of p50, CyclinD1 and Bcl-xL protein. The luciferase detection showed that the APS could reduce the P65 transcription activity in A549 cells. PMA can partially alleviate the inhibition activity of P65 transcription activity of APS in A549 cells, and Bay

can enhance the down-regulation of the P65 transcription activity induced by APS in A549 cells.
CONCLUSION: APS has a significant antitumor activity in human lung cancer cells A549 and NCI-H358. NF-κB inhibition may mediate the antitumor effect.

MISCELLANEOUS WORKS

Lung cancer diagnosis by trained dogs.
Guirao Montes Á1,2, Molins López-Rodó L1,2,3, Ramón Rodríguez I4, et al. Eur J Cardiothorac Surg. 2017 Dec 1;52(6):1206-1210. doi: 10.1093/ejcts/ezx152.
OBJECTIVES: Early lung cancer (LC) diagnosis is key to improve prognosis. We explored here the diagnostic performance of a trained dog to discriminate exhaled gas samples obtained from patients with and patients without LC and healthy controls. **METHODS:** After appropriate training, we exposed the dog (a 3-year-old cross-breed between a Labrador Retriever and a Pitbull) to 390 samples of exhaled gas collected from 113 individuals (85 patients with LC and 28 controls, which included 11 patients without LC and 17 healthy individuals) for a total of 785 times. **RESULTS:** The trained dog recognized LC in exhaled gas with a sensitivity of 0.95, a specificity of 0.98, a positive predictive value of 0.95 and a negative predictive value of 0.98. The area under the curve of the receiver-operating characteristics curve was 0.971. **CONCLUSIONS:** This study shows that a well-trained dog can detect the presence of LC in exhaled gas samples with an extremely high accuracy.

Healthcare experience among older cancer survivors: Analysis of the SEER-CAHPS dataset.
Halpern MT1, Urato MP2, Lines LM3, Cohen JB2, Arora NK4, Kent EE5. J Geriatr Oncol. 2017 Dec 14. pii: S1879-4068(17)30243-6. doi: 10.1016/j.jgo.2017.11.005. [Epub ahead of print]
OBJECTIVE: Little is known about factors affecting medical care experiences of cancer survivors. This study examined experience of care among cancer survivors and assessed associations of survivors' characteristics with their experience. **MATERIALS AND METHODS:** We used a newly-developed, unique data resource, SEER-CAHPS (NCI's Surveillance Epidemiology and End Results [SEER] data linked to Medicare Consumer Assessment of Healthcare Providers and Systems [CAHPS] survey responses), to examine experiences of care among breast, colorectal, lung, and prostate cancer survivors age >66years who completed CAHPS >1year after cancer diagnosis and survived ≥1year after survey completion. Experience of care was assessed by survivor-provided scores for overall care, health plan, physicians, customer service, doctor communication, and aspects of care. Multivariable logistic regression models assessed associations of survivors' sociodemographic and clinical characteristics with care experience. **RESULTS:** Among 19,455 cancer survivors with SEER-CAHPS data, higher self-reported general-health status was significantly associated with better care experiences for breast, colorectal, and prostate cancer survivors. In contrast, better mental-health status was associated with better care experience for lung cancer survivors. College-educated and Asian survivors were less likely to indicate high scores for care experiences. Few differences in survivors' experiences were observed by sex or years since diagnosis. **CONCLUSIONS:** The SEER-CAHPS data resources allows assessment of factors influencing experience of cancer among U.S. cancer survivors. Higher self-reported health status was associated with better experiences of care; other survivors' characteristics also predicted care experience. Interventions to improve cancer survivors' health status, such as increased access to supportive care services, may improve experience of care.

Impact of a Non-Small Cell Lung Cancer Educational Program for Interdisciplinary Teams.
Murgu S1, Rabito R2, Lasko G2, Jackson C2, Mino-Kenudson M3, Ettinger DS4, Ramalingam SS5, Edell ES6; GAIN collaborators. Chest. 2017 Dec 12. pii: S0012-3692(17)33212-9. doi: 10.1016/j.chest.2017.11.032. [Epub ahead of print]

BACKGROUND: Successful implementation of non-small cell lung cancer (NSCLC) evidence-based guideline recommendations requires effective educational programs that target all clinicians from interdisciplinary teams. This study describes and evaluates the EnGAging an Interdisciplinary Team for NSCLC (GAIN 3.0) experiential learning-based educational curriculum. **METHODS:** GAIN 3.0 was designed to enhance interdisciplinary collaboration for effective NSCLC diagnosis, assessment, and treatment. The program used a flipped classroom model that included an e-learning component prior to a live 6-hour interactive program. The interactive program included hands-on simulations, small group workshops, gamification, and case discussions. Participants included academic and community members of multidisciplinary lung cancer teams. Assessments included online baseline survey, pretest and posttest, program evaluation, long-term survey (LTS), and on-site faculty evaluation of participants. **RESULTS:** Of 416 attendees to 13 live GAIN 3.0 programs (9 US, 3 Europe), 304 (73%) completed the pretest and 187 (45%) completed the posttest. Out of a perfect score of 12 points, program participants had a mean test scores of 6.3 ± 2.1 on the pretest (52%) and 7.8 ± 2.1 on the posttest (65%), P=0.03. There was an overall knowledge increase of 13% from pretest to posttest. Most (65%) LTS respondents rated the GAIN 3.0 live programs as "High Impact." On the LTS, the areas with the greatest gains in participants who had very high confidence were communication across disciplines, use of a team-based approach, and personalized treatment. **CONCLUSIONS:** GAIN 3.0 was a highly successful interdisciplinary activity that improved participants' knowledge, competence, and likely the clinical care provided to patients with NSCLC.