Caring Ambassadors Lung Cancer Program
Literature Review, December 2016

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

PF4 Promotes Platelet Production and Lung Cancer Growth. Pucci F1, Rickelt S2, Newton AP1, et al. Cell Rep. 2016 Nov 8;17(7):1764-1772. doi: 10.1016/j.celrep.2016.10.031.
Co-option of host components by solid tumors facilitates cancer progression and can occur in both local tumor microenvironments and remote locations. At present, the signals involved in long-distance communication remain insufficiently understood. Here, we identify platelet factor 4 (PF4, CXCL4) as an endocrine factor whose overexpression in tumors correlates with decreased overall patient survival. Furthermore, engineered PF4 over-production in a Kras-driven lung adenocarcinoma genetic mouse model expanded megakaryopoiesis in bone marrow, augmented platelet accumulation in lungs, and accelerated de novo adenocarcinogenesis. Additionally, anti-platelet treatment controlled mouse lung cancer progression, further suggesting that platelets can modulate the tumor microenvironment to accelerate tumor outgrowth. These findings support PF4 as a cancer-enhancing endocrine signal that controls discrete aspects of bone marrow hematopoiesis and tumor microenvironment and that should be considered as a molecular target in anticancer therapy.

Nanoparticle delivery of chemotherapy combination regimen improves the therapeutic efficacy in mouse models of lung cancer. Tian J1, Rodgers Z2, Min Y2, et al.
Nanomedicine. 2016 Nov 21. pii: S1549-9634(16)30199-X. doi: 10.1016/j.nano.2016.11.007. [Epub ahead of print]
The combination chemotherapy regimen of cisplatin (CP) and docetaxel (DTX) is effective against a variety of cancers. However, combination therapies present unique challenges that can complicate clinical application, such as increases in toxicity and imprecise exposure of tumors to specific drug ratios that can produce treatment resistance. Drug co-encapsulation within a single nanoparticle (NP) formulation can overcome these challenges and further improve combinations' therapeutic index. In this report, we employ a CP prodrug (CPP) strategy to formulate poly(lactic-co-glycolic acid)-poly(ethylene glycol) (PLGA-PEG) NPs carrying both CPP and DTX. The dually loaded NPs display differences in drug release kinetics and in vitro cytotoxicity based on the structure of the chosen CPP. Furthermore, NPs containing

both drugs showed a significant improvement in treatment efficacy versus the free drug combination in vivo.

Identification of a seven-miRNA signature as prognostic biomarker for lung squamous cell carcinoma. Gao X1,2,3, Wu Y1,2,3, Yu W1,2,3, Li H1,4,2,3. Oncotarget. 2016 Nov 7. doi: 10.18632/oncotarget.13164. [Epub ahead of print]
BACKGROUND: Specific biomarkers for outcome prediction of lung squamous cell carcinoma (LUSC) are still lacking. This study assessed the prognostic value of differentially expressed miRNAs of LUSC patients. **RESULTS:** Twelve of the 133 most significantly altered miRNAs were associated with overall survival (OS) across different clinical subclasses of the Cancer Genome Atlas (TCGA) LUSC cohort. A linear prognostic model of seven miRNAs was developed to divide patients into high- and low-risk groups. Patients assigned to the high-risk group exhibited poor OS compared with patients in the low-risk group, which was further validated in the validation cohort and entire LUSC cohort. **METHODS:** MiRNA expression profiles with clinical information of 447 LUSC patients were obtained from TCGA. Most significantly altered miRNAs were identified between tumor and normal samples. Using survival analysis and supervised principal components method, a seven-miRNA signature for prediction of OS of LUSC patients was established. Survival receiver operating characteristic (ROC) analysis was used to assess the performance of survival prediction. The biological relevance of predicted miRNA targets was also analyzed using bioinformatics method. **CONCLUSIONS:** The current study suggests that seven-miRNA signature may have clinical implications in the outcome prediction of LUSC.

Efficacy of afatinib, an irreversible ErbB family blocker, in the treatment of intracerebral metastases of non-small cell lung cancer in mice. Zhang SR1,2, Zhu LC1,3, Jiang YP1, Zhang J1, Xu RJ4, Xu YS1,2, Xia B3, Ma SL1,2,5. Acta Pharmacol Sin. 2016 Nov 14. doi: 10.1038/aps.2016.107. [Epub ahead of print]
AIM: Few effective therapeutic options are currently available for the treatment of non-small cell lung cancer (NSCLC) with brain metastases (BM). Recent evidence shows that NSCLC patients with BMs respond well to afatinib, but little is known about the underlying mechanisms. In this study, we evaluated the efficacy of afatinib in treatment of BMs in mice and investigated whether afatinib could actively penetrate the brain-blood barrier and bind to its target. **METHODS:** NSCLC BM model was established in nude mice by intracerebral injection of PC-9.luc cells. The tumors were measured weekly using in vivo quantitative bioluminescence. The mice are administrated afatinib (15, 30 mg·kg-1·d-1, ig) for 14 d. The antitumor efficacy of afatinib was determined by tumor growth inhibition (TGI), which was calculated as [1-(change of tumor volume in treatment group/control group)×100]. Pharmacokinetic characteristics were measure in mice receiving a single dose of afatinib (30 mg/kg, ig). Pharmacodynamics of afatinib was also assessed by detecting the expression of pEGFR (Tyr1068) in brain tumor foci using immunohistochemistry. **RESULTS:** Administration of afatinib (15, 30 mg·kg-1·d-1) dose-dependently inhibited PC-9 tumor growth in the brain with a TGI of 90.2% and 105%, respectively, on d 14. After administration of afatinib (30 mg/kg), the plasma concentration of afatinib was 91.4±31.2 nmol/L at 0.5 h, reached a peak (417.1±119.9 nmol/L) at 1 h, and was still detected after 24 h. The cerebrospinal fluid (CSF) concentrations followed a similar pattern. The T1/2 values of afatinib in plasma and CSF were 5.0 and 3.7 h, respectively. The AUC(0-24 h) values for plasma and CSF were 2375.5 and 29.1 nmol/h, respectively. The plasma and CSF concentrations were correlated ($r=0.844$, $P<0.01$). Pharmacodynamics study showed that the expression levels of pEGFR were reduced by 90% 1 h after afatinib administration. The Emax was 86.5%, and the EC50 was 0.26 nmol/L. A positive correlation between CSF concentrations and pEGFR modulation was revealed. **CONCLUSION:** Afatinib penetrates the BBB in NSCLC BM mice and contributes to the brain tumor response. The CSF exposure level is correlated with

the plasma level, which in turn is correlated with the modulation of pEGFR in the tumor tissues. The results support for the potential application of afatinib in NSCLC patients with BMs.

KRAS driven expression signature has prognostic power superior to mutation status in non-small cell lung cancer. Nagy Á1,2, Pongor LS1,2, Szabó A2, Santarpia M3, Győrffy B1,2. Int J Cancer. 2016 Nov 8. doi: 10.1002/ijc.30509. [Epub ahead of print]
KRAS is the most frequently mutated oncogene in non-small cell lung cancer (NSCLC). However, the prognostic role of KRAS mutation status in NSCLC still remains controversial. We hypothesize that the expression changes of genes affected by KRAS mutation status will have the most prominent effect and could be used as a prognostic signature in lung cancer. We divided NSCLC patients with mutation and RNA-seq data into KRAS mutated and wild type groups. Mann-Whitney test was used to identify genes showing altered expression between these cohorts. Mean expression of the top five genes was designated as a "transcriptomic fingerprint" of the mutation. We evaluated the effect of this signature on clinical outcome in 2,437 NSCLC patients using univariate and multivariate Cox regression analysis. Mutation of KRAS was most common in adenocarcinoma. Mutation status and KRAS expression were not correlated to prognosis. The transcriptomic fingerprint of KRAS include FOXRED2, KRAS, TOP1, PEX3 and ABL2. The KRAS signature had a high prognostic power. Similar results were achieved when using the second and third set of strongest genes. Moreover, all cutoff values delivered significant prognostic power ($p < 0.01$). The KRAS signature also remained significant ($p < 0.01$) in a multivariate analysis including age, gender, smoking history and tumor stage. We generated a "surrogate signature" of KRAS mutation status in NSCLC patients by computationally linking genotype and gene expression. We show that secondary effects of a mutation can have a higher prognostic relevance than the primary genetic alteration itself.

SCREENING, DIAGNOSIS AND STAGING

Understanding Mechanisms of Resistance in the Epithelial Growth Factor Receptor in Non-Small Cell Lung Cancer and the Role of Biopsy at Progression. Socinski MA1, Villaruz LC2, Ross J3,4. Oncologist. 2016 Nov 7. pii: theoncologist.2016-0285. [Epub ahead of print]
Molecular profiling and the discovery of drugs that target specific activating mutations have allowed the personalization of treatment for non-small cell lung cancer (NSCLC). The epithelial growth factor receptor (EGFR) is frequently overexpressed and/or aberrantly activated in different cancers, including NSCLC. The most common activating mutations of EGFR in NSCLC fall within the tyrosine kinase-binding domain. Three oral EGFR tyrosine kinase inhibitors (TKIs) have been approved by the U.S. Food and Drug Administration (FDA) for first-line use in patients with EGFR mutation-positive NSCLC (exon 19 deletions or exon 21 [L858R] substitution mutations), as detected by an FDA-approved test. However, disease progression is common and is often the result of secondary mutations, of which the EGFR T790M mutation is the most prevalent. Few options were available upon progression until the introduction of osimertinib, a kinase inhibitor that targets the T790M mutation, which was recently approved for use in patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who progressed on or after EGFR TKI therapy. With the introduction of osimertinib, outcomes can now be improved in select patients. Therefore, performing a biopsy at progression to determine the underlying molecular cause of the acquired resistance is important for the enabling of individualized options that may provide the greatest opportunity for improved outcomes. This review discusses the latest updates in molecular testing at progression and outlines treatment options for this difficult-to-treat population.
IMPLICATIONS FOR PRACTICE: Although the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs)-gefitinib, erlotinib, and afatinib-have changed the treatment paradigm for non-small cell lung cancer among those with EGFR mutation-positive disease, most patients experience

progression after approximately 12 months of treatment. Until recently, options were limited for patients who progressed, but improvements in molecular profiling and the approval of osimertinib, which targets the resistance mutation T790M, afford the opportunity for improved outcomes in many patients with this mutation. This article explains the options available after progression on initial EGFR TKI therapy and the importance of molecular testing at progression in making treatment decisions.

Terminate lung cancer (TLC) study-A mixed-methods population approach to increase lung cancer screening awareness and low-dose computed tomography in Eastern Kentucky. Cardarelli R1, Reese D2, Roper KL3, et al. Cancer Epidemiol. 2016 Nov 17;46:1-8. doi: 10.1016/j.canep.2016.11.003. [Epub ahead of print]
For low dose CT lung cancer screening to be effective in curbing disease mortality, efforts are needed to overcome barriers to awareness and facilitate uptake of the current evidence-based screening guidelines. A sequential mixed-methods approach was employed to design a screening campaign utilizing messages developed from community focus groups, followed by implementation of the outreach campaign intervention in two high-risk Kentucky regions. This study reports on rates of awareness and screening in intervention regions, as compared to a control region.

Usefulness of Endobronchial Ultrasonography With a Guide Sheath and Virtual Bronchoscopic Navigation for Ground-Glass Opacity Lesions. Ikezawa Y1, Shinagawa N2, Sukoh N3, et al. Ann Thorac Surg. 2016 Nov 5. pii: S0003-4975(16)31163-8. doi: 10.1016/j.athoracsur.2016.09.001. [Epub ahead of print]
BACKGROUND: Endobronchial ultrasonography with guide sheath (EBUS-GS) could be useful for diagnosing ground-glass opacity (GGO) predominant-type lesions in the peripheral lung. Furthermore, several studies have reported that transbronchial biopsy using EBUS-GS and virtual bronchoscopic navigation (VBN) was safe and effective for diagnosing small peripheral lung lesions. Our objectives were to diagnose solitary peripheral GGO predominant-type lesions by transbronchial biopsy using EBUS-GS and VBN under radiographic fluoroscopic guidance, and to evaluate the clinical factors associated with diagnostic yield. **METHODS:** The medical records of 169 patients with GGO predominant-type lesions who underwent transbronchial biopsy using EBUS-GS and VBN under radiographic fluoroscopic guidance were retrospectively reviewed. **RESULTS:** Endobronchial ultrasonography images could be obtained for 156 (92%) of 169 GGO predominant-type lesions, and 116 (69%) were successfully diagnosed by this method (20 of 31 pure GGO lesions [65%]; 96 of 138 mixed GGO predominant-type lesions [70%]). The mean size of diagnosed lesions was significantly larger than that of nondiagnosed lesions (22 mm versus 18 mm, $p < 0.01$). Regarding diagnostic yield based on computed tomography sign, cases with presence of a bronchus leading directly to a lesion had significantly higher diagnostic yield than the other lesions ($p < 0.01$). **CONCLUSIONS:** The addition of VBN to EBUS-GS could be useful in clinical practice for diagnosing GGO predominant-type lesions in the peripheral lung.

A Prediction Model Based on Biomarkers and Clinical Characteristics for Detection of Lung Cancer in Pulmonary Nodules. Ma J1, Guarnera MA2, Zhou W3, Fang H3, Jiang F4. Transl Oncol. 2016 Nov 24;10(1):40-45. doi: 10.1016/j.tranon.2016.11.001. [Epub ahead of print]
Lung cancer early detection by low-dose computed tomography (LDCT) can reduce the mortality. However, LDCT increases the number of indeterminate pulmonary nodules (PNs), whereas 95% of the PNs are ultimately false positives. Modalities for specifically distinguishing between malignant and benign PNs are urgently needed. We previously identified a panel of peripheral blood mononucleated cell (PBMC)-miRNA (miRs-19b-3p and -29b-3p) biomarkers for lung cancer. This study aimed to evaluate efficacy of integrating biomarkers and clinical and radiological characteristics of smokers for

differentiating malignant from benign PNs. We analyzed expression of 2 miRNAs (miRs-19b-3p and -29b-3p) in PBMCs of a training set of 137 individuals with PNs. We used multivariate logistic regression analysis to develop a prediction model based on the biomarkers, radiographic features of PNs, and clinical characteristics of smokers for identifying malignant PNs. The performance of the prediction model was validated in a testing set of 111 subjects with PNs. A prediction model comprising the two biomarkers, spiculation of PNs and smoking pack-year, was developed that had 0.91 area under the curve of the receiver operating characteristic for distinguishing malignant from benign PNs. The prediction model yielded higher sensitivity (80.3% vs 72.6%) and specificity (89.4% vs 81.9%) compared with the biomarkers used alone (all P<.05). The performance of the prediction model for malignant PNs was confirmed in the validation set. We have for the first time demonstrated that the integration of biomarkers and clinical and radiological characteristics could efficiently identify lung cancer among indeterminate PNs.

Prognostic Impact of Newly Proposed M Descriptors in TNM Classification of Non-Small Cell Lung Cancer. Shin J1, Keam B2, Kim M1, Park YS1, Kim TM1, Kim DW1, Kim YW1, Heo DS1. J Thorac Oncol. 2016 Nov 17. pii: S1556-0864(16)33457-8. doi: 10.1016/j.jtho.2016.11.2216. [Epub ahead of print]

INTRODUCTION: The International Association for the Study of Lung Cancer recently proposed new M descriptors for the next edition of the TNM classification for NSCLC, subdividing the current M1b category into two subcategories: M1b, which indicates a solitary extrathoracic metastasis in a single organ, and M1c, which indicates multiple extrathoracic metastasis. The purpose of this study was to validate the prognostic value of the newly proposed M descriptors in an independent cohort with multivariate and subgroup analysis. **METHODS:** A total of 1024 patients in a consecutive lung cancer database who had stage IV NSCLC treated between 2011 and 2014 were analyzed. Newly proposed M staging was used for classification and comparison of survival. Adjustment for other clinical covariates and subgroup analysis was conducted. **RESULTS:** According to the newly proposed M descriptors, 262 patients (25.6%), 152 patients (14.8%), and 610 patients (59.6%) were classified into the subgroups M1a, M1b, and M1c, respectively. The median overall survival times were 22.5, 17.8, and 13.6 months for the M1a, M1b, and M1c groups, respectively ($p < 0.001$). After adjustment for other covariates, Cox proportional hazards regression revealed statistically significantly shorter overall survival for the M1b group than for the M1a group (hazard ratio = 1.30; 95% confidence interval: 1.03-1.65, $p = 0.03$) and for the M1c than the M1b group (hazard ratio = 1.57; 95% confidence interval: 1.28-1.93, $p < 0.001$). These differences showed a consistent tendency regardless of pathologic and molecular subtypes.
CONCLUSIONS: The newly proposed M descriptors have prognostic value in patients with stage IV NSCLC.

Endobronchial and Endoscopic Ultrasound-Guided Transvascular Biopsy of Mediastinal, Hilar, and Lung Lesions. Kazakov J1, Hegde P2, Tahiri M2, Thiffault V2, Ferraro P2, Liberman M2. Ann Thorac Surg. 2016 Nov 16. pii: S0003-4975(16)31248-6. doi: 10.1016/j.athoracsur.2016.08.111. [Epub ahead of print]

BACKGROUND: Endoscopic techniques, including endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS), are the initial approach for the diagnosis and staging of lung cancer and the diagnosis of mediastinal and hilar lesions. Historically, the transvascular approach has been avoided because of concerns of bleeding. Here we review our experience with EBUS and EUS transvascular biopsy of mediastinal, hilar, and lung lesions. **METHODS:** A prospective research database was used to retrospectively identify and review the records 33 consecutive patients who underwent EBUS and EUS transvascular biopsy in an outpatient setting over 4 years. Complications were identified as significant hematoma seen with endoscopic ultrasound, hemothorax, hemoptysis other than minor, hemodynamic

instability, hospital admission, and death. **RESULTS:** The biopsies in 14 patients were performed through branches of the pulmonary artery, and 19 were done through the aorta. All EUS biopsies were performed with a 22-gauge needle, and all EBUS biopsies were performed with a 21-gauge needle. Malignancy was diagnosed with specimens from a transvascular biopsy in 16 patients (48.5%). Samples from 8 biopsies (24%) were described as negative for malignancy, and 9 specimens (27%) were described as insufficient. No complications were seen in the immediate postprocedural period, and all 33 patients were discharged home the same day. The median follow-up after the procedure was 12 months, with no complications described. The overall yield was 73%. **CONCLUSIONS:** In this series, EBUS- and EUS-guided transvascular approach for biopsy of mediastinal, hilar, and lung lesions was not associated with significant complications. However, careful selection of potential candidates and close periprocedural observation are mandatory.

Predicting the Mortality Benefit of CT Screening for Second Lung Cancer in a High-Risk Population. Kinsey CM1, Hamlington KL1, O'Toole J2, Stapleton R1, Bates JH1. PLoS One. 2016 Nov 2;11(11):e0165471. doi: 10.1371/journal.pone.0165471. eCollection 2016.
Patients who survive an index lung cancer (ILC) after surgical resection continue to be at significant risk for a metachronous lung cancer (MLC). Indeed, this risk is much higher than the risk of developing an ILC in heavy smokers. There is currently little evidence upon which to base guidelines for screening at-risk patients for MLC, and the risk-reward tradeoffs for screening this patient population are unknown. The goal of this investigation was to estimate the maximum mortality benefit of CT screening for MLC. We developed a computational model to estimate the maximum rates of CT detection of MLC and surgical resection to be expected in a given population as a function of time after resection of an ILC. Applying the model to a hypothetical high-risk population suggests that screening for MLC within 5 years after resection of an ILC may identify only a very small number of treatable cancers. The risk of death from a potentially resectable MLC increases dramatically past this point, however, suggesting that screening after 5 years is imperative. The model also predicts a substantial detection gap for MLC that demonstrates the benefit to be gained as more sensitive screening methods are developed.

How Patients View Lung Cancer Screening. The Role of Uncertainty in Medical Decision Making. Schapira MM1,2, Aggarwal C3, Akers S4,5, et al. Ann Am Thorac Soc. 2016 Nov;13(11):1969-1976.
RATIONALE: Radiographic lung cancer screening guidelines and coverage requirements warrant a shared decision-making process. Guidance is needed regarding how to conduct shared decision making effectively. A useful organizing theme should include consideration of a patient's response to and tolerance of uncertainty associated with lung cancer screening. **OBJECTIVES:** The objectives of this study are to: (1) describe how patients respond to specific categories of uncertainty in the context of lung cancer screening, and (2) inform strategies for addressing concerns about uncertainty as part of the shared decision making. **METHODS:** We performed two series of structured interviews on participants in a convenience sample of current or former cigarette smokers recruited from primary care and pulmonary practices in Philadelphia. An interview guide included prompts related to benefits, harms, and responses to general and specific types of uncertainty (stochastic, statistical, and evidentiary) associated with lung cancer screening. Interviews were audio-recorded, transcribed, and independently coded by two investigators. An inductive analysis was conducted, and major themes were identified.
MEASUREMENTS AND MAIN RESULTS: Twenty-two adults participated in the study. Sixty-eight percent were men, 72% were black or African American, and 50% met U.S. Preventive Services Task Force criteria for lung cancer screening. The primary themes to emerge from our study were: (1) the desire to decrease uncertainty may motivate lung cancer screening decisions; (2) uncertainty is an attribute of health states that impacts how patients weigh benefits and harms of lung cancer screening; (3) patient understanding and tolerance of uncertainty varies across stochastic, statistical, and evidentiary

uncertainty; and (4) provider-patient communication may mitigate intolerance of uncertainty in the context of lung cancer screening. **CONCLUSIONS:** A systematic approach to understanding and addressing patients' concerns about uncertainty in the context of lung cancer screening can guide a patient-centered approach to shared decision making. The results of this study can inform provider-patient communication strategies regarding the decision to perform radiographic lung cancer screening.

Patients' Attitudes Regarding Lung Cancer Screening and Decision Aids. A Survey and Focus Group Study. Crothers K1, Kross EK1, Reisch LM1, et al. Ann Am Thorac Soc. 2016 Nov;13(11):1992-2001.
RATIONALE: Little is known about vulnerable patients' perceptions and understanding of, and preferences for, lung cancer screening decision aids. **OBJECTIVES:** To determine, in a low-income, racially diverse population, (1) participants' experience, preferences, and reactions to web-based and paper decision aids, and (2) their understanding of harms and benefits of lung cancer screening. **METHODS:** We enrolled outpatients at an urban county hospital in six focus group discussions that included review of a web-based and a paper-based lung-cancer screening decision aid. Participants completed surveys before and after the focus groups. **MEASUREMENTS AND MAIN RESULTS:** Forty-five patients participated (mean age, 61 yr; 76% current smokers; 24% former smokers); 27% had not completed high school; 50% had an annual income not exceeding $15,000; 42% were nonwhite; and 96% reported chronic illness requiring at least three health care visits yearly. Comparing the proportion with correct answers on pre- and postsurveys, participants' understanding of lung cancer screening increased, particularly of the harms of screening including the potential for false positives, extra testing, and complications. However, after conclusion of the focus groups, more than 50% believed that screening lowered the chance of getting lung cancer. Five major themes emerged from qualitative analyses. Participants (1) were not aware of the purpose of lung cancer screening; (2) wanted to know about the benefits and harms; (3) believed physicians need to communicate more effectively; (4) found decision aids helpful and influential for decision-making about screening; and (5) wanted the discussion to be personalized and tailored. Participants expressed surprise that the magnitude of their lung cancer risk and benefits of screening were lower than anticipated. **CONCLUSIONS:** Vulnerable patients find lung cancer screening decision aids helpful and generally show increased knowledge after reviewing decision aids, particularly of harms. Our results can inform future implementation efforts.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Joint effect of airflow limitation and emphysema on postoperative outcomes in early-stage nonsmall cell lung cancer. Shin S1, Park HY2,3, Kim H4, et al. Eur Respir J. 2016 Nov 3. pii: ERJ-01148-2016. doi: 10.1183/13993003.01148-2016. [Epub ahead of print]
This study aims to evaluate the joint effect of severity of airflow limitation and emphysema on postoperative pulmonary complications (PPCs) and overall survival after complete resection in patients with early-stage nonsmall cell lung cancer (NSCLC).We retrospectively studied 413 male patients with pathologic stage I or II NSCLC between 2007 and 2009. Severity of airflow limitation was defined based on forced expiratory volume in 1 s. Emphysema was defined by ≥5% low attenuation area at -950 HU.In multivariable-adjusted analyses, the adjusted odds ratio (aOR) for any PPC, comparing patients with moderate-to-severe airflow limitation to those without airflow limitation, was 2.23, and the aOR comparing patients with emphysema to those without emphysema was 1.77. However, the joint effect of airflow limitation and emphysema was much higher than expected from the independent effects of both factors (aOR 8.90). Moreover, patients with coexisting moderate-to-severe airflow limitation and

emphysema had significantly poorer overall survival than any other group. Patients with moderate-to-severe airflow limitation and emphysema had almost nine times the risk of PPCs and poorer survival than patients with neither of these conditions. Integrated assessment of airflow limitation severity and emphysema is necessary for the optimal selection of candidates for lung resection surgery of early-stage NSCLC.

Gender-specific survival after surgical resection for early stage non-small cell lung cancer. Bugge A1,2, Kongerud J2,3, Brunborg C4, Solberg S1,2, Lund MB2,3. Acta Oncol. 2016 Nov 16:1-7. [Epub ahead of print]
BACKGROUND: Lung cancer is the leading cause of cancer death worldwide. The incidence and mortality rate of lung cancer in women has increased. Studies have indicated that females with non-small cell lung cancer (NSCLC) have better survival than males. We aimed to examine the impact of gender on 1-, 5- and 10-year survival after surgery for stage I and II NSCLC. **MATERIALS AND METHODS:** During the period 2003-2013, 692 patients operated for stage I and II NSCLC were prospectively registered. Patients were stratified into four groups according to gender and age over or less than 66 years. The relationship between gender and age on overall survival was investigated. Adjustment for multiple confounders was performed using the Cox proportional hazard regression model. **RESULTS:** Surgical resection was performed in 368 (53.2%) males and 324 (46.8%) females. During the study period, mortality was 35.2% in younger females, 34.9% in younger males, 42.8% in older females and 51.2% in older males. Stratified by age, there were no significant gender differences with regard to survival [hazard ratio (HR) 1.16, 95% confidence interval (CI) 0.91-1.46, p = .23]. Comparing the younger and the older patients adjusted for confounders, the mortality risk was significantly increased in elderly patients [females, adjusted HR 1.60, 95% CI 1.12-2.28]. Compared with population data, standardized mortality ratio was increased to 4.1 (95% CI 3.5-4.7) in males and to 6.5 (95% CI 5.4-7.6) in females.
CONCLUSION: Overall survival did not differ significantly between males and females. Adjusted for confounding factors, we found a significantly increased mortality risk in elder patients compared to their younger counterparts. However, five-year overall survival of more than 50% for older patients with NSCLC should encourage surgical treatment also in elderly lung cancer patients.

NSCLC – Systemic Therapies (Chemotherapy, Targeted Therapy, and Immunotherapy)

A Randomized Trial of TLR-2 agonist CADI-05 targeting desmocollin-3 for advanced non-small-cell lung cancer. Belani CP1, Chakraborty B2, Modi R2, Khamar B3. Ann Oncol. 2016 Nov 9. pii: mdw608. [Epub ahead of print]
BACKGROUND: Randomised controlled trial to evaluate synergy between taxane plus platinum chemotherapy and CADI-05, a TLR-2 agonist targeting desmocollin-3 as a first line therapy in advanced Non Small cell lung cancer (NSCLC). **PATIENTS AND METHODS:** Patients with advanced NSCLC (stage IIIB or IV) were randomized to Cisplatin-Paclitaxel (Chemotherapy group, N=112) or Cisplatin-Paclitaxel plus CADI-05 (Chemoimmunotherapy group, N=109). CADI-05 was administered a week prior to chemotherapy and on day 8 and 15 of each cycle and every month subsequently for 12 months or disease progression. Overall survival was compared using a log-rank test. Computed tomography was performed at baseline, end of two cycles and four cycles. Response rate was evaluated using RECIST criteria by an independent radiologist. **RESULTS:** As per ITT analysis no survival benefit was observed between two groups (208 vs. 196 days; hazard ratio, 0.86; 95% CI, 0.63 to 1.19; P=0.3804). In a subgroup analysis, improvement in median survival by 127 days was observed in Squamous NSCC with chemoimmunotherapy (hazard ratio, 0.55; 95% CI, 0.32 to 0.95; P=0.046). In patients receiving planned four cycles of chemotherapy, there was improved median overall survival by 66 days (299 vs. 233 days; hazard ratio, 0.64; 95% CI, 0.41 to 0.98; P=0.04) in Chemoimmunotherapy group compared to

chemotherapy group This was associated with improved survival by 17.48% at the end of one year, in Chemoimmunotherapy group. Systemic adverse events were identical in both the groups. **CONCLUSION:** There was no survival benefit with the addition of CADI-05 to the combination of Cisplatin-Paclitaxel in patients with advanced NSCLC; however, the squamous cell subset did demonstrate a survival advantage.

Serum APE1 as a predictive marker for platinum-based chemotherapy of non-small cell lung cancer patients. Zhang S1, He L1, Dai N1, et al. Oncotarget. 2016 Nov 2. doi: 10.18632/oncotarget.13030. [Epub ahead of print]
PURPOSE: To define the role of the DNA repair protein apurinic/apyrimidinic endonuclease 1 (APE1) in predicting the prognosis and chemotherapeutic response of non-small cell lung cancer patients receiving platinum-containing chemotherapy. **RESULTS:** Our investigations found that serum APE1 level was significantly elevated in 229 of 412 NSCLC patients and correlated with its level in tissue ($r2 = 0.639$, $p < 0.001$). The elevated APE1 level in both tissue and serum of patients prior to chemotherapy was associated with worse progression-free survival (HR: 2.165, $p < 0.001$, HR: 1.421, $p = 0.012$), but not with overall survival. After 6 cycles of chemotherapy, a low APE1 serum level was associated with better overall survival (HR: 0.497, $p = 0.010$). **EXPERIMENTAL DESIGN:** We measured APE1 protein levels in biopsy tissue from 172 NSCLC patients and sera of 412 NSCLC patients receiving platinum-based chemotherapy by immunohistochemistry and a newly established sensitive and specific enzyme-linked immunosorbent assay, respectively. APE1 levels in sera of 523 healthy donors were also determined as control. **CONCLUSIONS:** Our studies indicate that APE1 is a biomarker for predicting prognosis and therapeutic efficacy in NSCLC. The chemotherapy-naïve serum APE1 level, which correlated with its tissue level inversely associated with progression-free survival of platinum-containing doublet chemotherapy, whereas post-treatment serum APE1 level was inversely associated with overall survival.

Continuing EGFR inhibition beyond progression in advanced non-small cell lung cancer. Yap TA1, Macklin-Doherty A2, Popat S3. Eur J Cancer. 2016 Nov 17;70:12-21. doi: 10.1016/j.ejca.2016.10.014. [Epub ahead of print]
The majority of patients with epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) respond to first-line EGFR tyrosine kinase inhibitors (TKIs), but nearly all inevitably acquire resistance and develop disease progression. Conventional practice would be to switch treatments to second-line therapy. However, continuing TKIs beyond progression is becoming increasingly commonplace in patients with indolent, small volume asymptomatic growth, who may potentially continue to derive ongoing clinical benefit and to avoid a 'withdrawal tumour flare'. Nevertheless, there are limitations to our current criteria for assessing disease response, which are based on radiological assessments without considering symptomatic benefit, or the complex molecular and clinical heterogeneity of tumour growth and drug response patterns. In this article, we review the rationale for continuing EGFR inhibitors in patients with EGFR mutant NSCLC beyond disease progression and discuss strategies that have been pursued in the context of molecularly and clinically heterogeneous populations of tumour growth depending on the different clinical scenarios encountered. We discuss the management of systemic disease progression, including continuing EGFR TKIs alone, introducing a drug holiday, or combining TKIs with chemotherapy or other molecularly targeted agents. We also focus on approaches in managing patients with indolent, small volume asymptomatic growth (non-CNS oligometastatic disease progression) and those with oligometastatic EGFR mutant NSCLC with involvement of the central nervous system. We envision future precision medicine strategies through the use of next generation sequencing strategies of serial tumour rebiopsies and circulating plasma DNA to individualise the management for such patients during disease progression.

A Phase 1/1b Study Evaluating Trametinib Plus Docetaxel or Pemetrexed in Patients With Advanced Non-Small Cell Lung Cancer. Gandara DR1, Leighl N2, Delord JP3, et al. J Thorac Oncol. 2016 Nov 19. pii: S1556-0864(16)33473-6. doi: 10.1016/j.jtho.2016.11.2218. [Epub ahead of print]
PURPOSE: This 2-part study evaluated trametinib, a MEK1/2 inhibitor, in combination with anticancer agents. Inhibition of MEK, a downstream effector of KRAS, demonstrated preclinical synergy with chemotherapy in KRAS-mutant non-small cell cancer (NSCLC) cell lines. Part 1 of this study identified recommended phase 2 doses of trametinib combinations. Part 2, reported herein, evaluated safety, tolerability, pharmacokinetics, and efficacy of trametinib combinations in patients with NSCLC with and without KRAS mutations. **METHODS:** Phase 1b evaluated trametinib plus docetaxel with growth factor support (trametinib 2.0 mg once daily [QD] and docetaxel 75 mg/m2 every 3 weeks [Q3W]) or pemetrexed (trametinib 1.5 mg QD and pemetrexed 500 mg/m2 Q3W). Eligibility criteria for expansion cohorts included metastatic NSCLC with measurable disease, known KRAS mutation status, Eastern Cooperative Oncology Group performance status ≤ 1, and ≤ 2 prior regimens. **RESULTS:** The primary endpoint of overall response rate (ORR) was met for both combinations. Among patients with NSCLC receiving trametinib+docetaxel, confirmed partial response (PR) was observed in 10 of 47 patients (21%). The ORR was 18% (4/22 PR) in patients with KRAS wild-type NSCLC vs 24% (6/25 PR) in those with KRAS-mutant NSCLC. In patients with NSCLC treated with trametinib+pemetrexed, 6/42 (14%) had PR; the ORR was 17% (4/23) in patients with KRAS-mutated NSCLC vs 11% (2/19) in KRAS wild-type NSCLC. Adverse events-most commonly diarrhea, nausea, and fatigue-were manageable.
CONCLUSION: Trametinib-chemotherapy combinations were tolerable. Clinical activity was observed, exceeding ORRs previously reported with docetaxel or pemetrexed alone in KRAS-mutated NSCLC and meeting prespecified criteria.

Variation in Hospital Adoption Rates of Video-Assisted Thoracoscopic Lobectomy for Lung Cancer and the Effect on Outcomes. Abdelsattar ZM1, Allen MS1, Shen KR1, Cassivi SD1, Nichols FC1, Wigle DA1, Blackmon SH2. Ann Thorac Surg. 2016 Nov 5. pii: S0003-4975(16)31159-6. doi: 10.1016/j.athoracsur.2016.08.091. [Epub ahead of print]
BACKGROUND: This study examined the variation in the adoption of video-assisted thoracoscopic surgery (VATS) for lobectomy across United States hospitals from a population-based national database.
METHODS: We used the National Cancer Data Base to identify patients undergoing lobectomy between 010 and 2012 and used hierarchical regression to estimate case-mix-adjusted VATS lobectomy rates using patient and tumor characteristics. We stratified hospitals into quintiles by adjusted VATS lobectomy rates. To account for lack of equipment to perform minimally invasive thoracoscopic operations, we also obtained data on VATS wedge resections. **RESULTS:** Of 55,972 cancer lobectomies performed at 905 hospitals, 17,072 (30.5%) were VATS. Crude hospital VATS use varied widely (mean was 25.5% of all lobectomies per hospital; interquartile range, 4.4% to 42.3%). Variation persisted after case-mix adjustment. For example, VATS rates at the highest and lowest quintiles were 76% vs 0.6%, respectively. Differences in patient and tumor characteristics across quintiles were negligible, and there was no indication that those hospitals lacked VATS equipment. The risk-adjusted same-hospital readmission (6.7% vs 7%; $p > 0.2$), 30-day mortality (1.5% vs 1.5%; $p > 0.2$), and 90-day mortality (2.9% vs 2.7%; $p = 0.038$) rates were similar between the highest and lowest quintiles. Length of stay was shorter at hospitals in the highest VATS quintile (6.6 vs 7.4 days; $p < 0.001$). **CONCLUSIONS:** Adoption of VATS lobectomy varies widely across United States hospitals. This variation cannot be explained by patient or tumor characteristics or by a shortage of VATS equipment. Efforts to reduce this variation will require the dissemination and implementation of novel training techniques and learning opportunities for surgeons.

Erlotinib, cabozantinib, or erlotinib plus cabozantinib as second-line or third-line treatment of patients with EGFR wild-type advanced non-small-cell lung cancer (ECOG-ACRIN 1512): a randomised, controlled, open-label, multicentre, phase 2 trial. Neal JW1, Dahlberg SE2, Wakelee HA3, et al. Lancet Oncol. 2016 Nov 4. pii: S1470-2045(16)30561-7. doi: 10.1016/S1470-2045(16)30561-7. [Epub ahead of print]

BACKGROUND: Erlotinib is approved for the treatment of all patients with advanced non-small-cell lung cancer (NSCLC), but is most active in the treatment of EGFR mutant NSCLC. Cabozantinib, a small molecule tyrosine kinase inhibitor, targets MET, VEGFR, RET, ROS1, and AXL, which are implicated in lung cancer tumorigenesis. We compared the efficacy of cabozantinib alone or in combination with erlotinib versus erlotinib alone in patients with EGFR wild-type NSCLC. **METHODS:** This three group, randomised, controlled, open-label, multicentre, phase 2 trial was done in 37 academic and community oncology practices in the USA. Patients were eligible if they had received one or two previous treatments for advanced non-squamous, EGFR wild-type, NSCLC. Patients were stratified by performance status and line of therapy, and randomly assigned using permuted blocks within strata to receive open-label oral daily dosing of erlotinib (150 mg), cabozantinib (60 mg), or erlotinib (150 mg) and cabozantinib (40 mg). Imaging was done every 8 weeks. At the time of radiographic progression, there was optional crossover for patients in either single-drug group to receive combination treatment. The primary endpoint was to compare progression-free survival in patients given erlotinib alone versus cabozantinib alone, and in patients given erlotinib alone versus the combination of erlotinib plus cabozantinib. We assessed the primary endpoint in the per-protocol population, which was defined as all patients who were eligible, randomly assigned, and received at least one dose of treatment. The safety analysis population included all patients who received study treatment irrespective of eligibility. This trial is registered with ClinicalTrials.gov, number NCT01708954. **FINDINGS:** Between Feb 7, 2013, and July 1, 2014, we enrolled and randomly assigned 42 patients to erlotinib treatment, 40 patients to cabozantinib treatment, and 43 patients to erlotinib plus cabozantinib treatment, of whom 111 (89%) in total were included in the primary analysis (erlotinib [n=38], cabozantinib [n=38], erlotinib plus cabozantinib [n=35]). Compared with erlotinib alone (median 1·8 months [95% CI 1·7-2·2]), progression-free survival was significantly improved in the cabozantinib group (4·3 months [3·6-7·4]; hazard ratio [HR] 0·39, 80% CI 0·27-0·55; one-sided p=0·0003) and in the erlotinib plus cabozantinib group (4·7 months [2·4-7·4]; HR 0·37, 0·25-0·53; one-sided p=0·0003). Among participants included in the safety analysis of the erlotinib (n=40), cabozantinib (n=40), and erlotinib plus cabozantinib (n=39) groups, the most common grade 3 or 4 adverse events were diarrhoea (three [8%] cases in the erlotinib group vs three [8%] in the cabozantinib group vs 11 [28%] in the erlotinib plus cabozantinib group), hypertension (none vs ten [25%] vs one [3%]), fatigue (five [13%] vs six [15%] vs six [15%]), oral mucositis (none vs four [10%] vs one [3%]), and thromboembolic event (none vs three [8%] vs two [5%]). One death due to respiratory failure occurred in the cabozantinib group, deemed possibly related to either drug, and one death due to pneumonitis occurred in the erlotinib plus cabozantinib group, deemed related to either drug or the combination. **INTERPRETATION:** Despite its small sample size, this trial showed that, in patients with EGFR wild-type NSCLC, cabozantinib alone or combined with erlotinib has clinically meaningful, superior efficacy to that of erlotinib alone, with additional toxicity that was generally manageable. Cabozantinib-based regimens are promising for further investigation in this patient population. **FUNDING:** ECOG-ACRIN Cancer Research Group, National Cancer Institute of the National Institutes of Health.

Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy. Agrawal S1, Feng Y1, Roy A1, Kollia G2, Lestini B3. J Immunother Cancer. 2016 Nov 15;4:72. eCollection 2016.

BACKGROUND: Immuno-oncology (I-O) therapies target the host immune system, providing the potential to choose a uniform dose and schedule across tumor types. However, dose selection for I-O agents usually occurs early in clinical development and is typically based on tumor response, which may not fully represent the potential for improved overall survival. Here, we describe an integrated approach which incorporates clinical safety and efficacy data with data obtained from analyses of dose-/exposure-response (D-R/E-R) relationships, used to select a monotherapy dose for nivolumab, a programmed death-1 inhibitor, in clinical studies of different tumor types. **METHODS:** Dose was selected based on anti-tumor activity and safety data from a large phase 1b, open-label, dose-escalation study of nivolumab at doses ranging from 0.1 to 10 mg/kg administered every 2 weeks (Q2W) in 306 patients with advanced malignancies, and quantitative analyses were performed to characterize D-R/E-R relationships for pharmacodynamic, safety, and efficacy endpoints. **RESULTS:** A maximum tolerated dose for nivolumab was not identified, and the safety profile was similar across tumor types and dose levels (0.1-10 mg/kg). Objective response rates (ORRs) were similar across doses in melanoma and renal cell carcinoma (RCC), while higher ORRs were observed in non-small cell lung cancer (NSCLC) at 3 mg/kg and 10 mg/kg versus 1 mg/kg. Peripheral receptor occupancy was saturated at doses ≥ 0.3 mg/kg. In D-R/E-R analyses, a positive dose-dependent objective response trend was observed for each tumor type, but appeared to plateau at nivolumab doses of ≥ 1 mg/kg for melanoma and RCC, and at ≥ 3 mg/kg for NSCLC. Although there was no apparent relationship between tumor shrinkage rate and exposure, tumor progression rate appeared to decrease with increasing exposure up to a dose of 3 mg/kg Q2W for NSCLC. **CONCLUSIONS:** Nivolumab monotherapy at 3 mg/kg Q2W provides unified dosing across tumor types. This dose and schedule has been validated in several phase II/III studies in which overall survival was an endpoint. Integrating D-R/E-R relationships with efficacy data and a safety profile that is unique to I-O therapy is a rational approach for dose selection of these agents.

NSCLC - RADIOTHERAPY

Efficacy of postoperative radiotherapy in patients with pathological stage N2 epidermal growth factor receptor wild type adenocarcinoma and squamous cell carcinoma lung cancer. Lin YK1, Hsu HL2,3, Lin WC4, et al. Oncotarget. 2016 Nov 9. doi: 10.18632/oncotarget.13257. [Epub ahead of print] **PURPOSE:** Few large, prospective, randomized studies have compared the effects of postoperative radiotherapy (PORT) in pathological N2 (pN2) with those of surgical resection alone. in terms of long-term survival in lung adenocarcinoma (adenoCA; wild-type [WT] epidermal growth factor receptor [EGFR]) and squamous cell carcinoma (squCA) settings. This nationwide cohort study clarifies the role of PORT in the survival of pN2 lung adenoCA (WT EGFR) and squCA patientsPatients and Methods: We analyzed data of patients with adenoCA (WT EGFR) and squCA collected from the Taiwan Cancer Registry database. The patients were categorized into five groups according to the treatment modality: Group 1 (surgery alone), Group 2 (adjuvant chemotherapy [CT] alone), Group 3 (adjuvant radiotherapy [RT] alone), Group 4 (adjuvant concurrent chemoradiotherapy [CCRT]), and Group 5 (adjuvant sequential CT and intensity-modulated RT [IMRT]). **RESULTS:** We enrolled 588 lung adenoCA (WT EGFR) and squCA patients without distant metastasis. After adjustments for age at surgery, surgical years, and Charlson comorbidity index scores, the multivariate Cox regression analysis demonstrated that adjusted HRs (aHRs; 95% confidence intervals [CIs]) for the overall mortality of female lung adenoCA (WT EGFR) patients were 0.257 (0.111-0.594), 0.530 (0.226-1.243), 0.192 (0.069-0.534), and 0.399 (0.172-0.928) in Groups 2, 3, 4, and 5, respectively. For male lung squCA patients, the aHRs (95% CIs) for overall mortality were 0.269 (0.160-0.451), 0.802 (0.458-1.327), 0.597 (0.358-0.998), and 0.456 (0.265-0.783) in Groups 2, 3, 4, and 5, respectively. **CONCLUSIONS:** Adjuvant CCRT or sequential CT and IMRT at ≥5000 cGy significantly reduced the mortality rate of female lung adenoCA (WT EGFR) and male squCA pN2 patients.

Clinical Outcomes After Lung Stereotactic Body Radiation Therapy in Patients With or Without a Prior Lung Resection. Hou Y1, Hermann G, Lewis JH, et al. Am J Clin Oncol. 2016 Nov 4. [Epub ahead of print]

OBJECTIVES: Tumor control (TC), toxicity and survival, following stereotactic body radiation therapy (SBRT) were compared between patients with and without a prior lung resection (PLR). **MATERIALS AND METHODS:** The study is comprised of 130 patients with 141 peripheral tumors treated with SBRT at our institution from 2009 to 2013. Primary TC and lobar control (LC) were defined per RTOG 0236. Toxicity was scored using Common Terminology Criteria for Adverse Events version 4.0. Survival/TC and toxicity were compared between patients with and without PLR using the Kaplan-Meier method and cumulative incidence, respectively. Fine and Gray regression was used for univariable/multivariable analysis for radiation pneumonitis (RP). **RESULTS:** Of the 130 patients with median age 70 years (range, 42 to 93 y), 50 had undergone PLR (median time between PLR and SBRT: 33 mo; range, 1 to 206), including pneumonectomy (12%), lobectomy (46%), wedge resection (42%). With a median follow-up of 21 months in survivors, the PLR group had better TC (1-y 100% vs. 93%; P<0.01) and increased grade ≥2 (RP; 1-y 12% vs. 1%; P<0.01). OS was not significantly different between the 2 groups (1-y 91% vs. 85%; P=0.24). On univariable/multivariable analyses, biologically effective dose was associated with TC (hazard ratios, 0.97; 95% confidence interval, 0.94-0.999; P=0.04). Chemotherapy use was associated with grade ≥2 RP for all patients (hazard ratios, 14.92; 95% confidence interval, 5.68-39.21; P<0.0001) in multivariable analysis. PLR was not associated with increased RP in multivariable analysis. **CONCLUSIONS:** Patients with PLR who receive lung SBRT for lung tumors have high local control and relatively low toxicity. SBRT is an excellent option to treat second lung tumors or pulmonary metastases in patients with PLR.

Multi-institutional Prospective Study of Reirradiation with Proton Beam Radiotherapy for Locoregionally Recurrent Non-Small Cell Lung Cancer. Chao HH1, Berman AT1, Simone CB 2nd1, et al. J Thorac Oncol. 2016 Nov 4. pii: S1556-0864(16)31237-0. doi: 10.1016/j.jtho.2016.10.018. [Epub ahead of print]

PURPOSE: The management of recurrent non-small cell lung cancer (NSCLC) in the setting of prior radiation therapy is challenging. Proton radiotherapy (PRT) is ideally suited to minimize toxicity to previously irradiated organs. We report the safety/feasibility of PRT for NSCLC reirradiation in a prospective multi-institutional study. **MATERIALS AND METHODS:** Between 10/2010-12/2015, 57 patients with recurrent NSCLC in/near their prior radiation field were treated at three proton centers. Patients were classified by tumor volume, location, and clinical characteristics. Toxicities were scored using CTCAE version 4.0. Survival outcomes were estimated using Kaplan-Meier analysis. **RESULTS:** Fifty-two patients (93%) completed the reirradiation course. Median age was 65 years (41-86). Patients with high tumor volume (CTV/ITV > 250 cc) were closed to enrollment due to infeasibility in August 2012. Concurrent systemic therapy was delivered in 67% of patients. Fourteen (25%) patients had evidence of local (n=9) or regional (n=5) recurrence. Six (11%) developed distant metastases following reirradiation. One year rates of overall and progression free survival were 59% and 58% respectively. In total, 24 (42%) patients developed grade ≥3 acute and/or late toxicity, 22 (39%) with acute toxicity, and 7 (12%) with late toxicity. Six grade 5 toxicities were observed. Increased overlap with the central airway region, mean esophagus and heart doses, and concurrent chemotherapy were associated with significantly higher rates of grade ≥3 toxicity. Decreased overall survival was seen with increased mean esophagus dose (p=.007). **CONCLUSIONS:** In this prospective study, PRT of recurrent NSCLC is feasible, but can be associated with significant toxicity. Providers should remain cautious in reirradiating NSCLC, paying close consideration to tumor volume, location, and relevant dosimetric parameters. Further research is needed for optimal patient selection to improve overall outcomes.

Radiosensitization of non-small-cell lung cancer cells and xenografts by the interactive effects of pemetrexed and methoxyamine. Oleinick NL1, Biswas T2, Patel R3, et al. Radiother Oncol. 2016 Nov 9. pii: S0167-8140(16)34345-6. doi: 10.1016/j.radonc.2016.10.007. [Epub ahead of print]
BACKGROUND AND PURPOSE: The anti-folate pemetrexed is a radiosensitizer. In pre-clinical models, pemetrexed is more effective along with the base-excision-repair inhibitor methoxyamine. We tested whether methoxyamine enhances pemetrexed-mediated radiosensitization of lung adenocarcinoma cells and xenografts. **MATERIALS AND METHODS:** A549 and H1299 cells were evaluated for cell cycle distribution by flow cytometry, radiosensitization by clonogenic assay, and DNA repair by neutral comet assay and repair protein activation. H460 cells were included in some studies. Xenografts in nude mice received drug(s) and/or radiation, and tumor growth was monitored by caliper and in vivo toxicity by animal weight. **RESULTS:** Exposure to pemetrexed/methoxyamine for 24 (H1299, H460) or 48 (A549)hours before irradiation resulted in accumulation of cells near the radiosensitive G1/S border; dose-enhancement factors of 1.62±0.19, 1.97±0.25, and 1.67±0.30, respectively; reduction of mean inactivation dose by 32%, 30%, and 46%, respectively; and significant reductions of SF2 and SF4 ($p<0.05$). Radiosensitization was associated with rapid DNA double-strand-break rejoining and increased levels of DNA-PKcs. Both tumor-growth rate and tumor-growth delay were significantly improved by adding methoxyamine to pemetrexed pre-irradiation ($p<0.0001$); no mice lost weight during treatment. **CONCLUSIONS:** Addition of methoxyamine to pemetrexed and fractionated radiotherapy may improve outcome for patients with locally advanced non-squamous non-small-cell lung cancer.

4DCT and CBCT based PTV margin in Stereotactic Body Radiotherapy(SBRT) of non-small cell lung tumor adhered to chest wall or diaphragm. Li Y1, Ma JL1, Chen X1, Tang FW1, Zhang XZ2. Radiat Oncol. 2016 Nov 15;11(1):152.
BACKGROUND: Large tumor motion often leads to larger treatment volumes, especially the lung tumor located in lower lobe and adhered to chest wall or diaphragm. The purpose of this work is to investigate the impacts of planning target volume (PTV) margin on Stereotactic Body Radiotherapy (SBRT) in non-small cell lung cancer (NSCLC). **METHODS:** Subjects include 20 patients with the lung tumor located in lower lobe and adhered to chest wall or diaphragm who underwent SBRT. Four-dimensional computed tomography (4DCT) were acquired at simulation to evaluate the tumor intra-fractional centroid and boundary changes, and Cone-beam Computer Tomography (CBCT) were acquired during each treatment to evaluate the tumor inter-fractional set-up displacement. The margin to compensate for tumor variations uncertainties was calculated with various margin calculated recipes published in the exiting literatures. **RESULTS:** The means (±standard deviation) of tumor centroid changes were 0.16 (±0.13) cm, 0.22 (±0.15) cm, and 1.37 (±0.81) cm in RL, AP, and SI directions, respectively. The means (±standard deviation) of tumor edge changes were 0.21 (±0.18) cm, 0.50 (±0.23) cm, and 0.19 (±0.44) cm in RL, AP, and SI directions, respectively. The means (±standard deviation) of tumor set-up displacement were 0.03 (±0.24) cm, 0.02 (±0.26) cm, and 0.02 (±0.43) cm in RL, AP, and SI directions, respectively. The PTV margin to compensate for lung cancer tumor variations uncertainties were 0.88, 0.98 and 2.68 cm in RL, AP and SI directions, which were maximal among all margin recipes. **CONCLUSIONS:** 4DCT and CBCT imaging are appropriate to account for the tumor intra-fractional centroid, boundary variations and inter-fractional set-up displacement. The PTV margin to compensate for lung cancer tumor variations uncertainties can be obtained. Our results show that a conventional 1.0 cm margin in the SI plane dose not suffice to compensate the geometrical variety of the tumor located in lower lobe and adhered to chest wall and diaphragm.

SMALL CELL LUNG CANCER - SCLC

CXCR4 antagonists suppress small cell lung cancer progression. Taromi S1, Kayser G2, Catusse J1, et al. Oncotarget. 2016 Nov 9. doi: 10.18632/oncotarget.13238. [Epub ahead of print]
Small cell lung cancer (SCLC) is an aggressive tumor with poor prognosis due to early metastatic spread and development of chemoresistance. Playing a key role in tumor-stroma interactions the CXCL12-CXCR4 axis may be involved in both processes and thus represent a promising therapeutic target in SCLC treatment. In this study we investigated the effect of CXCR4 inhibition on metastasis formation and chemoresistance using an orthotopic xenograft mouse model. This model demonstrates regional spread and spontaneous distant metastases closely reflecting the clinical situation in extensive SCLC. Tumor engraftment, growth, metabolism, and metastatic spread were monitored using different imaging techniques: Magnetic Resonance Imaging (MRI), Bioluminescence Imaging (BLI) and Positron Emission Tomography (PET). Treatment of mice bearing chemoresistant primary tumors with the specific CXCR4 inhibitor AMD3100 reduced the growth of the primary tumor by 61% ($P<0.05$) and additionally suppressed metastasis formation by 43%. In comparison to CXCR4 inhibition as a monotherapy, standard chemotherapy composed of cisplatin and etoposide reduced the growth of the primary tumor by 71% ($P<0.01$) but completely failed to suppress metastasis formation. Combination of chemotherapy and the CXCR4 inhibitor integrated the highest of both effects. The growth of the primary tumor was reduced to a similar extent as with chemotherapy alone and metastasis formation was reduced to a similar extent as with CXCR4 inhibitor alone. In conclusion, we demonstrate in this orthotopic mouse model that the addition of a CXCR4 inhibitor to chemotherapy significantly reduces metastasis formation. Thus, it might improve the overall therapy response and consequently the outcome of SCLC patients.

Prognostic role of patient gender in limited-disease small-cell lung cancer treated with chemoradiotherapy. Roengvoraphoj O1, Eze C2, Niyazi M2, Li M2, Hildebrandt G3, Fietkau R4, Belka C2, Manapov F2. Strahlenther Onkol. 2016 Nov 16. [Epub ahead of print]
BACKGROUND: Previous studies have demonstrated that female gender could be a prognostic factor in limited-disease (LD) small-cell lung cancer (SCLC), but the correlation between patient gender and survival parameters remains unclear. **PATIENTS AND METHODS:** Data from 179 LD SCLC patients treated with definitive chemoradiotherapy (CRT) were reviewed. Influence of patient gender on time to progression (TTP), local control (LC), brain metastasis-free (BMFS), distant metastasis-free (DMFS) and overall survival (OS) was analysed. **RESULTS:** Definitive CRT was completed by 179 (110 men/69 women) patients. Of these, 68 (38%; 34 men/34 women) patients were treated in concurrent and 111 (62%; 76 men/35 women) in sequential mode. Prophylactic cranial irradiation (PCI) was subsequently applied in 70 (39%; 36 men/34 women) patients with partial or complete response after CRT. Median OS was 20 (95% confidence interval [CI] 10-22) and 14 (95% CI 10-18) months in female and male patients, respectively ($p = 0.021$). In subgroups defined by remission status (complete and partial response) after CRT, an OS benefit for females compared to males was also detected. There was no correlation between patient gender and TTP, LC or DMFS, and no difference in OS in the female and male subgroups treated with PCI. The incidence of metachronous brain metastases (BMs) in the male and female subgroups differed significantly (40/110 men vs. 18/69 women, $p = 0.03$). Also, mean BMFS was significantly longer in women ($p = 0.023$). Patient gender also significantly correlated with OS on multivariate analysis after adjustment for other prognostic factors ($p = 0.04$, HR 1.38, 95% CI 1.08-1.92). **CONCLUSION:** In this heterogeneous LD SCLC patient cohort treated with definitive CRT, female gender was significantly associated with longer BMFS and OS, as well as with a lower incidence of metachronous brain failure.

The aqueous extract of Brucea javanica suppresses cell growth and alleviates tumorigenesis of human lung cancer cells by targeting mutated epidermal growth factor receptor. Kim SH1, Liu CY1, Fan PW1, Hsieh CH1, Lin HY1, Lee MC2, Fang K1.
As a practical and safe herbal medicine, the seeds of Brucea javanica (L.) Merr., were used to cure patients suffering from infectious diseases such as malaria. Recent advances revealed that the herb could also be a useful cancer therapy agent. The study demonstrated that aqueous B. javanica (BJ) extract attenuated the growth of human non-small-lung cancer cells bearing mutant L858R/T790M epidermal growth factor receptor (EGFR). The reduced cell viability in H1975 cells was attributed to apoptosis. Transfection of EGFR small hairpin RNA reverted the sensitivities. When nude mice were fed BJ extract, the growth of xenograft tumors, as established by H1975 cells, was suppressed. Additional histological examination and fluorescence analysis of the resected tissues proved that the induced apoptosis mitigated tumor growth. The work proved that the BJ extract exerted its effectiveness by targeting lung cancer cells carrying mutated EGFR while alleviating tumorigenesis. Aqueous BJ extract is a good candidate to overcome drug resistance in patients undergoing target therapy.

Vorinostat enhances the cisplatin-mediated anticancer effects in small cell lung cancer cells. Pan CH1, Chang YF2, Lee MS1, Wen BC2, Ko JC3, Liang SK4, Liang MC5,6. BMC Cancer. 2016 Nov 7;16(1):857.
BACKGROUND: Vorinostat, a histone deacetylase (HDAC) inhibitor, is a promising agent for cancer therapy. Combining vorinostat with cisplatin may relax the chromatin structure and facilitate the accessibility of cisplatin, thus enhancing its cytotoxicity. Studies have not yet investigated the effects of the combination of vorinostat and cisplatin on small cell lung cancer (SCLC). **METHODS:** We first assessed the efficacy of vorinostat with etoposide/cisplatin (EP; triple combination) and then investigated the effects of cotreatment with vorinostat and cisplatin on H209 and H146 SCLC cell lines. The anticancer effects of various combinations were determined in terms of cell viability, apoptosis, cell cycle distribution, and vorinostat-regulated proteins. We also evaluated the efficacy of vorinostat/cisplatin combination in H209 xenograft nude mice. **RESULTS:** Our data revealed that the triple combination engendered a significant reduction of cell viability and high apoptotic cell death. In addition, vorinostat combined with cisplatin enhanced cell growth inhibition, induced apoptosis, and promoted cell cycle arrest. We observed that the acetylation levels of histone H3 and α-tubulin were higher in combination treatments than in vorinostat treatment alone. Moreover, vorinostat reduced the expression of thymidylate synthase (TS), and TS remained inhibited after cotreament with cisplatin. Furthermore, an in vivo study revealed that the combination of vorinostat and cisplatin significantly inhibited tumor growth in xenograft nude mice (tumor growth inhibition T/C% = 20.5 %). **CONCLUSIONS:** Combined treatments with vorinostat promote the cytotoxicity of cisplatin and induce the expression of vorinostat-regulated acetyl proteins, eventually enhancing antitumor effects in SCLC cell lines. Triple combinations with a low dosage of cisplatin demonstrate similar therapeutic effects. Such triple combinations, if applied clinically, may reduce the undesired adverse effects of cisplatin. The effects of the combination of vorinostat and cisplatin should be evaluated further before conducting clinical trials for SCLC treatment.

PALLIATIVE AND SUPPORTIVE CARE

Chemotherapy treatment decision-making experiences of older adults with cancer, their family members, oncologists and family physicians: a mixed methods study. Puts MT1, Sattar S2, McWatters K2, Lee K2, et al. Support Care Cancer. 2016 Nov 9. [Epub ahead of print]
PURPOSE: Although comorbidities, frailty, and functional impairment are common in older adults (OA) with cancer, little is known about how these factors are considered during the treatment decision-making process by OAs, their families, and health care providers. Our aim was to better understand the treatment

decision process from all these perspectives. **METHODS:** A mixed methods multi-perspective longitudinal study using semi-structured interviews and surveys with 29 OAs aged ≥70 years with advanced prostate, breast, colorectal, or lung cancer, 24 of their family members,13 oncologists, and 15 family physicians was conducted. The sample was stratified on age (70-79 and 80+). All interviews were analyzed using thematic analysis. **RESULTS:** There was no difference in the treatment decision-making experience based on age. Most OAs felt that they should have the final say in the treatment decision, but strongly valued their oncologists' opinion. "Trust in my oncologist" and "chemotherapy as the last resort to prolong life" were the most important reasons to accept treatment. Families indicated a need to improve communication between them, the patient and the specialist, particularly around goals of treatment. Comorbidity and potential side-effects did not play a major role in the treatment decision-making for patients, families, or oncologists. Family physicians reported no involvement in decisions but desired to be more involved. **CONCLUSION:** This first study using multiple perspectives showed neither frailty nor comorbidity played a role in the treatment decision-making process. Efforts to improve communication were identified as an opportunity that may enhance quality of care. In a mixed methods study multiple perspective study with older adults with cancer, their family members, their oncologist and their family physician we explored the treatment decision making process and found that most older adults were satisfied with their decision. Comorbidity, functional status and frailty did not impact the older adult's or their family members' decision.

Physical activity and sedentary behavior in relation to lung cancer incidence and mortality in older women: The Women's Health Initiative. Wang A1, Qin F2, Hedlin H2, et al. Int J Cancer. 2016 Nov 15;139(10):2178-92. doi: 10.1002/ijc.30281.
Physical activity has been associated with lower lung cancer incidence and mortality in several populations. We investigated these relationships in the Women's Health Initiative Observational Study (WHI-OS) and Clinical Trial (WHI-CT) prospective cohort of postmenopausal women. The WHI study enrolled 161,808 women aged 50-79 years between 1993 and 1998 at 40 U.S. clinical centers; 129,401 were eligible for these analyses. Cox proportional hazards models were used to assess the association of baseline physical activity levels [metabolic equivalent (MET)-min/week: none <100 (reference), low 100 to <500, medium 500 to <1,200, high 1,200+] and sedentary behavior with total lung cancer incidence and mortality. Over 11.8 mean follow-up years, 2,148 incident lung cancer cases and 1,365 lung cancer deaths were identified. Compared with no activity, higher physical activity levels at study entry were associated with lower lung cancer incidence [$p = 0.009$; hazard ratios (95% confidence intervals) for each physical activity category: low, HR: 0.86 (0.76-0.96); medium, HR: 0.82 (0.73-0.93); and high, HR: 0.90 (0.79-1.03)], and mortality [$p < 0.0001$; low, HR: 0.80 (0.69-0.92); medium, HR: 0.68 (0.59-0.80); and high, HR: 0.78 (0.66-0.93)]. Body mass index (BMI) modified the association with lung cancer incidence ($p = 0.01$), with a stronger association in women with BMI < 30 kg/m(2) . Significant associations with sedentary behavior were not observed. In analyses by lung cancer subtype, higher total physical activity levels were associated with lower lung cancer mortality for both overall NSCLC and adenocarcinoma. In conclusion, physical activity may be protective for lung cancer incidence and mortality in postmenopausal women, particularly in non-obese women.

Mental and physical health correlates among family caregivers of patients with newly-diagnosed incurable cancer: a hierarchical linear regression analysis. Shaffer KM1,2, Jacobs JM1,2,3, et al. Support Care Cancer. 2016 Nov 19. [Epub ahead of print]
PURPOSE: Caregiver, relational, and patient factors have been associated with the health of family members and friends providing care to patients with early-stage cancer. Little research has examined whether findings extend to family caregivers of patients with incurable cancer, who experience unique

and substantial caregiving burdens. We examined correlates of mental and physical health among caregivers of patients with newly-diagnosed incurable lung or non-colorectal gastrointestinal cancer. **METHODS:** At baseline for a trial of early palliative care, caregivers of participating patients (N = 275) reported their mental and physical health (Medical Outcome Survey-Short Form-36); patients reported their quality of life (Functional Assessment of Cancer Therapy-General). Analyses used hierarchical linear regression with two-tailed significance tests. **RESULTS:** Caregivers' mental health was worse than the U.S. national population (M = 44.31, p < .001), yet their physical health was better (M = 56.20, p < .001). Hierarchical regression analyses testing caregiver, relational, and patient factors simultaneously revealed that younger (B = 0.31, p = .001), spousal caregivers (B = -8.70, p = .003), who cared for patients reporting low emotional well-being (B = 0.51, p = .01) reported worse mental health; older (B = -0.17, p = .01) caregivers with low educational attainment (B = 4.36, p < .001) who cared for patients reporting low social well-being (B = 0.35, p = .05) reported worse physical health. **CONCLUSIONS:** In this large sample of family caregivers of patients with incurable cancer, caregiver demographics, relational factors, and patient-specific factors were all related to caregiver mental health, while caregiver demographics were primarily associated with caregiver physical health. These findings help identify characteristics of family caregivers at highest risk of poor mental and physical health who may benefit from greater supportive care.

Respiratory symptoms, sleep, and quality of life in patients with advanced lung cancer. Lou VW1, Chen EJ2, Jian H3, Zhou Z3, Zhu J4, Li G4, He Y5. J Pain Symptom Manage. 2016 Nov 7. pii: S0885-3924(16)30760-6. doi: 10.1016/j.jpainsymman.2016.09.006. [Epub ahead of print]
OBJECTIVES: The study was designed to examine the relationships between respiratory symptoms, sleep disturbance, and quality of life among patients with advanced lung cancer. **MATERIALS AND METHODS:** A total of 128 patients with advanced lung cancer (from chest oncology inpatient-units in Shanghai, China) participated in the study. They completed two questionnaires: the Functional Assessment of Cancer Therapy - Lung (FACT-L), and the Pittsburgh Sleep Quality Index (PSQI). **RESULTS:** Symptomatic breathing difficulty, coughing, shortness of breath, and tightness in the chest were reported in 78.1%, 70.3%, 60.9%, and 60.2% of the patients, respectively. Sleep disturbance affected 62.5% of the patients. The patients with severe respiratory symptoms were more likely to be poor sleepers and to have a lower quality of life. After the covariates were controlled for, regression analysis showed that respiratory symptoms and sleep disturbance were significant indicators of quality of life. In addition, some of the effect of the respiratory symptoms on quality of life was mediated by sleep disturbance. **CONCLUSION:** Respiratory symptoms and sleep disturbance were common in the advanced lung cancer patients and had a negative impact on their quality of life; sleep disturbance may mediate the relationship between respiratory symptoms and quality of life.

Increasing Complexity in Rule-Based Clinical Decision Support: The Symptom Assessment and Management Intervention. Lobach DF1,2, Johns EB3,4, Halpenny B5, et al. JMIR Med Inform. 2016 Nov 8;4(4):e36.
BACKGROUND: Management of uncontrolled symptoms is an important component of quality cancer care. Clinical guidelines are available for optimal symptom management, but are not often integrated into the front lines of care. The use of clinical decision support (CDS) at the point-of-care is an innovative way to incorporate guideline-based symptom management into routine cancer care. **OBJECTIVE:** The objective of this study was to develop and evaluate a rule-based CDS system to enable management of multiple symptoms in lung cancer patients at the point-of-care. **METHODS:** This study was conducted in three phases involving a formative evaluation, a system evaluation, and a contextual evaluation of clinical use. In Phase 1, we conducted iterative usability testing of user interface prototypes with patients and health care providers (HCPs) in two thoracic oncology clinics. In Phase 2, we programmed complex

algorithms derived from clinical practice guidelines into a rules engine that used Web services to communicate with the end-user application. Unit testing of algorithms was conducted using a stack-traversal tree-spanning methodology to identify all possible permutations of pathways through each algorithm, to validate accuracy. In Phase 3, we evaluated clinical use of the system among patients and HCPs in the two clinics via observations, structured interviews, and questionnaires. **RESULTS:** In Phase 1, 13 patients and 5 HCPs engaged in two rounds of formative testing, and suggested improvements leading to revisions until overall usability scores met a priori benchmarks. In Phase 2, symptom management algorithms contained between 29 and 1425 decision nodes, resulting in 19 to 3194 unique pathways per algorithm. Unit testing required 240 person-hours, and integration testing required 40 person-hours. In Phase 3, both patients and HCPs found the system usable and acceptable, and offered suggestions for improvements. **CONCLUSIONS:** A rule-based CDS system for complex symptom management was systematically developed and tested. The complexity of the algorithms required extensive development and innovative testing. The Web service-based approach allowed remote access to CDS knowledge, and could enable scaling and sharing of this knowledge to accelerate availability, and reduce duplication of effort. Patients and HCPs found the system to be usable and useful.

Fatigue Self-Management Behaviors in Patients With Advanced Cancer: A Prospective Longitudinal Survey. Chan R1, Yates P2, McCarthy AL2. Oncol Nurs Forum. 2016 Nov 1;43(6):762-771.
PURPOSE/OBJECTIVES: To explore the fatigue self-management behaviors and factors associated with effectiveness of these behaviors in patients with advanced cancer. **DESIGN:** Prospective longitudinal interviewer-administered survey. **SETTING:** Royal Brisbane and Women's Hospital in Queensland, Australia. **SAMPLE:** 152 outpatients with metastatic breast, lung, colorectal, and prostate cancer experiencing fatigue were recruited. **METHODS:** Patients were surveyed on three occasions. **MAIN RESEARCH VARIABLES:** Fatigue self-management behavior (perceived effectiveness, self-efficacy, and frequency), medical and demographic characteristics (sites of primary cancer and metastasis, comorbidity, performance status), social support, depression, anxiety, and other symptoms were assessed. **FINDINGS:** The participants reported moderate levels of fatigue at baseline and maintained moderate levels at four and eight weeks. On average, participants consistently used about nine behaviors at each time point. Factors significantly associated with higher levels of perceived effectiveness of fatigue self-management behaviors were higher self-efficacy, higher education level, and lower levels of depressive symptoms. **CONCLUSIONS:** The findings of this study demonstrate that patients with cancer, even those with advanced disease, still want and are able to use a number of behaviors to control their fatigue. Self-management interventions that aim to enhance self-efficacy and address any concurrent depressive symptoms have the potential to reduce fatigue severity. **IMPLICATIONS FOR NURSING:** Nurses are well positioned to play a key role in supporting patients in their fatigue self-management.

Do cancer survivors develop healthier lifestyle behaviors than the cancer-free population in the PLCO study? Hawkins ML1,2, Buys SS3, Gren LH2, Simonsen SE2, Kirchhoff AC1,4, Hashibe M5,6. J Cancer Surviv. 2016 Nov 11. [Epub ahead of print]
BACKGROUND: Current studies report mixed results in health status and health behaviors after a diagnosis of cancer. The aim of our study is to investigate potential differences in lifestyle factors among cancer survivors and cancer-free individuals in a prospective cohort study conducted in the United States. **METHODS:** Using data from the Prostate, Lung, Colorectal and Ovarian (PLCO) Trial, 10,133 cancer survivors were identified and compared to 81,992 participants without cancer to evaluate differences in body mass index (BMI), smoking, NSAID use, and physical activity. **RESULTS:** Cancer survivors, compared to the cancer-free, were significantly less likely to engage in physical activity (odds ratio (OR) = 0.82, 95% CI = 0.77-0.88). Compared to those who were obese at baseline, cancer survivors were more

likely to be at normal BMI at follow-up compared to the cancer-free (OR = 1.90, 95% CI = 1.42-2.54). Cancer survivors were less likely to report regular aspirin use as compared to the cancer-free population (OR = 0.86, 95 % CI = 0.82-0.92). Of the current smokers, cancer survivors were more likely to be former smokers at follow-up compared to the cancer-free (OR = 1.50, 95% CI = 1.30-1.74). **CONCLUSION:** Upon stratification by baseline health markers, cancer survivors practice healthier lifestyle habits such as smoking cessation and maintenance of a healthy weight. However, cancer survivors are less likely to be physically active as compared to cancer-free individuals, regardless of baseline practices.

Screening for depression in cancer patients receiving radiotherapy: Feasibility and identification of effective tools in the NRG Oncology RTOG 0841 trial. Wagner LI1, Pugh SL2, Small W Jr3, et al. Cancer. 2016 Nov 10. doi: 10.1002/cncr.29969. [Epub ahead of print]
BACKGROUND: Brief tools are needed to screen oncology outpatients for depressive symptoms. **METHODS:** Patients starting radiotherapy for the first diagnosis of any tumor completed distress screening tools, including the 9-item Patient Health Questionnaire (PHQ-9), the 2-item Patient Health Questionnaire (PHQ-2), the National Comprehensive Cancer Network Distress Thermometer (NCCN-DT), and the Hopkins Symptom Checklist (HSCL) (25-item version). Patients exceeding validated cutoff scores and a systematic sample of patients whose screening was negative completed the Structured Clinical Interview for DSM-IV (SCID) mood disorder modules via telephone. **RESULTS:** Four hundred sixty-three patients from 35 community-based radiation oncology sites and 2 academic radiation oncology sites were recruited. Sixty-six percent of the 455 eligible patients (n = 299) were women, and the eligible patients had breast (45%), gastrointestinal (11%), lung (10%), gynecologic (6%), or other cancers (27%). Seventy-five (16.5%) exceeded screening cutoffs for depressive symptoms. Forty-two of these patients completed the SCID. Another 37 patients whose screening was negative completed the SCID. Among the 79 patients completing the SCID, 8 (10.1%) met the criteria for major depression, 2 (2.5%) met the criteria for dysthymia, and 6 (7.6%) met the criteria for an adjustment disorder. The PHQ-2 demonstrated good psychometric properties for screening for mood disorders with a cutoff score of ≥3 (receiver operating characteristic area under the curve [AUC], 0.83) and was comparable to the PHQ-9 (> 9; AUC = 0.85). The NCCN-DT did not detect depression (AUC = 0.59). **CONCLUSIONS:** The PHQ-2 demonstrated good psychometric properties for screening for mood disorders, which were equivalent to the PHQ-9 and superior to the NCCN-DT. These findings support using the PHQ-2

COMPLEMENTARY & ALTERNATIVE THERAPY

Honokiol Decreases Lung Cancer Metastasis through Inhibition of the STAT3 Signaling Pathway. Pan J1, Lee Y2, Zhang Q3, Xiong D1, Tina WC4, Wang Y1, You M5. Cancer Prev Res (Phila). 2016 Nov 14. pii: canprevres.0129.2016. [Epub ahead of print]
Lung cancer is the leading cause of cancer death in the United States. Metastasis to lymph nodes (LN) and distal organs, especially brain, leads to severe complications and death. Preventing lung cancer development and metastases is important strategy to reduce lung cancer mortality. Honokiol (HNK), a natural compound presents in extracts of magnolia bark, has a favorable bioavailability profile and recently has been shown to readily cross the blood-brain barrier (BBB). In the current study, we evaluated the anti-metastatic effects of HNK in both the LN and brain mouse models of lung tumor metastasis. We tested the efficacy of HNK in preventing H2030-BrM3 cell (brain seeking human lung tumor cells) migration to LN or brain, in orthotopic mouse model, HNK significantly decreased lung tumor growth compared to the vehicle control group. HNK also significantly reduced the incidence of lymph node metastasis and the weight of mediastinal lymph nodes ; in brain metastasis model, HNK inhibits metastasis of lung cancer cells to the brain to approximately one-third of that observed in control mice. We analyzed HNK's mechanism of action which indicated that its effect is mediated primarily by

inhibiting the signal transduction and activator of transcription 3 (STAT3) pathway. HNK specifically inhibits STAT3 phosphorylation irrespective of the mutation status of epidermal growth factor receptor (EGFR), and knockdown of STAT3 abrogated both the anti-proliferative and the anti-metastatic effects of HNK. These observations suggest that HNK could provide novel chemopreventive or therapeutic options for preventing both lung tumor progression and lung cancer metastasis.

MISCELLANEOUS WORKS

Mortality from respiratory diseases associated with opium use: a population-based cohort study. Rahmati A1, Shakeri R1, Khademi H1, et al. Thorax. 2016 Nov 24. pii: thoraxjnl-2015-208251. doi: 10.1136/thoraxjnl-2015-208251. [Epub ahead of print]

BACKGROUND: Recent studies have suggested that opium use may increase mortality from cancer and cardiovascular diseases. However, no comprehensive study of opium use and mortality from respiratory diseases has been published. We aimed to study the association between opium use and mortality from respiratory disease using prospectively collected data. **METHODS:** We used data from the Golestan Cohort Study, a prospective cohort study in northeastern Iran, with detailed, validated data on opium use and several other exposures. A total of 50 045 adults were enrolled from 2004 to 2008, and followed annually until June 2015, with a follow-up success rate of 99%. We used Cox proportional hazard regression models to evaluate the association between opium use and outcomes of interest. **RESULTS:** During the follow-up period, 331 deaths from respiratory disease were reported (85 due to respiratory malignancies and 246 due to non-malignant aetiologies). Opium use was associated with an increased risk of death from any respiratory disease (adjusted HR 95% CI 3.13 (2.42 to 4.04)). The association was dose-dependent with a HR of 3.84 (2.61 to 5.67) for the highest quintile of cumulative opium use versus never use (Ptrend<0.001). The HRs (95% CI) for the associations between opium use and malignant and non-malignant causes of respiratory mortality were 1.96 (1.18 to 3.25) and 3.71 (2.76 to 4.96), respectively. **CONCLUSIONS:** Long-term opium use is associated with increased mortality from both malignant and non-malignant respiratory diseases.

Differences in Health Care Use and Costs Among Patients With Cancer Receiving Intravenous Chemotherapy in Physician Offices Versus in Hospital Outpatient Settings. Fisher MD1, Punekar R1, Yim YM1, et al. J Oncol Pract. 2016 Nov 15:JOP2016012930. [Epub ahead of print]

PURPOSE: The current shift in site of care from community oncology practices to the hospital outpatient department to deliver oncology services may have significant implications for the economic and clinical outcomes of cancer care. Therefore, this study compares health care use and costs among patients with cancer receiving intravenous (IV) chemotherapy in physician offices (PO) versus in hospital outpatient settings (HOP). **METHODS:** This retrospective study, which was based on medical and pharmacy claims data, included patients (age, 18 to 64 years) initiating IV chemotherapy/biologic treatment between January 1, 2006, and August 31, 2012, who were diagnosed with early or metastatic breast cancer, metastatic lung cancer, metastatic colorectal cancer, or non-Hodgkin lymphoma or chronic lymphocytic leukemia. Patients were assigned to PO or HOP groups on the basis of where they received > 95% of their IV cancer therapy. **RESULTS:** The study sample included 18,740 patients (12,899 PO; 5,841 HOP) who had a mean age of 51.6 years and a Deyo-Charlson Comorbidity Index score of 5.37. Overall office visits (21.8 ± 13.8 PO v 21.2 ± 12.9, P < .005) and outpatient services (50.8 ± 35.5 PO v 48.5 ± 33.6, P < .001) were higher in the PO group than in the HOP group. Cancer-related inpatient hospitalizations (0.6 ± 1.2 PO v 0.7 ± 1.4 HOP, P = .002) were lower in the PO group than in the HOP group. Although quality-of-care metrics were similar between the HOP and PO groups, follow-up all-cause costs ($82,773 PO v $122,473 HOP) and cancer-related health care costs ($69,037 PO v $108,177 HOP) were higher in the HOP group than in the PO group. **CONCLUSION:** Despite similar resource use, all-cause and cancer-related health care costs in HOP were significantly higher compared with those in PO settings.

The impact of health insurance on cancer care in disadvantaged communities. Abdelsattar ZM1,2, Hendren S1,2, Wong SL1,3. Cancer. 2016 Nov 14. doi: 10.1002/cncr.30431. [Epub ahead of print]
BACKGROUND: Individuals from disadvantaged communities are among the millions of uninsured Americans gaining insurance under the Affordable Care Act. The extent to which health insurance can mitigate the effects of the social determinants of health on cancer care is unknown. **METHODS:** This study linked the Surveillance, Epidemiology, and End Results registries to US Census data to study patients diagnosed with the 4 leading causes of cancer deaths between 2007 and 2011. A county-level social determinant score was developed with 5 measures of wealth, education, and employment. Patients were stratified into quintiles, with the lowest quintile representing the most disadvantaged communities. Logistic regression and Cox proportional hazards models were used to estimate associations and cancer-specific survival. **RESULTS:** A total of 364,507 patients aged 18 to 64 years were identified (134,105 with breast cancer, 106,914 with prostate cancer, 62,606 with lung cancer, and 60,882 with colorectal cancer). Overall, patients from the most disadvantaged communities (median household income, $42,885; patients below the poverty level, 22%; patients completing college, 17%) were more likely to present with distant disease (odds ratio, 1.6; P < .001) and were less likely to receive cancer-directed surgery (odds ratio, 0.8; P < .001) than the least disadvantaged communities (median income, $78,249; patients below the poverty level, 9%; patients completing college, 42%). The differences persisted across quintiles regardless of the insurance status. The effect of having insurance on cancer-specific survival was more pronounced in disadvantaged communities (relative benefit at 3 years, 40% vs 31%). However, it did not fully mitigate the effect of social determinants on mortality (hazard ratio, 0.75 vs 0.68; P < .001). **CONCLUSIONS:** Cancer patients from disadvantaged communities benefit most from health insurance, and there is a reduction in disparities in outcome. However, the gap produced by social determinants of health cannot be bridged by insurance alone. Cancer 2016. © 2016 American Cancer Society.

Development of a Prognostic Survival Algorithm for Patients with Metastatic Spine Disease. Paulino Pereira NR1, Janssen SJ2, van Dijk E3, Harris MB4, Hornicek FJ5, Ferrone ML6, Schwab JH7. J Bone Joint Surg Am. 2016 Nov 2;98(21):1767-1776.
BACKGROUND: Current prognostication models for survival estimation in patients with metastatic spine disease lack accuracy. Identifying new risk factors could improve existing models. We assessed factors associated with survival in patients surgically treated for spine metastases, created a classic scoring algorithm, nomogram, and boosting algorithm, and tested the predictive accuracy of the three created algorithms at estimating survival. **METHODS:** We included 649 patients from two tertiary care referral centers in this retrospective study (2002 to 2014). A multivariate Cox model was used to identify factors independently associated with survival. We created a classic scoring system, a nomogram, and a boosting (i.e., machine learning) algorithm and calculated their accuracy by receiver operating characteristic analysis. **RESULTS:** Older age (hazard ratio [HR], 1.01; p = 0.009), poor performance status (HR, 1.54; p = 0.001), primary cancer type (HR, 1.68; p < 0.001), >1 spine metastasis (HR, 1.32; p = 0.009), lung and/or liver metastasis (HR, 1.35; p = 0.005), brain metastasis (HR, 1.90; p < 0.001), any systemic therapy for cancer prior to a surgical procedure (e.g., chemotherapy, immunotherapy, hormone therapy) (HR, 1.65; p < 0.001), higher white blood-cell count (HR, 1.03; p = 0.002), and lower hemoglobin levels (HR, 0.92; p = 0.009) were independently associated with decreased survival. The boosting algorithm was best at predicting survival on the training data sets (p < 0.001); the nomogram was more reliable at estimating survival on the test data sets, with an accuracy of 0.75 (30 days), 0.73 (90 days), and 0.75 (365 days). **CONCLUSIONS:** We identified risk factors associated with survival that should be considered in prognostication. Performance of the boosting algorithm and nomogram were comparable on the testing data sets. However, the nomogram is easier to apply and therefore more useful

to aid surgical decision-making. **LEVEL OF EVIDENCE:** Prognostic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Lung Cancer Among Firefighters: Smoking-Adjusted Risk Estimates in a Pooled Analysis of Case-Control Studies. Bigert C1, Gustavsson P, Straif K, et al. J Occup Environ Med. 2016 Nov;58(11):1137-1143.

OBJECTIVES: The aim of this study was to explore lung cancer risk among firefighters, with adjustment for smoking. **METHODS:** We used pooled information from the SYNERGY project including 14 case-control studies conducted in Europe, Canada, New Zealand, and China, with lifetime work histories and smoking habits for 14,748 cases of lung cancer and 17,543 controls. We estimated odds ratios by unconditional logistic regression with adjustment for smoking and having ever been employed in a job known to present an excess risk of lung cancer. **RESULTS:** There was no increased lung cancer risk overall or by specific cell type among firefighters (n=190), neither before nor after smoking adjustment. We observed no significant exposure-response relationship in terms of work duration. **CONCLUSIONS:** We found no evidence of an excess lung cancer risk related to occupational exposure as a firefighter.