Caring Ambassadors Lung Cancer Program
Literature Review, March 2020

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Gene variant profiles and tumor metabolic activity as measured by FOXM1 expression and glucose uptake in lung adenocarcinoma. Goodman A1, Mahmud W2, Buckingham L1,2. J Pathol Transl Med. 2020 Mar 4. doi: 10.4132/jptm.2020.02.08. [Epub ahead of print]

BACKGROUND: Cancer cells displaying aberrant metabolism switch energy production from oxidative phosphorylation to glycolysis. Measure of glucose standardized uptake value (SUV) by positron emission tomography (PET), used for staging of adenocarcinoma in high-risk patients, can reflect cellular use of the glycolysis pathway. The transcription factor, FOXM1 plays a role in regulation of glycolytic genes. Cancer cell transformation is driven by mutations in tumor suppressor genes such as TP53 and STK11 and oncogenes such as KRAS and EGFR. In this study, SUV and FOXM1 gene expression were compared in the background of selected cancer gene mutations. **MATERIALS AND METHODS:** Archival tumor tissue from cases of lung adenocarcinoma were analyzed. SUV was collected from patient records. FOXM1 gene expression was assessed by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). Gene mutations were detected by allele-specific PCR and gene sequencing. **RESULTS:** SUV and FOXM1 gene expression patterns differed in the presence of single and coexisting gene mutations. Gene mutations affected SUV and FOXM1 differently. EGFR mutations were found in tumors with lower FOXM1 expression but did not affect SUV. Tumors with TP53 mutations had increased SUV ($p = .029$). FOXM1 expression was significantly higher in tumors with STK11 mutations alone ($p < .001$) and in combination with KRAS or TP53 mutations ($p < .001$ and $p = .002$, respectively). **CONCLUSION:** Cancer gene mutations may affect tumor metabolic activity. These observations support consideration of tumor cell metabolic state in the presence of gene mutations for optimal prognosis and treatment strategy.

Drug sensitivity and allele-specificity of first-line osimertinib resistance EGFR mutations. Starrett JH1, Guernet AA2, Cuomo ME2, et al. Cancer Res. 2020 Mar 19. pii: canres.3819.2019. doi: 10.1158/0008-5472.CAN-19-3819. [Epub ahead of print]

Osimertinib, a mutant-specific third generation EGFR TKI, is emerging as the preferred first-line therapy for EGFR mutant lung cancer, yet resistance inevitably develops in patients. We modeled acquired resistance to osimertinib in transgenic mouse models of EGFR L858R-induced lung adenocarcinoma and

found that it is mediated largely through secondary mutations in EGFR - either C797S or L718V/Q. Analysis of circulating free DNA data from patients revealed that L718Q/V mutations almost always occur in the context of an L858R driver mutation. Therapeutic testing in mice revealed that both erlotinib and afatinib caused regression of osimertinib-resistant C797S-containing tumors, whereas only afatinib was effective on L718Q mutant tumors. Combination first-line osimertinib plus erlotinib treatment prevented the emergence of secondary mutations in EGFR. These findings highlight how knowledge of the specific characteristics of resistance mutations are important for determining potential subsequent treatment approaches and suggest strategies to overcome or prevent osimertinib resistance in vivo.

[Early variations in lymphocytes and T lymphocyte subsets are associated with radiation pneumonitis in lung cancer patients and experimental mice received thoracic irradiation.](#)
Zhou P1, Chen L1, Yan D2, et al. Cancer Med. 2020 Mar 24. doi: 10.1002/cam4.2987. [Epub ahead of print]
There were no ideal markers to predict the development of radiation pneumonitis (RP). We want to investigate the value of variations of lymphocytes and T lymphocyte subsets in predicting RP after radiotherapy (RT) of lung cancer based on previous clinical findings. A total of 182 lung cancer patients who received RT were retrospectively analyzed. Circulating lymphocytes and T lymphocyte subsets were measured before, during, and after RT. Patients were evaluated from the start of RT to 6 months post-RT. A mice model with acute radiation-induced lung injury was established and circulating lymphocytes were measured weekly until 8 weeks after irradiation. Univariate and multivariate analyses were adopted to identify risk factors of RP. Lymphocyte levels significantly decreased ($P < .001$) in patients before RP symptoms developed that also was able to be seen in the mice model and the values recovered during remission of symptoms. The decrease in lymphocyte count reflected the severity of RP. Meanwhile, CD4+ T lymphocyte count was significantly lower during the occurrence of symptoms in patients with RP than in those without RP ($P < .001$), and it improved along with RP recovery. Levels of lymphocytes and CD4+ T lymphocyte subsets proved as independent predictors of RP. Here we showed that lower peripheral blood levels of lymphocytes and CD4+ T lymphocyte were associated with an increased risk of RP, which was validated by this mice model, and thus are associated with differences in radiation-induced lung toxicity among individuals and help identify those who are susceptible to developing RP after RT.

SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

[Ethnic Disparities in PET/CT Utilization at Diagnosis of Non-Small Cell Lung Cancer.](#) Morgan RL1, Karam SD2, Bradley CJ3. J Natl Cancer Inst. 2020 Mar 5. pii: djaa034. doi: 10.1093/jnci/djaa034. [Epub ahead of print]
BACKGROUND: Prior research demonstrated statistically significant racial disparities related to lung cancer treatment and outcomes. We examined differences in initial imaging and survival between Blacks, Hispanics and non-Hispanic Whites. **METHODS:** The linked Surveillance, Epidemiology, and End Results-Medicare database between 2007 and 2015 was used to compare initial imaging modality for patients with lung cancer. Participants included 28,881 non-Hispanic Whites, 3,123 Black, and 1,907 Hispanics, patients age ≥66 years who were enrolled in Medicare fee-for-service and diagnosed with lung cancer. The primary outcome was comparison of PET/CT utilization between groups. A secondary outcome was 12-month cancer specific survival. Information on stage, treatment, and treatment facility were included in the analysis. Chi-Square test and logistic regression were used to evaluate factors associated with imaging utilization. Kaplan-Meier method and Cox proportional hazards regression were used to calculate adjust hazard ratios and survival. All statistical tests were two-sided. **RESULTS:** After adjusting for demographic, community, and facility characteristics, Blacks were less likely to undergo

PET/CT imaging at diagnosis compared to non-Hispanic Whites odds ratio (OR) 0.54; 95% CI 0.50, 0.59; P < 0.001). Hispanics were also less likely to receive PET/CT imaging (OR 0.72; 95% CI 0.65, 0.81 P < 0.001). PET/CT was associated with improved survival (HR = 0.61; 95% CI: 0.57, 0.65, P < 0.001). **CONCLUSION:** Blacks and Hispanics are less likely to undergo guideline recommended PET/CT imaging at diagnosis of lung cancer, which may partially explain differences in survival. Awareness of this issue will allow for future interventions aimed at reducing this disparity.

Reliability of self-reported smoking history and its implications for lung cancer screening. Volk RJ1, Mendoza TR2, Hoover DS3, Nishi SPE4, Choi NJ1,5, Bevers TB6. Prev Med Rep. 2020 Jan 2;17:101037. doi: 10.1016/j.pmedr.2019.101037. eCollection 2020 Mar.
Clinical guidelines endorse either a 30 or 20 pack-year smoking history threshold when determining eligibility for lung cancer screening (LCS). However, self-reported smoking history is subject to recall bias that can affect patient eligibility. We examined the reliability of smokers' self-reported tobacco use and its impact on eligibility for LCS. Current or former smokers aged 55-77 years completed questionnaires requesting demographic information and smoking history. Data were collected between December 2014 and September 2015. Total pack-year smoking history was calculated for each participant based on their responses at baseline and one month later. One hundred and two participants completed the study (mean age = 63.6 years). The intraclass correlation coefficient for the pack-year estimate was 0.93. For the 30 pack-year threshold, eight (7.8%) participants were eligible at one but not both assessment periods. For the 20 pack-year threshold, twelve participants (11.8%) were eligible at one but not both assessment periods. Inconsistent reporting was higher among current compared to former smokers. Smokers' self-reported tobacco use appears highly reliable over short time periods. Nevertheless, there is some inconsistent reporting. We recommend that clinicians carefully assess smoking history, probe patients' recall of duration and quantity of smoking, and collect tobacco use information at every encounter.

Current and future applications of liquid biopsy in nonsmall cell lung cancer from early to advanced stages. Guibert N1,2,3, Pradines A2,4, Favre G2,3,4, Mazieres J5,2,3. Eur Respir Rev. 2020 Feb 12;29(155). pii: 190052. doi: 10.1183/16000617.0052-2019. Print 2020 Mar 31.
Liquid biopsy refers to the analysis of any tumour-derived material circulating in the blood or any other body fluid. This concept is particularly relevant in lung cancer as the tumour is often difficult to reach and may need an invasive and potentially harmful procedure. Moreover, the multitude of anticancer drugs and their sequential use underline the importance of conducting an iterative assessment of tumour biology. Liquid biopsies can noninvasively detect any targetable genomic alteration and guide corresponding targeted therapy, in addition to monitoring response to treatment and exploring the genetic changes at resistance, overcoming spatial and temporal heterogeneity.In this article, we review the available data in the field, which suggest the potential of liquid biopsy in the area of lung cancer, with a particular focus on cell-free DNA and circulating tumour cells. We discuss their respective applications in patient selection and monitoring through targeted therapy, as well as immune checkpoint inhibitors. The current data and future applications of liquid biopsy in the early stage setting are also investigated. Liquid biopsy has the potential to help manage nonsmall cell lung cancer throughout all stages of lung cancer: screening, minimal residual disease detection to guide adjuvant treatment, early detection of relapse, systemic treatment initiation and monitoring of response (targeted or immune therapy), and resistance genotyping.

Subtyping and EGFR mutation testing from blocks of cytological materials, based on liquid-based cytology for lung cancer at bronchoscopic examinations. Tanaka R1, Ohtsuka K2, Ogura W2, et al. Diagn Cytopathol. 2020 Mar 3. doi: 10.1002/dc.24397. [Epub ahead of print]

BACKGROUND: Liquid-based cytology (LBC) allows immunohistochemistry (IHC), fluorescence in situ hybridization, and molecular testing to be performed in fixed cell materials. We examined the feasibility of subtyping and EGFR mutation testing of bronchoscopic samples from patients with lung cancer using cell blocks (CB) based on LBC fixation (LBC-CB). **METHODS:** We included 35 consecutive patients with peripheral lung nodules who underwent endobronchial ultrasonography with a guide sheath in our hospital. Thirty of these patients were diagnosed with lung cancer by obtaining cytological samples. Cytological subtyping was performed with IHC using LBC-CB, and the Cobas EGFR Mutation Test ver. 2 was performed using extracted genomic DNA from the LBC-CB, formalin-fixed paraffin-embedded (FFPE) tissue, and matched plasma. **RESULTS:** Of the 30 cases, 25 were classified cytomorphologically as adenocarcinoma (ADC, n = 17) and squamous-cell carcinoma (SQCC, n = 8). The remaining five cases were classified by IHC as favor ADC (n = 3) and favor SQCC (n = 2) according to the WHO criteria. In the final ADC group (n = 20), EGFR mutations on the LBC-CB were identified in eight cases (40%; 1 exon 19 deletion, 6 L858R, and 1 L861Q). Mutations in FFPE samples were identified in seven cases (35%) at the same site in each case. Plasma EGFR mutations were identified in four cases (20%) at the same site. The CB detection rate was higher than for FFPE and plasma. **CONCLUSION:** LBC-CB is suitable for subtyping and EGFR mutation testing in lung cancers.

IMPORTANCE: The overall low survival rate of patients with lung cancer calls for improved detection tools to enable better treatment options and improved patient outcomes. Multivariable molecular signatures, such as blood-borne microRNA (miRNA) signatures, may have high rates of sensitivity and specificity but require additional studies with large cohorts and standardized measurements to confirm the generalizability of miRNA signatures. **OBJECTIVE:** To investigate the use of blood-borne miRNAs as potential circulating markers for detecting lung cancer in an extended cohort of symptomatic patients and control participants. **DESIGN, SETTING, AND PARTICIPANTS:** This multicenter, cohort study included patients from case-control and cohort studies (TREND and COSYCONET) with 3102 patients being enrolled by convenience sampling between March 3, 2009, and March 19, 2018. For the cohort study TREND, population sampling was performed. Clinical diagnoses were obtained for 3046 patients (606 patients with non-small cell and small cell lung cancer, 593 patients with nontumor lung diseases, 883 patients with diseases not affecting the lung, and 964 unaffected control participants). No samples were removed because of experimental issues. The collected data were analyzed between April 2018 and November 2019. **MAIN OUTCOMES AND MEASURES:** Sensitivity and specificity of liquid biopsy using miRNA signatures for detection of lung cancer. **RESULTS:** A total of 3102 patients with a mean (SD) age of 61.1 (16.2) years were enrolled. Data on the sex of the participants were available for 2856 participants; 1727 (60.5%) were men. Genome-wide miRNA profiles of blood samples from 3046 individuals were evaluated by machine-learning methods. Three classification scenarios were investigated by splitting the samples equally into training and validation sets. First, a 15-miRNA signature from the training set was used to distinguish patients diagnosed with lung cancer from all other individuals in the validation set with an accuracy of 91.4% (95% CI, 91.0%-91.9%), a sensitivity of 82.8% (95% CI, 81.5%-84.1%), and a specificity of 93.5% (95% CI, 93.2%-93.8%). Second, a 14-miRNA signature from the training set was used to distinguish patients with lung cancer from patients with nontumor lung diseases in the validation set with an accuracy of 92.5% (95% CI, 92.1%-92.9%), sensitivity of 96.4% (95% CI, 95.9%-96.9%), and specificity of 88.6% (95% CI, 88.1%-89.2%). Third, a 14-miRNA signature from the training set was used to distinguish patients with early-stage lung cancer from all individuals without lung cancer in the validation set with an accuracy of 95.9% (95% CI, 95.7%-96.2%), sensitivity of 76.3% (95% CI, 74.5%-78.0%), and specificity of 97.5% (95% CI, 97.2%-97.7%). **CONCLUSIONS**

AND RELEVANCE: The findings of the study suggest that the identified patterns of miRNAs may be used as a component of a minimally invasive lung cancer test, complementing imaging, sputum cytology, and biopsy tests.

[A stepped-wedge randomized trial protocol of a community intervention for increasing lung screening through engaging primary care providers (I-STEP).](#) Salazar AS1, Sekhon S2, Rohatgi KW3, et al. Contemp Clin Trials. 2020 Mar 14;91:105991. doi: 10.1016/j.cct.2020.105991. [Epub ahead of print]

Lung cancer screening with low-dose computed tomography (LDCT) reduces lung cancer mortality, yet few eligible high-risk patients receive it annually. This protocol describes a community-partnered intervention (Toolkit) designed to support primary care practices in making referrals for lung screening and guiding patients into appropriate screening pathways. This study uses a stepped-wedge implementation design. Screening centers are randomized by readiness level to enter the intervention phase in three-month "steps" with pre-intervention data serving as the control. The primary outcome is whether delivery of the Toolkit to primary care practices results in a monthly increase in number of initial LDCT screenings. Six participating centers will identify 10 practices and reach 2-3 providers per practice to train them to use the Toolkit. The Toolkit will address known barriers to screening and referral at the patient and provider levels and provide support for required elements of screening. Toolkit components include adaptable evidence-based interventions to maximize compatibility with workflows. We hypothesize that after nine months of intervention delivery, the number of initial screening per center will double. Involving 60 practices achieves 80% power at 5% level of significance. Implementation outcomes such as adoption, acceptability, feasibility, adaptation, and sustainability will be assessed through field-notes and activity logs. LDCT for lung cancer screening currently reaches a small fraction of eligible adults. To reach the full potential to reduce mortality, primary care practices are an important venue for increasing appropriate referrals. This multidisciplinary trial will encourage acceptability and sustainability by using local knowledge and promoting partnership between providers and patients. Trial registration: ClinicalTrials.gov, NCT03958253.

[Implementing Decision Coaching for Lung Cancer Screening in the Low-Dose Computed Tomography Setting.](#) Lowenstein LM1, Godoy MCB2, Erasmus JJ2, Zirari Z1, Bennett A3, Leal VB1, Housten AJ1, Volk RJ1. JCO Oncol Pract. 2020 Mar 24:JOP1900453. doi: 10.1200/JOP.19.00453. [Epub ahead of print]

PURPOSE: The uptake of shared decision making (SDM) for lung cancer screening (LCS) as required by the Centers for Medicare & Medicaid Services (CMS) is suboptimal. Alternative models for delivering SDM are needed, such as decision coaching in the low-dose computed tomography (LDCT) setting. **METHODS AND MATERIALS:** The Replicating Effective Programs framework guided our implementation of decision coaching, which included a patient-facilitated component before screening followed by in-person coaching that addressed the required elements for the SDM visit from CMS. We surveyed two LCS patient cohorts (pre-implementation and implementation of decision coaching) about their knowledge of LCS and perception of the SDM process. We conducted time-motion studies to assess the feasibility of implementing decision coaching and audio recorded clinical encounters from the implementation cohort to assess fidelity of the SDM conversation to the CMS requirements. **RESULTS:** Compared with the pre-implementation cohort (n = 51), the implementation cohort (n = 30) had greater knowledge of LCS (P < .01) and reported a better SDM process (P = .01). Coaching took 7.6 ± 4.1 minutes and did not increase visit time (P = .72). Coaches addressed an average of 6.4 of 7 SDM elements required by CMS. **CONCLUSION:** Decision coaching in the LDCT setting provides an opportunity for patients to confirm their screening decision by ensuring that patients are truly informed about the potential

harms and benefits of LCS. The decision coaching had excellent fidelity in addressing the required SDM elements from CMS and is feasible.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[Postoperative outcomes of robotic-assisted lobectomy in obese patients with non-small-cell lung cancer.](#) Casiraghi M1, Sedda G1, Diotti C1, Mariolo AV1, Galetta D1, Tessitore A1, Maisonneuve P2, Spaggiari L1,3. Interact Cardiovasc Thorac Surg. 2020 Mar 1;30(3):359-365. doi: 10.1093/icvts/ivz273.
OBJECTIVES: The aim of this study was to assess the postoperative outcomes of robotic-assisted lobectomy in obese patients to determine the impact of the robotic approach on a high-risk population who were candidates for major pulmonary resection for non-small-cell lung cancer (NSCLC).
METHODS: Between January 2007 and August 2018, we retrospectively reviewed the medical records of 224 obese patients (body mass index ≥ 30) who underwent pulmonary lobectomy at our institution via robotic-assisted thoracic surgery (RATS, n = 51) or lateral muscle-sparing thoracotomy (n = 173).
RESULTS: Forty-two patients were individually matched with those who had the same pathological tumour stage and similar comorbidities and presurgical treatment. The median operative time was significantly longer in the RATS group compared to that in the thoracotomy group (200 vs 158 min; P = 0.003), whereas the length of stay was significantly better for the RATS group (5 vs 6 days; P = 0.047). Postoperative complications were significantly more frequent after open lobectomy than in the RATS group (42.9% vs 16.7%; P = 0.027). After a median follow-up of 4.4 years, the 5-year overall survival rate was 67.6% [95% confidence interval (CI) 45.7-82.2] for the RATS group, and 66.1% (95% CI 46.8-79.9) for the open surgery group (log-rank P = 0.54). The 5-year cumulative incidence of cancer-related deaths was 24.8% (95% CI 9.7-43.5) for the RATS group and 23.6% (95% CI 10.8-39.2) for the open surgery group (Gray's test, P = 0.69). **CONCLUSIONS:** RATS is feasible and safe for obese patients with NSCLC with advantages compared to open surgery in terms of early postoperative outcomes. In addition, the long-term survival rate was comparable to that of the open approach.

[Osimertinib in T790M-positive and -negative patients with EGFR-mutated advanced non-small cell lung cancer (the TREM-study).](#) Eide IJZ1, Helland Å2, Ekman S3, Mellemgaard A4, Hansen KH5, Cicenas S6, Koivunen J7, Grønberg BH8, Brustugun OT9. Lung Cancer. 2020 Mar 12;143:27-35. doi: 10.1016/j.lungcan.2020.03.009. [Epub ahead of print]
OBJECTIVES: In non-small cell lung cancer patients with acquired resistance to first- or second-generation EGFR-TKIs, osimertinib is approved in the presence of the T790 M resistance mutation. We assessed the efficacy of osimertinib in both T790M-positive and T790M-negative patients.
MATERIALS AND METHODS: The TREM-study is an investigator-initiated, multi-centre, single-arm, phase 2 clinical trial conducted in five Northern European countries. Patients with progression on at least one previous EGFR-TKI were assigned to treatment with 80 mg of osimertinib daily until radiological progression or death. Patients were included regardless of the presence of T790 M. The primary endpoint was objective response rate (ORR). **RESULTS:** Of 199 included patients, 120 (60 %) were T790M-positive, 52 (26 %) were T790M-negative and 27 (14 %) had unknown T790M-status. 24 % had brain metastases and 15 % had an ECOG performance status of 2. Overall ORR was 48 % (95 % CI, 41 %-55 %), 60 % (51 %-69 %) for T790M-positive patients and 28 % (15 %-41 %) for T790M-negative patients, p < 0.001. ORR for patients with co-occurring del19 vs L858R was 61 % vs 32 %, p = 0.001. Duration of response was similar between the T790M-positive and -negative groups (11.8 vs 10.7 months, p = 0.229). Overall median progression-free survival (PFS) was 8.9 months (95 % CI, 7.4-10.5), and 10.8 vs 5.1 months for T790M-positive vs -negative patients (HR 0.62, p = 0.007). Median overall survival

(OS) was 17.9 months (95 % CI, 14.4-21.3). For T790M-positive vs -negative median OS was 22.5 vs 13.4 months, (HR 0.55, p = 0.002). **CONCLUSIONS:** This study confirms the efficacy of osimertinib for T790M-positive patients. There was also clinically significant activity of osimertinib in a proportion of T790M-negative patients.

[**Comparing textbook outcomes among patients undergoing surgery for cancer at U. S. News & World Report ranked hospitals.**](#) Mehta R1, Tsilimigras DI1, Paredes AZ1, et al. J Surg Oncol. 2020 Mar 2. doi: 10.1002/jso.25833. [Epub ahead of print]
BACKGROUND: The objective of the current study was to define and compare rates of textbook outcomes (TO) among patients undergoing colorectal, lung, esophagus, liver, and pancreatic surgery for cancer at U.S. News & World Report (USNWR) ranked hospitals. **METHODS:** Medicare Inpatient Standard Analytic Files 2013-2015 were utilized to examine the relationship of TO and USNWR hospital ratings following surgery for colorectal, lung, esophageal, pancreatic, and liver cancer. TO was defined as no postoperative surgical complications, no prolonged length of hospital stay, no readmission within 90 days after discharge, and no postoperative mortality within 90 days after surgery. **RESULTS:** Among the 35,352 Medicare patients included in the cohort, 16,820 (47.6%) underwent surgery at honor roll hospitals, whereas 18 532 (52.4%) underwent surgery at non-honor roll hospitals. The overall proportion of patients who achieved TO was 50.1%. In examining the clinical outcomes of patients who underwent surgery, there was no difference in the odds of achieving TO at honor roll vs non-honor roll hospitals (colorectal: odds ratio [OR], 0.87; 95% confidence interval [CI], 0.69-1.10; lung: OR, 1.07; 95% CI, 0.87-1.32; esophagus: OR, 1.44; 95% CI, 0.72-2.89; liver: OR, 1.27; 95% CI, 0.87-1.84; pancreas: OR, 1.04; 95% CI, 0.67-1.62). **CONCLUSION AND RELEVANCE:** Patients undergoing surgery for lung, esophageal, liver, pancreatic, and colorectal cancer had comparable rates of TO at honor roll vs non-honor roll hospitals. No linear association was observed between hospital position in the rank and postoperative outcomes such as TO indicating that patients should not overly focus on the exact position within USNWR ranked hospitals. These data highlight to patients and physicians that up to one-half of patients undergoing surgery for cancer should anticipate at least one adverse outcome.

[**Image-guided video-assisted thoracoscopic resection (iVATS): Translation to clinical practice-real-world experience.**](#) Gill RR1, Barlow J2, Jaklitsch MT2, Schmidlin EJ3, Hartigan PM4, Bueno R2. J Surg Oncol. 2020 Mar 12. doi: 10.1002/jso.25897. [Epub ahead of print]
OBJECTIVE: We developed a novel approach for localization and resection of lung nodules, using image-guided video-assisted thoracoscopic surgery (iVATS). We report our experience of translating iVATS into clinical care. **METHODS:** Methodology and workflow for iVATS developed as part of the Phase I/II trial were used to train surgeons, radiologists, anesthesiologists, and radiology technologists. Radiation dose, time from induction to incision, placement of T-bar to incision and incision to closure, hospital stay, and complication rates were recorded. **RESULTS:** Fifty patients underwent iVATS for resection of 54 nodules in a clinical hybrid operating room (OR) by six surgeons. Fifty-two (97%) nodules were successfully resected. Forty-two (84%) patients underwent wedge resection, four (7%) lobectomies, and two (4%) segmentectomy all with lymph node dissection. Median time from induction to incision was 89 minutes (range: 13-256 minutes); T-bar placement was 14 minutes (10-29 minutes); and incision to closure, 107 minutes (41-302 minutes). Average and total procedure radiation dose were: median = 6 mSieverts (range: 2.9-35 mSieverts). No deaths were reported and median length of stay was 3 days (range: 1-12 days). **CONCLUSIONS:** Translation of iVATS into clinical practice has been initiated using a safe step-wise process, combining intraoperative C-arm computed tomography scanning and thoracoscopic surgery in a hybrid OR.

Enhanced recovery after surgery: adherence and outcomes in elderly patients undergoing VATS lobectomy. Mazza F1,2, Venturino M3, Turello D3, Gorla A3, Degiovanni C4, Gambera G4, Locatelli A4, Melloni G3. Gen Thorac Cardiovasc Surg. 2020 Mar 12. doi: 10.1007/s11748-020-01331-4. [Epub ahead of print]

OBJECTIVES: To evaluate whether ERAS is feasible and beneficial in elderly patients undergoing VATS lobectomy for lung cancer. **METHODS:** From February 2016 to March 2019, 182 patients were included into a 17-items ERAS pathway. Patients were divided into two groups according to age: Group A (< 75 years) 138 patients and Group B (≥ 75 years) 44 patients. End points were: length of stay (LoS), 30-day morbidity, 90-day mortality, 30-day re-admittance rate, and ERAS-score (number of ERAS objectives achieved). **RESULTS:** Elderly patients had significantly more chronic renal failure ($p = 0.039$) and a worse pulmonary function. Mean FEV1% was 101.6% ($\pm 21.0\%$ SD) and 90.8% ($\pm 19.1\%$ SD) and mean FEV1/FVC was 0.75 (± 0.10 SD) and 0.68 (± 0.12 SD) for group A and B, respectively ($p = 0.02$ and $p = 0.01$). Median LoS was longer in Group B (6 days) than in Group A (5 days; $p = 0.006$). Morbidity was higher for elderly patients (A 32.6% vs B 56.8%; $p = 0.007$), major complication rates were similar ($p = 0.782$). No post-operative mortality was observed, re-admittance rates were similar (A 7.8% vs B 11.5%; $p = 0.548$). Mean ERAS-scores were 13.8 (± 1.83 SD) for Group A and 13.4 (± 1.98 SD) for Group B ($p = 0.240$). Multivariable analysis showed previous major surgery ($p = 0.028$), COPD ($p = 0.027$), history of arrhythmic disease ($p = 0.015$), post-operative complications ($p < 0.001$), and ERAS-score ($p < 0.001$) as independent predictive factors of LoS, age did not significantly influence LoS. **CONCLUSIONS:** Elderly patients adhere to an ERAS protocol similarly to younger ones. ERAS pathway in VATS lobectomy patients seems to be beneficial regardless the age.

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

Treatment options after first-line immunotherapy in metastatic NSCLC. Santos ES1,2. Expert Rev Anticancer Ther. 2020 Mar;20(3):221-228. doi: 10.1080/14737140.2020.1738930. Epub 2020 Mar 12.

INTRODUCTION: The recent approvals of checkpoint inhibitors as single agents or in combination with chemotherapy with programmed death ligand 1 expression of $<$ or $\geq 1\%$ have challenged clinicians when it is time to begin a metastatic lung cancer patient in second-line therapy. The advantages given by immunotherapy over conventional chemotherapy such as improved overall survival and a better toxicity profile make the second-line clinical scenario more difficult for a patient who faces a likely inferior regimen as well as toxicity which may significantly impact the quality of life. **AREAS COVERED:** Options given today by the National Comprehensive Cancer Network are very limited, and essentially, we go back to conventional cytotoxic agents alone or in combination with biological agents if possible. In this article, we discuss the actual treatment available for this difficult scenario and some of the ongoing trials which aim to address this dilemma. **EXPERT COMMENTARY:** This is an unmet need in lung cancer management; we need a better understanding of the mechanism of resistance to immunotherapy so we can target them once the patient moves to second-line treatment.

First-line crizotinib versus platinum-pemetrexed chemotherapy in patients with advanced ROS1-rearranged non-small-cell lung cancer. Shen L1, Qiang T1, Li Z1, Ding D2, Yu Y1, Lu S1. Cancer Med. 2020 Mar 13. doi: 10.1002/cam4.2972. [Epub ahead of print]

OBJECTIVES: Food and Drug Administration (FDA) approved crizotinib for advanced ROS1-rearranged (ROS1+) non-small-cell lung cancer (NSCLC) patients due to a single-arm study PROFILE 1001. However, there is no direct comparison between crizotinib and platinum-pemetrexed chemotherapy. **MATERIALS AND METHODS:** Clinical data of advanced ROS1+NSCLC patients treated with first-line crizotinib or platinum-pemetrexed chemotherapy between August 2010 and December 2017 were analyzed. **RESULTS:** Seventy-seven patients were eligible, including 30 (39.0%) in the crizotinib group

and 47 (61.0%) in the platinum-pemetrexed chemotherapy group. The median follow-up was 28.1 months (95% confidence interval [CI]: 19.2-39.0). The objective response rate (ORR) of crizotinib (86.7%, 95% CI: 73.3-96.7) was higher than that of platinum-pemetrexed chemotherapy (44.7%, 95% CI: 29.8-57.4, P < .001). The disease control rate (DCR) was 96.7% (95% CI: 90.0-100) in the crizotinib group and 85.1% (95% CI: 74.5-95.7) in the chemotherapy group (P = .140). Significantly longer progression-free survival (PFS) was observed in the patients treated with crizotinib (18.4 months, 95% CI: 6.4-30.3) versus platinum-pemetrexed chemotherapy (8.6 months, 95% CI: 6.9-10.3, P < .001). Overall survival (OS) was also compared between the two groups and no significant difference was seen (Not reach vs 28.4 months [95% CI: 20.7-36.0], P = .176). Notably, a total of 37 patients have treatment crossover after the failure of first-line treatment. Among those patients, difference in OS was not statistically significant between seven patients who have given first-line crizotinib (38.6 months, 95% CI: 0-81.0) and 30 patients who have given platinum-pemetrexed chemotherapy initially (32.8 months, 95% CI: 11.9-53.8, P = .805). **CONCLUSIONS:** Our results suggested that first-line crizotinib had higher ORR and longer PFS than platinum-pemetrexed chemotherapy in patients with advanced ROS1+NSCLC, but the differences were not observed for OS.

[Outcomes associated with immune-related adverse events in metastatic non-small cell lung cancer treated with nivolumab: a pooled exploratory analysis from a global cohort.](#) Naqash AR1,2, Ricciuti B3,4, et al. Cancer Immunol Immunother. 2020 Mar 5. doi: 10.1007/s00262-020-02536-5. [Epub ahead of print]
BACKGROUND: Immune-related adverse events (irAEs) comprise a distinct spectrum of auto-inflammatory manifestations triggered due to immune checkpoint inhibitors (ICI). Current data on the association of irAEs with outcomes in NSCLC treated with nivolumab are limited. **METHODS AND OBJECTIVES:** We pooled data from 531 metastatic NSCLC patients from five centers treated with nivolumab after failing platinum-based chemotherapy. The primary objective was to investigate the relationship between irAEs with clinical benefit to nivolumab as well as to elucidate patterns of irAE-related ICI discontinuations and their impact on survival. **RESULTS:** 33.0% (173/531) of patients treated with nivolumab were noted to have an irAE. Patients with irAEs had a significantly longer median PFS [6.1 vs. 3.1 months, HR 0.68 95% CI (0.55-0.85); p = 0.001] and OS [14.9 vs. 7.4 months, HR 0.66 95% CI (0.52-0.82); p < 0.001)] compared to those without irAEs. In multivariate analysis, the presence of irAEs showed a significantly better PFS [HR 0.69, 95% CI (0.55-0.87); p = 0.002] and a trend for better OS [HR 0.62, 95% CI (0.55-1.03); p = 0.057]. Patients with permanent ICI discontinuation secondary to index irAE had a significantly shorter median PFS [2.3 vs. 6.6 months, HR 1.74 95% CI (1.06-2.80); p = 0.02] and median OS [3.6 vs. 17.6 months; HR 2.61 95% CI (1.61-4.21); p < 0.001] compared to those that did not have permanent ICI discontinuation. **CONCLUSIONS:** Our pooled exploratory analysis demonstrates improved clinical benefit to nivolumab in NSCLC patients experiencing irAEs. We also observed negative impact of irAE-related treatment discontinuation on survival in this group of patients.

[Crizotinib vs platinum-based chemotherapy as first-line treatment for advanced non-small cell lung cancer with different ROS1 fusion variants.](#) Xu H1, Zhang Q2, Liang L3, et al. Cancer Med. 2020 Mar 13. doi: 10.1002/cam4.2984. [Epub ahead of print]
BACKGROUND: ROS1 gene fusion represents a specific subtype of non-small cell lung cancer (NSCLC). Crizotinib is recommended for ROS1-positive NSCLC due to its favorable outcome in published clinical trials. However, due to the low incidence of ROS1-positive NSCLC, there is limited information on real-world clinical outcomes in patients treated with either crizotinib or platinum-based doublet chemotherapy. **METHODS:** Outcomes were recorded in 102 patients with stage IIIb or IV NSCLC who were treated at four Chinese hospitals between April, 2010 and June, 2019. **RESULTS:** Of the 102 patients followed, 71.6% were females, 81.4% were non-smokers, and 98.0% had

adenocarcinoma. First-line treatment with crizotinib achieved a significantly longer median progression-free survival (PFS) compared with platinum-based chemotherapy (14.9 months vs 8.5 months, respectively; P < .001). Next-generation sequencing (NGS) identified 61 patients who had ROS1 fusion variants, including CD74 (n = 33) and non-CD74 (n = 28) variants. In patients harboring CD74 fusion variants, the median PFS with first-line crizotinib treatment was significantly longer than in those harboring non-CD74 fusion variants (20.1 months vs 12.0 months, respectively; P = .046). However, in patients treated with platinum-based chemotherapy, there was no significant difference in PFS between the CD74 and non-CD74 variant groups (8.6 months vs 4.3 months, respectively; P = .115). Overall survival (OS) was not reached. **CONCLUSIONS:** First-line therapy with crizotinib is more beneficial than platinum-based chemotherapy in patients with advanced NSCLC with different ROS1 fusion variants. Patients harboring CD74 fusion variants appear to respond better to crizotinib.

[Early-Onset Pulmonary Events Associated With Brigatinib Use in Advanced Non-Small Cell Lung Cancer.](#) Ng TL1, Narasimhan N2, Gupta N3, Venkatakrishnan K3, Kerstein D3, Camidge DR4. J Thorac Oncol. 2020 Mar 2. pii: S1556-0864(20)30133-7. doi: 10.1016/j.jtho.2020.02.011. [Epub ahead of print]
INTRODUCTION: We evaluated pulmonary adverse events observed within 7 days after drug initiation in phase 1-3 studies of the anaplastic lymphoma kinase (ALK) inhibitor brigatinib. **METHODS:** The phase 1/2 study enrolled patients with advanced malignancies (dose range, 30-300 mg qd), the phase 2 ALTA study treated patients with advanced ALK+ non-small cell lung cancer (NSCLC) post-crizotinib at either 90 mg qd or 90 mg qd for 7 days followed by 180 mg qd, and the phase 3 ALTA-1L study treated inhibitor-naive ALK+ NSCLC patients with brigatinib (90 mg → 180 mg qd) or crizotinib (250 mg bid). Early-onset pulmonary events (EOPEs) at least possibly associated with brigatinib were captured. **RESULTS:** In phase 1/2, ALTA, and ALTA-1L, 8% (11/137), 6% (14/219), and 3% (4/136) of patients, respectively, had at least possible EOPEs on brigatinib, with frequency appearing to increase with starting dose. Across trials, at the 90-mg qd starting dose (alone or step-up dosing), 4.5% of patients (20/440) had at least possible events (median time to onset, 2 days). Twelve (3%) patients had grade ≥3 events leading to brigatinib discontinuation. Seven (1.5%) patients had grade 1-2 events and successfully continued brigatinib with or without brigatinib interruption and/or steroids/supplemental oxygen. In pooled analysis of these trials, occurrence of EOPEs was significantly associated with continuous 10-year increases in patient age in unadjusted logistic regression analysis and with ECOG performance status and number of prior regimens in multivariate regression. **CONCLUSIONS:** Clinically apparent EOPEs can occur within days of commencing brigatinib in a subset of patients with NSCLC. Identifying clinical parameters associated with a higher risk of developing such events may help mitigate these events.

[Osimertinib, a third-generation EGFR tyrosine kinase inhibitor: A retrospective multicenter study of its real-world efficacy and safety in advanced/recurrent non-small cell lung carcinoma.](#) Kishikawa T1, Kasai T1, Okada M2, Nakachi I2, Soda S3, Arai R3, Takigami A4, Sata M4. Thorac Cancer. 2020 Mar 4. doi: 10.1111/1759-7714.13378. [Epub ahead of print]
BACKGROUND: Osimertinib is recommended for T790M mutation-positive advanced non-small cell lung cancer (NSCLC) resistant to first- and second-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs). Recently, some reports exist on the real-world use of osimertinib; however, reports involving third/later-line use are few. Hence, this study was conducted to evaluate the efficacy and safety of osimertinib used in various treatment lines for T790M-positive NSCLC patients. **METHODS:** This retrospective, observational, multicenter study included T790M-positive advanced/recurrent NSCLC patients treated with osimertinib from May 2016 to March 2018. The clinical characteristics, efficacy, and adverse events were retrospectively investigated. The Kaplan-Meier method was used to analyze progression-free survival (PFS) and overall survival (OS). PFS-associated clinical characteristics were evaluated using the Cox proportional hazards model. **RESULTS:** The objective

response rate (ORR) and disease control rate (DCR) were 60.7% and 91.1%, respectively; the median PFS was 11.0 months. There were no significant differences in the median PFS for patients treated with osimertinib as second-line and third-/later-line (14.5 vs. 11.0 months respectively, P = 0.327). Analysis using the Cox proportional hazards model for clinical features affecting PFS also revealed no significant factors. Adverse events of grade ≥ 3 were reported in 15 patients (26.8%); the most common were anemia (n = 3) and cutaneous toxicity (n = 3). Grade 4 neutropenia was observed in one patient; any-grade pneumonitis was observed in six patients (10.7%), including one with grade 3 pneumonitis. **CONCLUSIONS:** Osimertinib demonstrated efficacy even when administered as third-/later-line treatment to NSCLC patients. Osimertinib-related pneumonitis was observed more frequently than previously reported. **KEY POINTS:** Significant findings of the study Osimertinib shows efficacy even as later-line treatment in T790M mutation-positive NSCLC patients previously treated with EGFR-TKIs. However, the incidence of ≥ grade 3 adverse events, especially pneumonitis, was higher than that previously reported by other studies. What this study adds Osimertinib was approved for previously EGFR-TKI-treated EGFR T790M-positive NSCLC. With the increasing frequency of its use as first-line treatment, this study provides valuable evidence for the efficacy and safety of osimertinib for previously EGFR-TKI-treated NSCLC.

[MAPK pathway alterations correlate with poor survival and drive resistance to therapy in patients with lung cancers driven by ROS1 fusions.](#) Sato H1, Schoenfeld AJ2, Siau E3, et al. Clin Cancer Res. 2020 Mar 2. pii: clincanres.3321.2019. doi: 10.1158/1078-0432.CCR-19-3321. [Epub ahead of print] **PURPOSE:** ROS1 tyrosine kinase inhibitors (TKIs) provide significant benefit in lung adenocarcinoma (LUAD) patients with ROS1 fusions. However, as observed with all targeted therapies, resistance arises. Detecting mechanisms of acquired resistance (AR) is crucial to finding novel therapies and improve patient outcomes. **EXPERIMENTAL DESIGN:** ROS1 fusions were expressed in in HBEC and NIH-3T3 cells either by cDNA overexpression (CD74/ROS1, SLC34A2/ROS1) or CRISPR-Cas9-mediated genomic engineering (EZR/ROS1). We reviewed targeted large-panel sequencing data (using the MSK-IMPACT assay) patients treated with ROS1 TKIs, and genetic alterations hypothesized to confer AR were modeled in these cell lines. **RESULTS:** Eight of the 75 patients with a ROS1 fusion had a concurrent MAPK pathway alteration and this correlated with shorter overall survival. In addition, the induction of ROS1 fusions stimulated activation of MEK/ERK signaling in comparison with AKT signaling, suggesting the importance of the MAPK pathway in driving ROS1 fusion-positive cancers. Of 8 patients, 2 patients harbored novel in-frame deletions in MEK1 (MEK1delE41_L54) and MEKK1 (MEKK1delH907_C916) that were acquired after ROS1-TKIs, and 2 patients harbored NF1 loss-of-function mutations. Expression of MEK1del or MEKK1del, and knockdown of NF1 in ROS1 fusion-positive cells activated MEK/ERK signaling and conferred resistance to ROS1-TKIs. Combined targeting of ROS1 and MEK inhibited growth of cells expressing both ROS1 fusion and MEK1del. **CONCLUSIONS:** We demonstrate that the activation of MAPK pathway is mechanisms of innate or acquired resistance and that patients harboring ROS1 fusion and concurrent MAPK alterations have worse survival. Our findings suggest a treatment strategy to target both aberrations.

[Outcomes with durvalumab by tumour PD-L1 expression in unresectable, Stage III non-small-cell lung cancer in the PACIFIC trial.](#) Paz-Ares L1, Spira A2, Raben D3, et al. Ann Oncol. 2020 Mar 21. pii: S0923-7534(20)36374-2. doi: 10.1016/j.annonc.2020.03.287. [Epub ahead of print] **BACKGROUND:** In PACIFIC, durvalumab significantly improved progression-free and overall survival (PFS/OS) versus placebo, with manageable safety, in unresectable, Stage III NSCLC patients without progression after chemoradiotherapy (CRT). We report exploratory analyses of outcomes by tumour-cell (TC) PD-L1 expression. **PATIENTS AND METHODS:** Patients were randomised (2:1) to durvalumab 10 mg/kg intravenously every-2-weeks or placebo ≤12 months, stratified by age, sex and smoking history

but not PD-L1 status. Where available, pre-CRT samples were tested for PD-L1 expression (immunohistochemistry) and scored at pre-specified (25%) and post-hoc (1%) TC cutoffs. Treatment-effect HRs were estimated from unstratified-Cox-proportional-hazards models (Kaplan-Meier-estimated medians). **RESULTS:** 709/713 randomised patients received durvalumab (n=473) or placebo (n=236). 451 (63%) were PD-L1-evaluable: 35%, 65%, 67%, 33%, and 32% had TC ≥25%, <25%, ≥1%, <1%, and 1-24%, respectively. As of 31-January-2019, median follow-up was 33.3 months. Durvalumab improved PFS versus placebo (primary-analysis data cutoff [DCO], 13-February-2017) across all subgroups (HR, 95% CI; medians): TC ≥25% (0.41, 0.26-0.65; 17.8 versus 3.7 months), <25% (0.59, 0.43-0.82; 16.9 versus 6.9 months), ≥1% (0.46, 0.33-0.64; 17.8 versus 5.6 months), <1% (0.73, 0.48-1.11; 10.7 versus 5.6 months), 1-24% (0.49, 0.30-0.80; NR versus 9.0 months), and unknown (0.59, 0.42-0.83; 14.0 versus 6.4 months). Durvalumab improved OS across most subgroups (31-January-2019 DCO; HR, 95% CI; medians): TC ≥25% (0.50, 0.30-0.83; NR versus 21.1 months), <25% (0.89, 0.63-1.25; 39.7 versus 37.4 months), ≥1% (0.59, 0.41-0.83; NR versus 29.6 months), 1-24% (0.67, 0.41-1.10; 43.3 versus 30.5 months), and unknown (0.60, 0.43-0.84; 44.2 versus 23.5 months), but not <1% (1.14, 0.71-1.84; 33.1 versus 45.6 months). Safety was similar across subgroups. **CONCLUSIONS:** PFS benefit with durvalumab was observed across all subgroups, and OS benefit across all but TC <1%, for which limitations and wide HR CI preclude robust conclusions.

NSCLC - RADIOTHERAPY

The post-treatment neutrophil-to-lymphocyte ratio and changes in this ratio predict survival after treatment of stage III non-small-cell lung cancer with conventionally fractionated radiotherapy.

Wang D1,2, Guo D3, Li A1,2, Wang P2, Teng F2, Yu J2. Future Oncol. 2020 Mar;16(9):439-449. doi: 10.2217/fon-2019-0837. Epub 2020 Mar 6.

AIM: To investigate the predictive potential of post-treatment neutrophil-to-lymphocyte ratio (NLR) and changes in this ratio (ΔNLR) for stage III non-small-cell lung cancer (NSCLC) patients who received conventionally fractionated radiotherapy (CFRT). **PATIENTS & METHODS:** The data of 168 NSCLC patients treated at the Shandong Cancer Hospital were analyzed retrospectively. The relationship between progression-free survival (PFS), overall survival (OS) and post-treatment NLR and ΔNLR were analyzed using both Kaplan-Meier and Cox regression methods. **RESULTS:** Kaplan-Meier survival analyses showed that post-treatment NLR and ΔNLR were associated with PFS (p < 0.001) and OS (p < 0.001) after CFRT. Multivariate analyses revealed that ΔNLR was an independent predictor of PFS (p = 0.001) and OS (p = 0.018). Post-treatment NLR can only be used as an independent predictor of PFS (p = 0.040). **CONCLUSION:** Our results demonstrated the prognostic value of the ΔNLR in predicting PFS and OS in stage III NSCLC patients undergoing CFRT. However, post-treatment NLR has predictive value only for PFS.

Efficacy and Safety of Apatinib Plus Vinorelbine in Patients With Wild-Type Advanced Non-Small Cell Lung Cancer After Second-Line Treatment Failure: A Nonrandomized Clinical Trial.

Zhang X1, Xiong Y1, Xia Q2, et al. AMA Netw Open. 2020 Mar 2;3(3):e201226. doi: 10.1001/jamanetworkopen.2020.1226.

IMPORTANCE: There is currently no standard treatment strategy for patients with advanced non-small cell lung cancer (NSCLC) without driver gene variation after failure of 2 or more lines of chemotherapy. **OBJECTIVE:** To assess the efficacy and safety of apatinib combined with oral vinorelbine. **DESIGN, SETTING, AND PARTICIPANTS:** This phase 2 prospective nonrandomized clinical trial evaluating the efficacy and safety of apatinib plus vinorelbine recruited patients from Hunan Cancer Center, Hunan, China, from January 1, 2017, to November 30, 2018. Eligible patients were those with wild-type advanced NSCLC whose disease did not respond to at least 2 lines of chemotherapy. Patients were

evaluated until December 31, 2019. Data were analyzed from July 2019 to December 2019. **INTERVENTION:** Apatinib at an initial dose of 500 mg once daily and oral vinorelbine 60 mg/m2 once weekly were administered until disease progression, patient withdrawal, or occurrence of unacceptable toxic effects. **MAIN OUTCOMES AND MEASURES:** The primary end point was overall response rate. Secondary end points were overall survival, progression-free survival, and safety. **RESULTS:** The potential efficacy of apatinib plus vinorelbine was identified using drug susceptibility assay based on 3-dimensional coculture of tumor cells derived from 3 patients with lung adenocarcinoma. Among 30 patients enrolled, the median (range) age was 63 (34-78) years and 18 (60%) were men. Most patients (27 patients [90%]) had stage IV disease, and the median (range) number of prior unsuccessful treatments was 2 (2-5) lines of chemotherapy. Twenty-five patients (83%) completed the treatment, while 5 patients (17%) discontinued treatment owing to intolerable adverse events. The overall response rate was 36.7% (11 patients) and the disease control rate was 76.7% (23 patients). The median progression-free survival was 4.5 (95% CI, 2.4-6.6) months, and the median overall survival was 10.0 (95% CI, 4.8-17.1) months. Hand-foot syndrome was the most common adverse event observed, including grade 3 hand-foot syndrome observed in 5 patients (17%) and grade 4 hand-foot observed in 1 patient (3%). Grade 3 weakness was observed in 1 patient (3%). **CONCLUSIONS AND RELEVANCE:** These findings suggest that apatinib combined with oral vinorelbine is a potentially effective regimen with an acceptable safety profile. This regimen may have potential as a treatment option for patients with wild-type advanced NSCLC whose disease failed at least 2 prior lines of chemotherapy.

Predictors of chemoradiotherapy versus single modality therapy and overall survival among patients with unresectable, stage III non-small cell lung cancer. Bobbili P1, Ryan K2, DerSarkissian M1, Dua A1, Yee C1, Duh MS1, Gomez JE3. PLoS One. 2020 Mar 18;15(3):e0230444. doi: 10.1371/journal.pone.0230444. eCollection 2020.
INTRODUCTION: Concurrent chemoradiotherapy (cCRT) was the standard of care for patients with unresectable stage III non-small cell lung cancer (NSCLC) prior to the PACIFIC trial, however, patients also received single modality therapy. This study identified predictors of therapy and differences in overall survival (OS). **METHODS:** This retrospective study included stage III NSCLC patients aged ≥65 years, with ≥1 claim for systemic therapy (ST) or radiotherapy (RT) within 90 days of diagnosis, identified in SEER-Medicare data (2009-2014). Patients who had overlapping claims for chemotherapy and RT ≤90 days from start of therapy were classified as having received cCRT. Patients who received sequential CRT or surgical resection of tumor were excluded. Predictors of cCRT were analyzed using logistic regression. OS was compared between therapies using adjusted Cox proportional hazards models. **RESULTS:** Of 3,799 patients identified, 21.7% received ST; 26.3% received RT; and 52.0% received cCRT. cCRT patients tended to be younger (p <0.001), White (p = 0.002), and have a good predicted performance status (p<0.001). Patients who saw all three specialist types (medical oncologist, radiation oncologist, and surgeon) had increased odds of receiving cCRT (p<0.001). ST and RT patients had higher mortality risk versus cCRT patients (hazard ratio [95% CI]: ST: 1.38 [1.26-1.51]; RT: 1.75 [1.61, 1.91]); p<0.001). **CONCLUSIONS:** Several factors contributed to treatment selection, including patient age and health status, and whether the patient received multidisciplinary care. Given the survival benefit of receiving cCRT over single-modality therapy, physicians should discuss treatment within a multidisciplinary team, and be encouraged to pursue cCRT for patients with unresectable stage III NSCLC.

[**Brain metastases treated with radiosurgery or hypofractionated stereotactic radiotherapy: outcomes and predictors of survival.**](#) Sallabanda M1, García-Berrocal MI2, Romero J2, García-Jarabo V2, Expósito MJ2, Rincón DF2, Zapata I2, Magallón MR2. Clin Transl Oncol. 2020 Mar 2. doi: 10.1007/s12094-020-02321-x. [Epub ahead of print]

INTRODUCTION: To assess treatment outcome and prognostic factors associated with prolonged survival in patients with brain metastases (BM) treated with stereotactic radiosurgery (SRS) or hypofractionated stereotactic radiotherapy (HFSRT). **METHODS/PATIENTS:** This study retrospectively reviewed 200 patients with 324 BM treated with one fraction (15-21 Gy) or 5-10 fractions (25-40 Gy) between January 2010 and August 2016. 26.5% of patients received whole brain radiotherapy (WBRT) and 25% initial surgery. Demographics, prognostic scales, systemic and local controls, patterns of relapse and rescue, toxicity, and cause of death were analyzed. A stratified analysis by primary tumor was done. **RESULTS:** Median overall survival (OS) was 8 months from SRS/HFSRT. Breast cancer patients had a median OS of 17 months, followed by renal (11 months), lung (8 months), colorectal (5 months), and melanoma (4 months). The univariate analysis showed improved OS in females (p 0.004), RPA I-II (p < 0.001) initial surgery (p < 0.001), absence of extracranial disease (p 0.023), and good disease control (p 0.002). There were no differences in OS or local control between SRS and HFSRT or in patients receiving WBRT. Among 44% of brain recurrences, 11% were in field. 174 patients died, 10% from confirmed intracranial progression. **CONCLUSIONS:** SRS and HSFRT are equally effective and safe for the treatment of BM, with no exceptions among different primary tumors. Disease control, surgery, age, and prognostic scales correlated with OS. However, the lack of survival benefit regarding WBRT might become logical evidence for its omission in a subset of patients.

[**Clinical and radiation dose-volume factors related to pneumonitis after treatment with radiation and durvalumab in locally advanced non-small cell lung cancer.**](#) Inoue H1, Ono A2, Kawabata T3, et al. Invest New Drugs. 2020 Mar 3. doi: 10.1007/s10637-020-00917-2. [Epub ahead of print]

INTRODUCTION: Durvalumab has been shown to confer a survival benefit after definitive chemoradiotherapy in the patients with locally advanced non-small cell lung cancer, but no studies have attempted to identify risk factors for pneumonitis after durvalumab therapy. The purpose of this study was to investigate associations between clinical and radiation dose-volume factors, and the severity of pneumonitis. **METHODS:** We retrospectively assessed the cases of 30 patients who had been started on durvalumab therapy between July 2018 and February 2019. In this study we evaluated the percentage of lung volume receiving radiation dose in excess of 20 Gy (V20) as radiation dose-volume factor. We compared V20 and some baseline factors between a grade 0 or 1 (Gr 0/1) pneumonitis group and a grade 2 or more (≥Gr 2) pneumonitis group, and we performed a logistic regression analysis to establish the associations between variables and ≥ Gr 2 pneumonitis. **RESULTS:** Pneumonitis had developed in 22 patients (73.3%): Gr 1/2/3-5 in 8 (26.7%)/14 (46.7%) /0 (0%), respectively. The difference in V20 between the Gr 0/1 group and Gr 2 group (median: 20.5% vs. 23.5%, p = 0.505) was not statistically significant, and thus V20 was not a risk factor for Gr 2 pneumonitis (odds ratio: 1.047, p = 0.303). None of the clinical factors, including sex, age, smoking history, presence of baseline pneumonitis, type of radiation therapy, location of lesion and facility, were risk factors. **CONCLUSIONS:** Our study suggest that the severity of pneumonitis after durvalumab is unrelated to V20 or any of the clinical factors assessed in this study.

[**Systemic Immunostimulatory Effects of Radiation Therapy Improves the Outcomes of Patients With Advanced NSCLC Receiving Immunotherapy.**](#) D'Andrea MA1, Reddy GK. Am J Clin Oncol. 2020 Mar;43(3):218-228. doi: 10.1097/COC.0000000000000651.

The understanding of localized radiation therapy's immunostimulatory properties combined with its well-known effects on the cell cycle and insights into the immunomodulation mechanisms that occur at the

molecular and cellular levels has changed our traditional view of the anticancer effects of ionizing radiation. The potential interactions between the tumor's immune system and radiation therapy have revealed that local radiation has the ability to induce systemic antitumor responses in patients with advanced cancers. The recognition of systemic antitumor effects of radiation therapy has allowed investigators to begin uncovering the integral players in these pathways. Parallel to this, there has been progress in understanding how tumor immunology leads to the development of novel immunotherapies using immune checkpoint blockade therapies in the treatment of advanced cancers. To date there has been limited success in this benefiting only a small fraction of patients. The concept of priming the body's immune system by radiation to make less responsive tumors more responsive to immunotherapy provides an opportunity to explore the use of the combination of radiation therapy and immunotherapy for the treatment of advanced non-small cell lung cancer and other cancers. This article provides an overview of the current state of knowledge of the clinical experience using radiation therapy in combination with immune therapy and discusses the rationale for integrating these 2 modalities in the treatment of advanced non-small cell lung cancer. Available data supports the use of radiation therapy in combination with immunotherapy to achieve improved local and systemic tumor control. Evidence from the early clinical trials has shown that using radiation therapy and immune checkpoint blockade therapies together produces a greater clinical effect than using either modality alone. To maximize the clinical benefit and successful integration of these two modalities as well as optimizing radiation therapy dosing and its schedule, improvement in its field design and the development of reliable predictors of clinical tumor response needs to be established.

SMALL CELL LUNG CANCER - SCLC

Does surgically resected small-cell lung cancer without lymph node involvement benefit from prophylactic cranial irradiation? Lou Y1, Zhong R1, Xu J1, et al. Thorac Cancer. 2020 Mar 6. doi: 10.1111/1759-7714.13381. [Epub ahead of print]
BACKGROUND: It has previously been demonstrated that surgically resected small-cell lung cancer (SCLC) patients could benefit from prophylactic cranial irradiation (PCI). However, PCI in patients without lymph node involvement remains controversial. This study includes a larger sample size to evaluate the benefit of PCI therapy in this specific population. **METHODS:** The records of surgically resected SCLC patients without lymph node involvement (N0M0) in Shanghai Chest Hospital were retrospectively reviewed. **RESULTS:** Between January 2006 and May 2017, a total of 146 cases of surgically resected SCLC without lymph node involvement were included. A total of 46 patients received PCI therapy and 100 patients received no therapy. During the observation period, 12.0% (12/100) of the patients who did not receive PCI therapy developed brain metastases while 10.9% (5/46) of patients who received PCI therapy developed brain metastases. With regard to time to recurrence, no significant difference was observed among the groups (P = 0.798). Moreover, there was no significant difference in either the overall survival benefit (hazard ratio [HR] = 0.84, 95% confidence interval [CI]: 0.49-1.45, P = 0.532) or disease-free survival rate (HR = 0.95, 95% CI: 0.52-1.75, P = 0.864). **CONCLUSIONS:** The evidence obtained does not support PCI therapy in the management of surgically resected SCLC with no lymph node involvement. **KEY POINTS:** Prophylactic cranial irradiation (PCI) remains controversial for resected small-cell lung cancer (SCLC) without lymph node involvement. In this study, the results indicated that PCI does not reduce the risk of cerebral recurrence of resected p-T1-2N0M0 SCLC. This is the largest sample size study focused on PCI in resected p-T1-2N0M0 SCLC. Future revised versions of the guidelines should address this issue.

[**Genomic and pathological heterogeneity in clinically diagnosed small cell lung cancer in never/light smokers identifies therapeutically targetable alterations.**](#) Ogino A1, Choi J1, Lin M1, et al. Mol Oncol. 2020 Mar 19. doi: 10.1002/1878-0261.12673. [Epub ahead of print]

Small cell lung cancer (SCLC) occurs infrequently in never/former light smokers. We sought to study this rare clinical subset through next generation sequencing (NGS) and by characterizing a representative patient derived model. We performed targeted NGS, as well as comprehensive pathological evaluation, in 11 never/former light smokers with clinically diagnosed SCLC. We established a patient derived model from one such patient (DFCI168) harboring an NRASQ61K mutation and characterized the sensitivity of this model to MEK and TORC1/2 inhibitors. Despite the clinical diagnosis of SCLC, the majority (8/11) of cases were either of non-pulmonary origin or of mixed histology and included atypical carcinoid (n=1), mixed non-small cell lung carcinoma (NSCLC) and SCLC (n=4), unspecified poorly differentiated carcinoma, (n=1) or small cell carcinoma from different origins (n=2). RB1 and TP53 mutations were found in 4 and 5 cases, respectively. Predicted driver mutations were detected in EGFR (n=2), NRAS (n=1), KRAS (n=1), BRCA1 (n=1), ATM (n=1) and one case harbored a TMPRSS2-ERG fusion. DFCI168 (NRASQ61K) exhibited marked sensitivity to MEK inhibitors in vitro and in vivo. The combination of MEK and mTORC1/2 inhibitors synergized to prevent compensatory mTOR activation, resulting in prolonged growth inhibition in this model and in three other NRAS-mutant lung cancer cell lines. SCLC in never/former light smokers is rare and is potentially a distinct disease entity comprised of oncogenic driver mutation-harboring carcinomas morphologically and/or clinically mimicking SCLC. Comprehensive pathologic review integrated with genomic profiling is critical in refining the diagnosis and in identifying potential therapeutic options.

[**Oridonin inhibits the migration and epithelial-to-mesenchymal transition of small cell lung cancer cells by suppressing FAK-ERK1/2 signalling pathway.**](#) Xu L1,2,3, Bi Y4, Xu Y1, Zhang Z2, Xu W2, Zhang S2, Chen J2. J Cell Mol Med. 2020 Mar 13. doi: 10.1111/jcmm.15106. [Epub ahead of print]

Small cell lung cancer (SCLC) is a severe malignant with high morbidity; however, few effective and secure therapeutic strategy is used in current clinical practice. Oridonin is a small molecule from the traditional Chinese herb Rabdosia rubescens. This study mainly aimed to investigate the role of oridonin on inhibiting the process of H1688, a kind of small cell lung cancer cells from human. Oridonin could suppress H1688 cell proliferation and induce their apoptosis in a high dosage treatment (20 μmol/L). Meanwhile, cell migration was suppressed by oridonin (5 and 10 μmol/L) that did not affect cell proliferation and apoptosis. The expression level of E-cadherin was significantly increased, and the expression of vimentin, snail and slug was reduced after administration of oridonin. These expression changes were associated with the suppressed integrin β1, phosphorylation of focal adhesion kinase (FAK) and ERK1/2. In addition, oridonin (5 and 10 mg/kg) inhibited tumour growth in a nude mouse model; however, HE staining revealed a certain degree of cytotoxicity in hepatic tissue after treatment oridonin (10 mg/kg). Furthermore, the concentration of alanine aminotransferase (ALP) was significantly increased and lactate dehydrogenase (LDH) was reduced after oridonin treatment (10 mg/kg). Immunohistochemical analysis further revealed that oridonin increased E-cadherin expression and reduced vimentin and phospho-FAK levels in vivo. These findings indicated that oridonin can inhibit the migration and epithelial-to-mesenchymal transition (EMT) of SCLC cells by suppressing the FAK-ERK1/2 signalling pathway. Thus, oridonin may be a new drug candidate to offer an effect of anti-SCLC with relative safety.

[**Nab-paclitaxel Monotherapy for Relapsed Small Cell Lung Cancer: Retrospective Analysis and Review.**](#) Nakao M1, Fujita K2, Suzuki Y2, Arakawa S2, Sakai Y2, Sato H2, Muramatsu H2. Anticancer Res. 2020 Mar;40(3):1579-1585. doi: 10.21873/anticanres.14105.

BACKGROUND/AIM: The utility of nanoparticle albumin-bound paclitaxel (nab-PTX) monotherapy in patients with relapsed small-cell lung cancer (SCLC) has not been fully evaluated. We aimed to investigate the efficacy and safety of nab-PTX monotherapy in relapsed SCLC patients, including heavily treated patients. **PATIENTS AND METHODS:** We retrospectively analysed data from 17 patients with relapsed SCLC who were treated with weekly nab-PTX monotherapy at our hospital. We also reviewed past studies on nab-PTX monotherapy for relapsed SCLC. **RESULTS:** The response rate, progression-free survival, and overall survival were 29.4%, 48 days (95%CI=33-89), and 134 days (95%CI=64-223), respectively. The most common adverse event of grade ≥3 was leukopenia (17.6%), followed by neutropenia, neuropathy, fatigue, and infections. Our results were consistent with previous studies. **CONCLUSION:** The efficacy of nab-PTX monotherapy for heavily treated relapsed SCLC patients might be moderate. Further studies to improve outcomes are warranted.

IRS2 Amplification as a Predictive Biomarker in Response to Ceritinib in Small Cell Lung Cancer.

Lee MS1,2, Jung K1,2, Song JY1, et al. Mol Ther Oncolytics. 2020 Jan 10;16:188-196. doi: 10.1016/j.omto.2019.12.009. eCollection 2020 Mar 27.

Small cell lung cancer (SCLC) is a fast-growing and malignant cancer that responds well to chemotherapy; however, the survival rate is less than 15% after 2 years of diagnosis. Therefore, novel therapeutic agents for treating SCLC patients need to be evaluated. This study aims to identify the therapeutic targets based on the comprehensive genomic profiling of SCLC patients. Among the molecular-profiled SCLC samples obtained using targeted sequencing, the array-based comparative genomic hybridization (array CGH) identified focal insulin receptor substrate 2 (IRS2) amplification in the SCLC patients. IRS2 amplification was confirmed in 5% of 73 SCLC patients. To determine whether IRS2 amplification could act as a therapeutic target, we generated a patient-derived xenograft (PDX) model and subsequently screened 43 targeted agents using the PDX-derived cells (PDCs). Ceritinib significantly inhibited the cell growth and impaired the tumor sphere formation in IRS2-expressing PDCs. Its effects were confirmed in various in vitro assays and were further validated in the mouse xenograft models. In this study, we present that IRS2 amplification and/or expression serve as preclinical implications for a novel therapeutic target in SCLC progression. Furthermore, we suggest that insulin-like growth factor-1 (IGF-1) receptor inhibitor-based therapy could be used for treating SCLC with IRS2 amplification.

PALLIATIVE AND SUPPORTIVE CARE

Psychological stress enhances tumor growth and diminishes radiation response in preclinical model of lung cancer.

Zhang Y1, Zanos P2, Jackson IL3, Zhang X3, Zhu X4, Gould T5, Vujaskovic Z6. Radiother Oncol. 2020 Mar 5;146:126-135. doi: 10.1016/j.radonc.2020.02.004. [Epub ahead of print]

BACKGROUND AND PURPOSE: Patients with life-threatening illnesses, such as cancer, experience emotional distress. This study was to investigate the molecular and cellular mechanisms of relevant psychological stressor on tumor growth and therapeutic resistance. **MATERIALS AND METHODS:** Stress was induced in C57BL/6J mice bearing LLC lung tumors by exposure to a conspecific mice receiving inescapable foot shocks. Mice were irradiated at 7 Gy for 3 consecutive days. Behaviors were monitored by open field test (OFT), elevated plus maze (EPM), sucrose preference test (SPT), and learned helplessness (LH) test. Protein expression in tissues and cultured cells were measured by Western blot. **RESULTS:** This study in animals showed that observing a conspecific mouse receiving foot shocks induced depression like behaviors with increased plasma corticosterone and adrenaline levels which increased tumor growth and radioresistance. Stress increased Wnt1, Drosha, and vimentin expression and decreased E-cadherin expression in tumor tissues. The combination of stress and irradiation enhanced radioresistance along with the increase in vimentin expression. The in vitro study showed that a β2-

adrenergic receptor (β2-AR) agonist blocked irradiation-induced cell apoptosis and decreased cell viability, while silencing β2-AR expression reduced the protective effects of β2-AR agonist. β2-AR agonist obviously increased Wnt1 and Drosha expression in LLC-1 cells. **CONCLUSION:** Psychological stress increased tumor growth and enhanced radioresistance associated with the activation of epithelial-mesenchymal transition by stress hormone-stimulated adrenergic receptors.

[**The Association of Increasing Hospice Use With Decreasing Hospital Mortality: An Analysis of the National Inpatient Sample.**](#) Schorr CA1, Angelo M, John G, LeCompte K, Dellinger RP. J Healthc Manag. 2020 Mar-Apr;65(2):107-120. doi: 10.1097/JHM-D-18-00280.
Usage of hospice services for patients facing life-limiting illness has steadily increased. In these services, hospitals discharge patients to various hospice settings, including the inpatient model, where a patient may remain in the discharging hospital to receive hospice services. In this discharge practice, the patient is considered a hospital survivor and subsequent hospice death. The purpose of the study was to determine if the decline of in-hospital mortality for six common high-volume admission diagnoses could be attributed in part to an increase in discharges to a hospice setting for end-of-life care. In this retrospective study using the National Inpatient Sample database from 2007 to 2011, we identified patients ≥18 years for six acute and chronic diagnoses: heart failure, chronic obstructive pulmonary disease, acute myocardial infarction, acute myocardial infarction with cardiogenic shock, septic shock, and lung neoplasm (cancer). We categorized patients according to their hospital discharge disposition as hospice or in-hospital mortality. A total of 10,458,728 patients met our criteria, of which 2.72% were discharged to hospice and 6.38% died. Compared to patients who died in the hospital, hospice patients were older, had a shorter length of stay, and experienced more comorbidities. Hospice use was more common in Medicare patients, in nonteaching hospitals, and in the South. White individuals were more likely to be discharged to hospice compared to nonwhites. Among the six selected diagnoses over the 5-year period, hospice use rose as observed mortality decreased. Our findings suggest that variability among hospitals in hospice use will affect benchmarked hospital mortality comparisons and could inappropriately reward or penalize hospitals in their public reporting.

[**Concurrent Hospice Care and Cancer-Directed Treatment for Advanced Lung Cancer and Receipt of Aggressive Care at the End of Life in the Veteran's Health Administration.**](#) Presley CJ1, Han L2, O'Leary JR2, et al. J Palliat Med. 2020 Mar 2. doi: 10.1089/jpm.2019.0485. [Epub ahead of print]
BACKGROUND: Aggressive care at the end of life (EOL) is a persistent issue for patients with stage IV nonsmall cell lung cancer (NSCLC). We evaluated the use of concurrent care (CC) with hospice care and cancer-directed treatment simultaneously within the Veteran's Health Administration (VHA) and aggressive care at the EOL. Objective: To determine whether VHA facility-level CC is associated with changes in aggressive care at the EOL. **DESIGN/SETTING:** Veterans with stage IV NSCLC who died between 2006 and 2012 and received lung cancer care within the VHA. Measurements: The primary outcome was aggressive care at EOL (i.e., hospital admissions, chemotherapy, and intensive care unit) within the last month of life. To compare aggressive care across VHA facilities, we used a random intercept multilevel logistic regression model to examine the association between facility-level CC within each study year (<10%, 10% to 19%, and ≥20%) and aggressive care at the EOL among the decedents as a binary outcome. **RESULTS:** In total, 18,371 veterans with NSCLC at 154 VHA facilities were identified. Facilities delivering CC for ≥20% of veterans (high CC) increased from 20.0% in 2006 to 43.2% in 2012 (p < 0.001). Overall, hospice care significantly increased and aggressive care at EOL decreased over the study period. However, facility-level CC adoption was not associated with any difference in aggressive care at EOL (adjusted odds ratio high CC vs. low CC: 0.91 [95% CI, 0.79 to 1.05], p = 0.21). **CONCLUSIONS:** Although the VHA adoption of CC increased hospice use among patients with NSCLC, additional measures may be needed to decrease aggressive care at the EOL.

[Rates of appropriate laxative prophylaxis for opioid-induced constipation in veterans with lung cancer: a retrospective cohort study.](#) Brown TJ1, Keshvani N1, Gupta A2, Yang H3, Agrawal D4,5, Le TC1,6, Gerber DE1,6,7, Alvarez CA8,9,10. Support Care Cancer. 2020 Mar 2. doi: 10.1007/s00520-020-05364-6. [Epub ahead of print]

PURPOSE: Opioid-induced constipation (OIC) is the most common side effect in patient-prescribed opioids for cancer pain treatment. Current guidelines recommend routine prescription of a laxative for preventing OIC in all patients prescribed an opioid unless a contraindication exists. We determined patterns of prescription of laxative agents in patients with lung cancer initiating opioids. **METHODS:** We performed a retrospective cohort study evaluating the prescription of laxatives for OIC to adult patients with incident lung cancer seen in the Veteran's Affairs (VA) system, between January 1, 2003, and December 31, 2016. Exposure to laxative agents was categorized as follows: none, docusate monotherapy, docusate plus another laxative, and other laxatives only. Prevalence of OIC prophylaxis was analyzed using descriptive statistics. Linear regression was performed to identify time trends in the prescription of OIC prophylaxis. **RESULTS:** Overall, 130,990 individuals were included in the analysis. Of these, 87% of patients received inadequate prophylaxis (75% no prophylaxis and 12% docusate alone), while 5% received OIC prophylaxis with the unnecessary addition of docusate to another laxative. Through the study period, laxative prescription significantly decreased, while all other categories of OIC prophylaxis were unchanged. We noted an inverse relationship with OIC prophylaxis and likelihood of a diagnosis of constipation at 3 and 6 months. **CONCLUSIONS:** In this study of veterans with lung cancer, almost 90% received inadequate or inappropriate OIC prophylaxis. Efforts to educate physicians and patients to promote appropriate OIC prophylaxis in combination with systems-level changes are warranted.

COMPLEMENTARY & ALTERNATIVE THERAPY

[Comparing the Efficacy of Integrative Body-Mind-Spirit Intervention With Cognitive Behavioral Therapy in Patient-Caregiver Parallel Groups for Lung Cancer Patients Using a Randomized Controlled Trial](#)

PURPOSES/OBJECTIVES: This paper reports the comparative efficacies of integrative body-mind-spirit intervention (I-BMS) and cognitive behavioral therapy (CBT) in patient-caregiver parallel groups for Chinese patients with lung cancer. **DESIGN:** Randomized controlled trial (RCT). **METHODS:** One hundred and fifty-seven patient-caregiver dyads with no marked functional impairment were randomized into one of the two interventions with eight weekly patient-caregiver parallel groups. Assessments were conducted at baseline, within one, eight- and sixteen-weeks post-intervention. Effects of treatment group across time were analyzed by multilevel modeling. **FINDINGS:** CBT led to greater reduction in emotional vulnerability than I-BMS. I-BMS resulted in greater increase in overall QoL and spiritual self-care, and more reduction in depression than CBT. Patients in both interventions experienced improvement in physical, emotional and spiritual, except social, domains of QoL. **CONCLUSION:** I-BMS was more efficacious for diverse domains of QoL, and CBT was more effective for emotional well-being, despite the relatively small between-group effect sizes. Implications for psychosocial providers/policy: (1) With the expanding repertoire of psychosocial interventions for families facing lung cancer, it has become imperative to investigate the comparative efficacies of empirically supported and culturally adapted interventions. (2) Our findings show that I-BMS was more effective for diverse domains of QoL, while CBT was more efficacious with emotional well-being, although both interventions led to significant improvements in physical, emotional and spiritual domains of patient QoL. (3) Patient-caregiver parallel groups have been shown to be effective for enhancing QoL of Chinese lung cancer patients. (4) Care

professionals are encouraged to dispense interventions based on the idiosyncratic needs and preferences of the patients to maximize the treatment effects.

Adjuvant Chemotherapy with Chinese Herbal Medicine Formulas Versus Placebo in Patients with Lung Adenocarcinoma after Radical Surgery: a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Wang Q#1, Jiao L#1,2, et al. Biol Proced Online. 2020 Mar 1;22:5. doi: 10.1186/s12575-020-00117-5. eCollection 2020.

BACKGROUND: The toxicity and side effects caused by adjuvant chemotherapy (ACT) after radical surgery for lung adenocarcinoma (LAC) lead to early termination frequently. This study was conducted to provide an objective basis for the effect of Chinese herbal medicine formulas (CHMFs) combined with chemotherapy in reducing toxicity and enhancing efficacy of ACT. **METHOD:** From February 17th, 2012 to March 20th, 2015, 233 patients from 7 hospitals diagnosed with LAC in IB~IIIA stage were randomly assigned into ACT + CHMF group (116 patients) and ACT + placebo group (117 patients). CHMF was taken orally until the end of chemotherapy. Chemotherapy-related toxic, side effects were investigated as the primary outcome. Disease-free survival (DFS) and overall survival (OS) were used as the secondary outcome. **RESULTS:** At one week following chemotherapy, the incidence of dry mouth, diarrhea and thrombocytopenia significantly decreased in CHMF group (P = 0.017, P = 0.033, P = 0.019, respectively). At two weeks following chemotherapy, fatigue and diarrhea were more obvious in the placebo group (P = 0.028, P = 0.025, respectively). In addition, patients in the CHMF group showed an increase in median DFS from 37.1 to 51.5 months compared with placebo group although there was no statistical significance (P = 0.16). In the stage IB subgroup, the CHMF group had a significantly better DFS (HR (95% CI) = 0.53 (0.28-0.99), P = 0.046). There was no significant difference in OS between the groups (P = 0.72). **CONCLUSION:** For patients with LAC, ACT combined with CHMF after radical surgery can prolong the DFS time especially in the early stage, and reduces the chemotherapy-related toxic and side effects.

MISCELLANEOUS WORKS

Early Impact of the Affordable Care Act and Medicaid Expansion on Racial and Socioeconomic Disparities in Cancer Care. Mahal AR1, Chavez J2, Yang DD3, et al. Am J Clin Oncol. 2020 Mar;43(3):163-167. doi: 10.1097/COC.0000000000000588.

OBJECTIVES: We sought to evaluate sociodemographic disparities in insurance coverage among nonelderly adults with a common cancer after Affordable Care Act (ACA) implementation. **PATIENTS AND METHODS:** In total, 109,182 patients aged 18 to 64 years diagnosed with a common cancer (lung, breast, or prostate cancer) were identified from 2010 to 2014. Multivariable logistic regressions analyzed associations between ACA implementation and uninsured rates on the basis of state approach to Medicaid expansion, stratified by race (black, white), and income (stratified at 138% Federal Poverty Line). **RESULTS:** Uninsured rates declined after ACA implementation, with the greatest rate reductions associated with traditional Medicaid expansion (Pinteraction <0.001). Racial disparities in insurance coverage were eliminated with traditional Medicaid expansion where the uninsured rate went from 10.0% to 0.95% among black patients (adjusted odds ratio [AOR]pre-aca 1.52 to AORpost-aca 0.47) but persisted with other state approaches (AORpre-aca 1.15 to AORpost-aca 1.12) (Pinteraction =0.002). Furthermore, socioeconomic coverage gaps were eliminated with traditional Medicaid expansion, where the uninsured rate went from 8.4% to 1.4% among low-income (≤138% Federal Poverty Line) patients, but not with other state approaches (Pinteraction <0.001). **CONCLUSIONS:** Traditional Medicaid expansion was associated with the elimination of racial and socioeconomic insurance coverage gaps. These results highlight the potential benefits and challenges of the ACA and its provisions, and could instruct ongoing policy.

[**Trends in Cancer Incidence Among American Indians and Alaska Natives and Non-Hispanic Whites in the United States, 1999-2015.**](#) Gopalani SV1, Janitz AE1, Martinez SA1, Gutman P2, Khan S2, Campbell JE1. Epidemiology. 2020 Mar;31(2):205-213. doi: 10.1097/EDE.0000000000001140. **BACKGROUND:** Female breast, prostate, lung, and colorectal cancers are the leading incident cancers among American Indian and Alaska Native (AI/AN) and non-Hispanic White (NHW) persons in the United States. To understand racial differences, we assessed incidence rates, analyzed trends, and examined geographic variation in incidence by Indian Health Service regions. **METHODS:** To assess differences in incidence, we used age-adjusted incidence rates to calculate rate ratios (RRs) and 95% confidence intervals (CIs). Using joinpoint regression, we analyzed incidence trends over time for the four leading cancers from 1999 to 2015. **RESULTS:** For all four cancers, overall and age-specific incidence rates were lower among AI/ANs than NHWs. By Indian Health Service regions, incidence rates for lung cancer were higher among AI/ANs than NHWs in Alaska (RR: 1.46; 95% CI: 1.37, 1.56) and Northern (RR: 1.29; 95% CI: 1.25, 1.33) and Southern (RR: 1.06; 95% CI: 1.03, 1.09) Plains. Similarly, colorectal cancer incidence rates were higher in AI/ANs than NHWs in Alaska (RR: 2.29; 95% CI: 2.14, 2.45) and Northern (RR: 1.04; 95% CI: 1.00, 1.09) and Southern (RR: 1.11; 95% CI: 1.07, 1.15) Plains. Also, AI/AN women in Alaska had a higher incidence rate for breast cancer than NHW women (RR: 1.05; 95% CI: 1.05, 1.20). From 1999 to 2015, incidence rates for all four cancers decreased in NHWs, but only rates for prostate (average annual percent change: -4.70) and colorectal (average annual percent change: -1.80) cancers decreased considerably in AI/ANs. **CONCLUSION:** Findings from this study highlight the racial and regional differences in cancer incidence.

[**Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study.**](#) Wang Y1, Dong C1, Hu Y1, Li C1, Ren Q1, Zhang X1, Shi H1, Zhou M1. Radiology. 2020 Mar 19:200843. doi: 10.1148/radiol.2020200843. [Epub ahead of print] **BACKGROUND:** CT may play a central role in the diagnosis and management of COVID-19 pneumonia. **PURPOSE:** To perform a longitudinal study to analyze the serial CT findings over time in patients with COVID-19 pneumonia. Materials and Methods During January 16 to February 17, 2020, 90 patients (male:female, 33:57; mean age, 45 years) with COVID-19 pneumonia were prospectively enrolled and followed up until they were discharged or died, or until the end of the study. A total of 366 CT scans were acquired and reviewed by 2 groups of radiologists for the patterns and distribution of lung abnormalities, total CT scores and number of zones involved. Those features were analyzed for temporal change. **RESULTS:** CT scores and number of zones involved progressed rapidly, peaked during illness days 6-11 (median: 5 and 5), and followed by persistence of high levels. The predominant pattern of abnormalities after symptom onset was ground-glass opacity (35/78 [45%] to 49/79 [62%] in different periods). The percentage of mixed pattern peaked (30/78 [38%]) on illness days 12-17, and became the second most predominant pattern thereafter. Pure ground-glass opacity was the most prevalent sub-type of ground-glass opacity after symptom onset (20/50 [40%] to 20/28 [71%]). The percentage of ground-glass opacity with irregular linear opacity peaked on illness days 6-11 (14/50 [28%)]) and became the second most prevalent subtype thereafter. The distribution of lesions was predominantly bilateral and subpleural. 66/70 (94%) patients discharged had residual disease on final CT scans (median CT scores and zones involved: 4 and 4), with ground-glass opacity (42/70 [60%]) and pure ground-glass opacity (31/42 [74%]) the most common pattern and subtype. **CONCLUSION:** The extent of lung abnormalities on CT peaked during illness days 6-11. The temporal changes of the diverse CT manifestations followed a specific pattern, which might indicate the progression and recovery of the illness.