



Caring Ambassadors Lung Cancer Program Literature Review, February 2017

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BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Microfluidic Biopsy Trapping Device for the Real-Time Monitoring of Tumor Microenvironment.](#)

Holton AB1,2,3, Sinatra FL1, Krehling J2, Conway AJ1, Landis DA1, Altiok S2. PLoS One. 2017 Jan 13;12(1):e0169797. doi: 10.1371/journal.pone.0169797. eCollection 2017.

The tumor microenvironment is composed of cellular and stromal components such as tumor cells, mesenchymal cells, immune cells, cancer associated fibroblasts and the supporting extracellular matrix. The tumor microenvironment provides crucial support for growth and progression of tumor cells and affects tumor response to therapeutic interventions. To better understand tumor biology and to develop effective cancer therapeutic agents it is important to develop preclinical platforms that can faithfully recapitulate the tumor microenvironment and the complex interaction between the tumor and its surrounding stromal elements. Drug studies performed in vitro with conventional two-dimensional cancer cell line models do not optimally represent clinical drug response as they lack true tumor heterogeneity and are often performed in static culture conditions lacking stromal tumor components that significantly influence the metabolic activity and proliferation of cells. Recent microfluidic approaches aim to overcome such obstacles with the use of cell lines derived in artificial three-dimensional supportive gels or micro-chambers. However, absence of a true tumor microenvironment and full interstitial flow, leads to less than optimal evaluation of tumor response to drug treatment. Here we report a continuous perfusion microfluidic device coupled with microscopy and image analysis for the assessment of drug effects on intact fresh tumor tissue. We have demonstrated that fine needle aspirate biopsies obtained from patient-derived xenograft models of adenocarcinoma of the lung can successfully be analyzed for their response to ex vivo drug treatment within this biopsy trapping microfluidic device, wherein a protein kinase C inhibitor, staurosporine, was used to assess tumor cell death as a proof of principle. This approach has the potential to study tumor tissue within its intact microenvironment to better understand tumor response to drug treatments and eventually to choose the most effective drug and drug combination for individual patients in a cost effective and timely manner.

LAG-3 Protein Expression in Non-small Cell Lung Cancer and Its Relationship with PD-1/PD-L1 and Tumor-Infiltrating Lymphocytes.

He Y1, Yu H2, Rozeboom L2, Rivard CJ2, Ellison K2, Dziadziuszko R3, Suda K4, Ren S5, Wu C6, Hou L6, Zhou C7, Hirsch FR8. J Thorac Oncol. 2017 Jan 26. pii: S1556-0864(17)30043-6. doi: 10.1016/j.jtho.2017.01.019. [Epub ahead of print]

BACKGROUND: Immunotherapy targeting the programmed death-1 (PD-1) / programmed death ligand-1 (PD-L1) checkpoint has shown promising efficacy in patients with non-small cell lung cancer (NSCLC). Lymphocyte activation gene-3 (LAG-3) is another important checkpoint, and its role in NSCLC is still not clear. In this study, we investigated LAG-3 protein expression and its correlation with PD-1, PD-L1, tumor-infiltrating lymphocytes (TILs), and association with survival in NSCLC.

METHODS: The expression of LAG-3 (EPR4392, Abcam) protein was assessed in 55 NSCLC cell lines by immunohistochemistry (IHC). LAG-3, PD-1 (NAT 105, Cell Marque) and PD-L1 (22C3, Dako) protein expression was evaluated by IHC, and TILs abundance was scored, in 139 surgically resected specimens from patients with NSCLC. We also verified results in 62 untreated NSCLC patient samples, and detected the correlation between LAG-3 expression and EGFR, KRAS mutation as well as EML4-ALK rearrangement. **RESULTS:** LAG-3 was not expressed on any of the 55 NSCLC cell lines. However LAG-3 was expressed on the TILs in 36 (25.9%) patients with NSCLC. 60 patient samples (43.2%) were positive for PD-1 on the TILs, and 25 (18.0%) were positive for PD-L1 on tumor cells. Neither LAG-3 nor PD-1 was expressed on the tumor cells. LAG-3 was over expressed on the TILs in non-adenocarcinoma compared to adenocarcinoma (P=0.031). LAG-3 expression on TILs was significantly correlated to that of PD-1 on TILs (P<0.001), PD-L1 on tumor cells (P=0.041), but not TILs percentage (P=0.244). With the logistic regression model, the odds ratio for LAG-3 was 0.320 (95% CI: 0.110-0.929) and 4.364 (95% CI: 1.898-10.031) when compared non-adenocarcinoma to adenocarcinoma and compared TILs negative PD-1 to positive. Recurrence-free survival (RFS) was significantly different in patients whose TILs were LAG-3 negative as opposed to LAG-3 positive (1.91 years, 95% CI 0.76-3.06, vs. 0.87 years, 95% CI 0.27-1.47, P=0.025). Likewise, LAG-3 status of TILs (negative vs. positive) did significantly affect overall survival (OS) (3.04 years, 95% CI 2.76-3.32 vs. 1.08 years, 95% CI 0.42-1.74, P=0.039). Using Kaplan-Meier analysis, we found that patients with both PD-L1 negative tumor cells and LAG-3 negative TILs have longer RFS than patients who are either PD-L1 or LAG-3 positive or both PD-L1 and LAG-3 positive (2.09 years, 95% CI 0.90-3.28 vs. 1.42 years, 95% CI 0.46-2.34 vs. 0.67 years, 95% CI 0.00-1.45, P=0.007). In verification stage, high expression of LAG-3 was also significantly correlated with higher expression of PD-1 on TILs (P=0.016) and PD-L1 on tumor cells (P=0.014). There was no correlation between LAG-3 expression and EGFR (P=0.325), KRAS mutation (P=1.000), and ALK fusion (P=0.562). **CONCLUSIONS:** LAG-3 expresses on TILs in tumor tissues of some NSCLC patients. Its expression was higher in non-adenocarcinoma and was correlated with PD-1/PD-L1 expression. LAG-3 positive or both LAG-3 and PD-L1 positive was correlated with early postoperative recurrence. LAG-3 was related to poor prognostic.

Patient-Derived Xenograft Models of Non-Small Cell Lung Cancer and Their Potential Utility in Personalized Medicine.

Morgan KM1, Riedlinger GM2, Rosenfeld J2, Ganesan S3, Pine SR3. Front Oncol. 2017 Jan 19;7:2. doi: 10.3389/fonc.2017.00002. eCollection 2017.

Traditional preclinical studies of cancer therapeutics have relied on the use of established human cell lines that have been adapted to grow in the laboratory and, therefore, may deviate from the cancer they were meant to represent. With the emphasis of cancer drug development shifting from non-specific cytotoxic agents to rationally designed molecularly targeted therapies or immunotherapy comes the need for better models with predictive value regarding therapeutic activity and response in clinical trials. Recently, the diversity and accessibility of immunodeficient mouse strains has greatly enhanced the production and utility of patient-derived xenograft (PDX) models for many tumor types, including non-small cell lung cancer (NSCLC). Combined with next-generation sequencing, NSCLC PDX mouse models offer an

exciting tool for drug development and for studying targeted therapies while utilizing patient samples with the hope of eventually aiding in clinical decision-making. Here, we describe NSCLC PDX mouse models generated by us and others, their ability to reflect the parental tumors' histomorphological characteristics, as well as the effect of clonal selection and evolution on maintaining genomic integrity in low-passage PDXs compared to the donor tissue. We also raise vital questions regarding the practical utility of PDX and humanized PDX models in predicting patient response to therapy and make recommendations for addressing those questions. Once collaborations and standardized xenotransplantation and data management methods are established, NSCLC PDX mouse models have the potential to be universal and invaluable as a preclinical tool that guides clinical trials and standard therapeutic decisions.

[Propofol inhibits lung cancer cell viability and induces cell apoptosis by upregulating microRNA-486 expression.](#) Yang N1, Liang Y2, Yang P1, Yang T1, Jiang L1. *Braz J Med Biol Res.* 2017 Jan 5;50(1):e5794. doi: 10.1590/1414-431X20165794.

Propofol is a frequently used intravenous anesthetic agent. Recent studies show that propofol exerts a number of non-anesthetic effects. The present study aimed to investigate the effects of propofol on lung cancer cell lines H1299 and H1792 and functional role of microRNA (miR)-486 in these effects. H1299 and/or H1792 cells were treated with or without propofol and transfected or not with miR-486 inhibitor, and then cell viability and apoptosis were analyzed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and flow cytometry. The expression of miR-486 was determined by quantitative real-time polymerase chain reaction (qRT-PCR) with or without propofol treatment. Western blot was performed to analyze the protein expression of Forkhead box, class O (FOXO) 1 and 3, Bcl-2 interacting mediator of cell death (Bim), and pro- and activated caspases-3. Results showed that propofol significantly increased the miR-486 levels in both H1299 and H1792 cells compared to untreated cells in a dose-dependent manner ($P < 0.05$ or $P < 0.01$). Propofol statistically decreased cell viability but increased the percentages of apoptotic cells and protein expressions of FOXO1, FOXO3, Bim, and pro- and activated caspases-3; however, miR-486 inhibitor reversed the effects of propofol on cell viability, apoptosis, and protein expression ($P < 0.05$ or $P < 0.01$). **In conclusion**, propofol might be an ideal anesthetic for lung cancer surgery by effectively inhibiting lung cancer cell viability and inducing cell apoptosis. Modulation of miR-486 might contribute to the anti-tumor activity of propofol.

[Increased Expression of Long Non-Coding RNA BCAR4 Is Predictive of Poor Prognosis in Patients with Non-Small Cell Lung Cancer.](#) Gong J1, Zhang H, He L, Wang L, Wang J. *Tohoku J Exp Med.* 2017;241(1):29-34. doi: 10.1620/tjem.241.29.

Lung cancer is the most common human cancer, and the majority of lung cancer cases are categorized as non-small cell lung cancer (NSCLC). Long non-coding RNAs (lncRNAs) play key roles in the development and progression of human cancers. LncRNA breast cancer anti-estrogen resistance 4 (BCAR4) has been identified as an oncogenic lncRNA involved in the progression of breast cancer and osteosarcoma. However, the clinical significance of the lncRNA BCAR4 in NSCLC remains largely unclear. In the present study, real-time quantitative reverse transcriptase-polymerase chain reaction was used to examine the relative level of lncRNA BCAR4 in 68 cases of NSCLC tissues and their adjacent non-tumor tissues. Our data showed that the expression level of lncRNA BCAR4 was significantly higher in NSCLC tissues compared to their matched non-tumor tissues. Moreover, BCAR4 expression was significantly upregulated in NSCLC cell lines, when compared to the normal human bronchial epithelial cell line BEAS-2B. In addition, the BCAR4 expression was associated with the lymph node metastasis, distant metastasis and clinical stage, but not with the age, sex, tumor size, histological grade, and histological type. The increased expression of BCAR4 was significantly associated with poorer 5-year overall survival rate of NSCLC patients. Multivariate survival analysis indicated that BCAR4 was an

independent prognostic factor for NSCLC patients. Taken together, our study suggests that the upregulation of lncRNA BCAR4 expression plays a promoting role in the malignant progression of NSCLC. Thus, BCAR4 is a potential biomarker for NSCLC progress and a therapeutic target for NSCLC.

[Puerarin inhibits M2 polarization and metastasis of tumor-associated macrophages from NSCLC xenograft model via inactivating MEK/ERK 1/2 pathway.](#) Kang H1, Zhang J1, Wang B1, Liu M1, Zhao J1, Yang M1, Li Y2. *Int J Oncol.* 2017 Feb;50(2):545-554. doi: 10.3892/ijo.2017.3841. Epub 2017 Jan 5.

Non-small cell lung carcinoma (NSCLC) metastasis is responsible for most of cancer-related mortality. The tumor associated macrophages (TAMs) are known to be crucial cells in lung cancer and are usually divided into two antagonistic types, M1 and M2. Puerarin has a wide spectrum of pharmacological properties. The present study explores puerarin on macrophage polarization and metastasis of NSCLC. The results demonstrated that puerarin inhibited tumor growth and tumor volumes in NSCLC xenograft model, increased M1 markers [CD197+, inducible nitric oxide synthase (iNOS)+, CD40+] and reduced M2 markers (CD206+, Arg-1+ and CD163+). Besides, puerarin elevated the level of pro-inflammatory cytokine interferon (IFN)- γ , tumor necrosis factor (TNF)- α and interleukin (IL)-12, decreased the expression of pro-tumor cytokines IL-10, IL-4 and transforming growth factor (TGF)- β . To explore whether puerarin directly acts on macrophages, we purified macrophages from NSCLC model, the results showed that puerarin inhibited macrophages polarized to M2 phenotype and did not require the auxiliary of other cells. In addition, puerarin suppressed the invasion and migration of NSCLC macrophages, restrained the expression of angiogenesis factors. Puerarin also inhibited the activation of mitogen-activated extracellular signal-regulated kinase (MEK)/extracellular signal-regulated kinase (ERK) 1/2 pathway through inhibition of ERK nucleus translocation. Finally, IL-4 induced M2 macrophage polarization and metastasis were partially offset by puerarin through inactivating the MEK/ERK 1/2 pathway. Taken together, this study validated that puerarin is able to skew macrophage populations back to M1 subsets to stimulate antitumor effects and suggests puerarin is a negative metastatic regulator of NSCLC.

SCREENING, DIAGNOSIS AND STAGING

[Diagnostic Yield for Cancer and Diagnostic Accuracy of Computed Tomography-guided Core Needle Biopsy of Subsolid Pulmonary Lesions.](#) Munir S1, Koppikar S, Hopman WM, Boag AH, Dhillon G, Salahudeen SR, Nolan RL, Flood J. *J Thorac Imaging.* 2017 Jan;32(1):50-56. doi: 10.1097/RTI.0000000000000245.

PURPOSE: We aimed to determine the diagnostic yield for cancer and diagnostic accuracy of computed tomography-guided core needle biopsy (CTNB) in subsolid pulmonary lesions. **MATERIALS AND METHODS:** Fifty-two biopsies of 52 subsolid lesions in 51 patients were identified from a database of 912 lung biopsies and analyzed for the diagnostic yield for cancer and diagnostic accuracy of core CTNB diagnosis as well as complication rates. **RESULTS:** When indeterminate biopsy results were included in the analysis, the diagnostic yield for cancer was 80.8% and the diagnostic accuracy of core needle biopsy was 84.6% (n=52). It was 85.7% and 91.7%, respectively, when indeterminate results were excluded (n=48) and 82.4% and 82.4%, respectively, for biopsies with surgical confirmation (n=17). Attenuation was statistically significant for diagnostic yield for cancer (P=0.028) and diagnostic accuracy of core needle biopsy (P=0.001) when the indeterminate results were excluded (n=48). Attenuation and size were not statistically significant for diagnostic yield for cancer and diagnostic accuracy of needle biopsy (n=52), and size was not statistically significant for either when the indeterminate results were excluded. These results were achieved without any major complications as per the Society of Interventional Radiology Standards of Practice. **CONCLUSIONS:** CTNB offers a high yield in establishing a

histopathologic diagnosis of subsolid pulmonary lesions, with both ground-glass and solid-predominance. The pure ground-glass category of lesions requires further research to determine the true diagnostic yield and diagnostic accuracy of core needle biopsies.

[Accuracy of transbronchial biopsy as a rebiopsy method for patients with relapse of advanced non-small-cell lung cancer after systemic chemotherapy.](#) Ishii H1, Azuma K1, Yamada K1, Matsuo N1, Nakamura M1, Tokito T1, Kinoshita T1, Hoshino T1.

BMJ Open Respir Res. 2017 Jan 10;4(1):e000163. doi: 10.1136/bmjresp-2016-000163. eCollection 2017.

INTRODUCTION: Rebiopsy in patients with advanced non-small-cell lung cancer (NSCLC) resistant to systemic chemotherapy may yield information on the mechanisms of resistance and planning of subsequent treatment. Transbronchial biopsy (TBB) using a flexible bronchoscope has been commonly used for establishing the initial diagnosis of lung cancer. The aim of this study was to assess the accuracy and safety of TBB in patients with NSCLC relapse, and the factors affecting its diagnostic yield.

METHODS: We retrospectively screened patients with advanced NSCLC who underwent TBB for rebiopsy after developing resistance to systemic chemotherapy at Kurume University Hospital between January 2012 and June 2016. A positive diagnostic result obtained by TBB was defined as malignancy determined on the basis of histological features that were adequate for mutational analysis or immunohistochemistry. Severe postprocedural complications were defined as those requiring invasive medical procedures or prolonged hospitalisation. **RESULTS:** 109 patients were enrolled in this retrospective study. Adequate tumour samples were collected from 88 of these patients, giving a high diagnostic yield of 80.7%. The diagnostic yield of TBB was not associated with tumour mutational status, the previous treatment regimen, or efficacy of the previous treatment. There were no severe postprocedural complications such as pneumothorax or serious haemorrhage. **CONCLUSIONS:** TBB is considered one of the safest and most useful procedures for rebiopsy of NSCLC that has relapsed after chemotherapy, regardless of patient background and treatment history.

[Percutaneous Lung Biopsy in the Molecular Profiling Era: A Survey of Current Practices.](#) Lee C1, Guichet PL, Abtin F. J Thorac Imaging. 2017 Jan;32(1):63-67. doi: 10.1097/RTI.0000000000000237.

PURPOSE: This study aimed to assess the current practice patterns of radiologists performing percutaneous lung biopsies. **MATERIALS AND METHODS:** This cross-sectional study used a web-based survey sent to the Society of Thoracic Radiology membership from August to October 2015. Responses were collected anonymously, and results were tallied. **RESULTS:** A total of 244 Society of Thoracic Radiology members responded to the survey. One hundred thirty-seven radiologists regularly perform percutaneous lung biopsies, of whom 102 (74%) practice at an academic teaching hospital. Computed tomography (CT) and CT fluoroscopy were the modalities of choice for image guidance, preferred by 82 (60%) and 48 (35%) respondents, respectively. Twenty (15%) respondents preferred fine-needle aspiration (FNA) alone, 57 (42%) preferred core needle biopsy (CNB) alone, and 59 (43%) preferred both FNA and CNB in the same setting. On-site cytology was routinely requested by 70 (71%) respondents with access to such services. In cases of suspected lung cancer, 79 (60%) respondents estimated sending tissue for molecular analysis >25% of the time. Forty-three (32%) respondents reported using intraprocedural preventive measures to minimize risk of pneumothorax. **CONCLUSIONS:** Among surveyed radiologists who perform percutaneous lung biopsies, most utilize CT guidance with either CNB alone or in conjunction with FNA. A small minority routinely performs FNA alone, which may negatively impact diagnostic accuracy and provide insufficient tissue for molecular profiling. Education of all radiologists regarding the importance of routinely acquiring and sending greater amounts of tissue for molecular/genomic assessment of suspected lung cancer is needed.

[Management of stage I and II nonsmall cell lung cancer.](#) McDonald F1,2, De Waele M3,2, Hendriks LE4,2, Faivre-Finn C5,6, Dingemans AC4, Van Schil PE7. Eur Respir J. 2017 Jan 3;49(1). pii: 1600764. doi: 10.1183/13993003.00764-2016. Print 2017 Jan.

The incidence of stage I and II nonsmall cell lung cancer is likely to increase with the ageing population and introduction of screening for high-risk individuals. Optimal management requires multidisciplinary collaboration. Local treatments include surgery and radiotherapy and these are currently combined with (neo)adjuvant chemotherapy in specific cases to improve long-term outcome. Targeted therapies and immunotherapy may also become important therapeutic modalities in this patient group. For resectable disease in patients with low cardiopulmonary risk, complete surgical resection with lobectomy remains the gold standard. Minimally invasive techniques, conservative and sublobar resections are suitable for a subset of patients. Data are emerging that radiotherapy, especially stereotactic body radiation therapy, is a valid alternative in compromised patients who are high-risk candidates for surgery. Whether this is also true for good surgical candidates remains to be evaluated in randomised trials. In specific subgroups adjuvant chemotherapy has been shown to prolong survival; however, patient selection remains important. Neoadjuvant chemotherapy may yield similar results as adjuvant chemotherapy. The role of targeted therapies and immunotherapy in early stage nonsmall cell lung cancer has not yet been determined and results of randomised trials are awaited.

[Targeting ALK: Precision Medicine Takes on Drug Resistance.](#) Lin JJ1, Riely GJ2, Shaw AT3. Cancer Discov. 2017 Jan 25. doi: 10.1158/2159-8290.CD-16-1123. [Epub ahead of print]

Anaplastic lymphoma kinase (ALK) is a validated molecular target in several ALK-rearranged malignancies, including non-small cell lung cancer. However, the clinical benefit of targeting ALK using tyrosine kinase inhibitors (TKI) is almost universally limited by the emergence of drug resistance. Diverse mechanisms of resistance to ALK TKIs have now been discovered, and these basic mechanisms are informing the development of novel therapeutic strategies to overcome resistance in the clinic. In this review, we summarize the current successes and challenges of targeting ALK. **SIGNIFICANCE:** Effective long-term treatment of ALK-rearranged cancers requires a mechanistic understanding of resistance to ALK TKIs so that rational therapies can be selected to combat resistance. This review underscores the importance of serial biopsies in capturing the dynamic therapeutic vulnerabilities within a patient's tumor and offers a perspective into the complexity of on-target and off-target ALK TKI resistance mechanisms. Therapeutic strategies that can successfully overcome, and potentially prevent, these resistance mechanisms will have the greatest impact on patient outcome.

[A comparison of FLT to FDG PET/CT in the early assessment of chemotherapy response in stages IB-IIIa resectable NSCLC.](#)

Crandall JP1, Tahari AK2, Juergens RA3, et al. EJNMMI Res. 2017 Dec;7(1):8. doi: 10.1186/s13550-017-0258-3. Epub 2017 Jan 19.

BACKGROUND: The aim of this study was to compare the percentage change in 18F-fluorothymidine (FLT) standard uptake value (SUV) between baseline and after one cycle of chemotherapy in patients categorized by RECIST 1.1 computed tomography (CT) as responders or non-responders after two cycles of therapy. Change in 18F-fluorodeoxyglucose (FDG) uptake was also compared between these time points. Nine patients with newly diagnosed, operable, non-small cell lung cancer (NSCLC) were imaged with FDG positron emission tomography/CT (PET), FLT PET/CT, and CT at baseline, following one cycle of neoadjuvant therapy (75 mg/m² docetaxel + 75 mg/m² cisplatin), and again after the second cycle of therapy. All patients had a biopsy prior to enrollment and underwent surgical resection within 4 weeks of post-cycle 2 imaging. **RESULTS:** Between baseline and post-cycle 1, non-responders had mean SULmax (maximum standard uptake value adjusted for lean body mass) increases of 7.0 and 3.4% for FDG and FLT, respectively. Responders had mean decreases of 44.8 and 32.0% in FDG and FLT

SULmax, respectively, between baseline and post-cycle 1 imaging. On post-cycle 1 imaging, primary tumor FDG SUL values were significantly lower in responders than in non-responders ($P = 0.016$). Primary tumor FLT SUL values did not differ significantly between these groups. Using the change from baseline to post-cycle 1, receiver-operating characteristic (ROC) analysis showed an area under the curve (AUC) of 0.94 for FDG and 0.78 for FLT in predicting anatomic tumor response after the second cycle of therapy. **CONCLUSIONS:** Fractional decrease in FDG SULmax from baseline to post-cycle 1 imaging was significantly different between anatomic responders and non-responders, while percentage changes in FLT SULmax were not significantly different between these groups over the same period of time.

[Implementation of Lung Cancer Screening in the Veterans Health Administration.](#) Kinsinger LS1, Anderson C2, Kim J1, et al. JAMA Intern Med. 2017 Jan 30. doi: 10.1001/jamainternmed.2016.9022. [Epub ahead of print]

IMPORTANCE: The US Preventive Services Task Force recommends annual lung cancer screening (LCS) with low-dose computed tomography for current and former heavy smokers aged 55 to 80 years. There is little published experience regarding implementing this recommendation in clinical practice. **OBJECTIVES:** To describe organizational- and patient-level experiences with implementing an LCS program in selected Veterans Health Administration (VHA) hospitals and to estimate the number of VHA patients who may be candidates for LCS. **DESIGN, SETTING, AND PARTICIPANTS:** This clinical demonstration project was conducted at 8 academic VHA hospitals among 93 033 primary care patients who were assessed on screening criteria; 2106 patients underwent LCS between July 1, 2013, and June 30, 2015. **INTERVENTIONS:** Implementation Guide and support, full-time LCS coordinators, electronic tools, tracking database, patient education materials, and radiologic and nodule follow-up guidelines. **MAIN OUTCOMES AND MEASURES:** Description of implementation processes; percentages of patients who agreed to undergo LCS, had positive findings on results of low-dose computed tomographic scans (nodules to be tracked or suspicious findings), were found to have lung cancer, or had incidental findings; and estimated number of VHA patients who met the criteria for LCS. **RESULTS:** Of the 4246 patients who met the criteria for LCS, 2452 (57.7%) agreed to undergo screening and 2106 (2028 men and 78 women; mean [SD] age, 64.9 [5.1] years) underwent LCS. Wide variation in processes and patient experiences occurred among the 8 sites. Of the 2106 patients screened, 1257 (59.7%) had nodules; 1184 of these patients (56.2%) required tracking, 42 (2.0%) required further evaluation but the findings were not cancer, and 31 (1.5%) had lung cancer. A variety of incidental findings, such as emphysema, other pulmonary abnormalities, and coronary artery calcification, were noted on the scans of 857 patients (40.7%). **CONCLUSIONS AND RELEVANCE:** It is estimated that nearly 900 000 of a population of 6.7 million VHA patients met the criteria for LCS. Implementation of LCS in the VHA will likely lead to large numbers of patients eligible for LCS and will require substantial clinical effort for both patients and staff.

[Medical Oncologists' Experiences in Using Genomic Testing for Lung and Colorectal Cancer Care.](#)

Gray SW1, Kim B1, Sholl L1, et al. Oncol Pract. 2017 Jan 17;JOP2016016659. doi: 10.1200/JOP.2016.016659. [Epub ahead of print]

PURPOSE: Genomic testing improves outcomes for many at-risk individuals and patients with cancer; however, little is known about how genomic testing for non-small-cell lung cancer (NSCLC) and colorectal cancer (CRC) is used in clinical practice. **PATIENTS AND METHODS:** In 2012 to 2013, we surveyed medical oncologists who care for patients in diverse practice and health care settings across the United States about their use of guideline- and non-guideline-endorsed genetic tests. Multivariable regression models identified factors that are associated with greater test use. **RESULTS:** Of oncologists, 337 completed the survey (participation rate, 53%). Oncologists reported higher use of guideline-endorsed tests (eg, KRAS for CRC; EGFR for NSCLC) than non-guideline-endorsed tests (eg, Onco typeDX

Colon; ERCC1 for NSCLC). Many oncologists reported having no patients with CRC who had mismatch repair and/or microsatellite instability (24%) or germline Lynch syndrome (32%) testing, and no patients with NSCLC who had ALK testing (11%). Of oncologists, 32% reported that five or fewer patients had KRAS and EGFR testing for CRC and NSCLC, respectively. Oncologists, rather than pathologists or surgeons, ordered the vast majority of tests. In multivariable analyses, fewer patients in nonprofit integrated health care delivery systems underwent testing than did patients in hospital or office-based single-specialty group settings (all $P < .05$). High patient volume and patient requests (CRC only) were also associated with higher test use (all $P < .05$). **CONCLUSION:** Genomic test use for CRC and NSCLC varies by test and practice characteristics. Research in specific clinical contexts is needed to determine whether the observed variation reflects appropriate or inappropriate care. One potential way to reduce unwanted variation would be to offer widespread reflexive testing by pathology for guideline-endorsed predictive somatic tests.

The Emerging Role of "Liquid Biopsies," Circulating Tumor Cells, and Circulating Cell-Free Tumor DNA in Lung Cancer Diagnosis and Identification of Resistance Mutations. Esposito A1, Criscitiello C1, Trapani D1, Curigliano G2. *Curr Oncol Rep.* 2017 Jan;19(1):1. doi: 10.1007/s11912-017-0564-y.

Therapeutic advances in the treatment of lung cancer are in part due to a more complete understanding of its genomic portrait. The serial monitoring of tumor genotypes, which are unstable and prone to changes under selective pressure, is becoming increasingly needed. Although tumor biopsies remain the reference standard for the diagnosis and genotyping of lung cancer, they are invasive and not always feasible. The "liquid biopsies" have the potential to overcome many of these hurdles, allowing a rapid and accurate identification of de novo and resistant genetic alterations and a real-time monitoring of treatment responses. In this review, we provide insights into new liquid diagnostic platforms and discuss the role of circulating tumor cells and circulating tumor DNA in the diagnosis and identification of resistance mutations in lung cancer.

Preoperative Localization of Lung Nodules With Fiducial Markers: Feasibility and Technical Considerations. Sharma A1, McDermott S2, Mathisen DJ3, Shepard JO2. *Ann Thorac Surg.* 2017 Jan 25. pii: S0003-4975(16)31465-5. doi: 10.1016/j.athoracsur.2016.09.112. [Epub ahead of print]

BACKGROUND: The purpose of this study was to determine whether computed tomography-guided fiducial placement is a feasible and safe localization procedure to aid resection of small pulmonary nodules. **METHODS:** A retrospective review was performed of 20 nodules (mean size 11 mm; range, 6 to 19 mm) referred for preoperative computed tomography-guided fiducial placement in 19 patients (average age 64 ± 11 years; 13 women and 6 men). **RESULTS:** The technical success rate for the placement of fiducials was 95%, with deployment of fiducials into the pleural space in 1 case. Biopsy specimen was obtained at time of the fiducial placement in 4 cases, with sensitivity of 75% and specificity of 100% for malignancy. Two procedures (10%) were complicated by a pneumothorax requiring chest tube placement. The median time between fiducial placement and surgery was 7 days (range, 1 to 123). One to four fiducials were placed a median distance of 0 mm (range, 0 to 7 mm) from the edge of the nodule. Fiducials were identified by on-table fluoroscopy in all cases, and all nodules were completely excised with negative surgical margins. Mean fluoroscopy time was 46 seconds, and mean radiation dose was 12.97 mGy. The final diagnosis was primary lung cancer in 85% of cases, with organizing pneumonia and sarcoidosis accounting for the three benign nodules. **CONCLUSIONS:** Computed tomography-guided fiducial placement is a feasible and safe technique that allows biopsy at the time of the procedure and aids localization of small pulmonary nodules during video-assisted thoracic surgery.

[A qualitative study exploring why individuals opt out of lung cancer screening.](#) Carter-Harris L1, Brandzel S2, Wernli KJ2, Roth JA3, Buist DS2. Fam Pract. 2017 Jan 24. pii: cmw146. doi: 10.1093/fampra/cmw146. [Epub ahead of print]

BACKGROUND: Lung cancer screening with annual low-dose computed tomography is relatively new for long-term smokers in the USA supported by a US Preventive Services Task Force Grade B recommendation. As screening programs are more widely implemented nationally and providers engage patients about lung cancer screening, it is critical to understand behaviour among high-risk smokers who opt out to improve shared decision-making processes for lung cancer screening. **OBJECTIVE:** The purpose of this study was to explore the reasons for screening-eligible patients' decisions to opt out of screening after receiving a provider recommendation. **METHODS:** Semi-structured qualitative telephone interviews were performed with 18 participants who met lung cancer screening criteria for age, smoking and pack-year history in Washington State from November 2015 to January 2016. Two researchers with cancer screening and qualitative methodology expertise conducted data analysis using thematic content analytic procedures from audio-recorded interviews. **RESULTS:** Five primary themes emerged for reasons of opting out of lung cancer screening: (i) Knowledge Avoidance; (ii) Perceived Low Value; (iii) False-Positive Worry; (iv) Practical Barriers; and (v) Patient Misunderstanding. **CONCLUSION:** The participants in our study provided insight into why some patients make the decision to opt out of low-dose computed tomography screening, which provides knowledge that can inform intervention development to enhance shared decision-making processes between long-term smokers and their providers and decrease decisional conflict about screening.

[Liquid biopsy for early detection of lung cancer.](#) Hofman P1. Curr Opin Oncol. 2017 Jan;29(1):73-78.

PURPOSE OF REVIEW: The possibility of complete recovery for a lung cancer patient depends on very early diagnosis, as it allows total surgical resection. Screening for this cancer in a high-risk population can be performed using a radiological approach, but this holds a certain number of limitations. Liquid biopsy could become an alternative and complementary screening approach to chest imaging for early diagnosis of lung cancer. **RECENT FINDINGS:** Several circulating biomarkers indicative of lung cancer can be investigated in blood, such as circulating tumor cells, circulating free nucleic acids (RNA and DNA) and proteins. However, none of these biomarkers have yet been adopted in routine clinical practice and studies are ongoing to confirm or not the usefulness and practical interest in routine early diagnosis and screening for lung cancers. **SUMMARY:** Several potential circulating biomarkers for the early detection of lung cancer exist. When coupled to thoracic imaging, these biomarkers must give diagnosis of a totally resectable lung cancer and potentially provide new recommendations for surveillance by imagery of high-risk populations without a detectable nodule. Optimization of the specificity and sensitivity of the detection methods as well as standardization of the techniques is essential before considering for daily practice a liquid biopsy as an early diagnostic tool, or possibly as a predictive test, of lung cancer.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[Comparison of segmentectomy and lobectomy in stage IA adenocarcinomas >1 and ≤2 cm: a brief report.](#) Zhao ZR1, Situ DR2, Lau RW1, Mok TS3, Chen GG1, Underwood MJ1, Ng CS4. J Thorac Oncol. 2017 Jan 19. pii: S1556-0864(17)30036-9. doi: 10.1016/j.jtho.2017.01.012. [Epub ahead of print]

INTRODUCTION: Recent studies have suggested that segmentectomy may be an acceptable alternative treatment to lobectomy, for surgical management of smaller lung adenocarcinomas. The objective of this

study was to compare survival after lobectomy and segmentectomy among patients with pathological stage IA adenocarcinoma categorized as the new T1b (>10 to ≤20 mm) according to the eighth TNM system. **METHODS:** In total, 7,989 patients were identified from the Surveillance, Epidemiology, and End Results registry. Propensity scores, generated from logistic regression on preoperative characteristics, were used to balance the selection bias of undergoing segmentectomy. Overall and lung cancer-specific survival of patients undergoing segmentectomy and lobectomy were compared in propensity score-matched groups. **RESULTS:** Overall, 564 (7.1%) patients underwent segmentectomy. Lobectomy led to better overall and lung cancer-specific survival than segmentectomy for the entire cohort (log-rank $P < 0.01$). After 1:2 propensity score matching, segmentectomy ($n = 552$) was no longer associated with significant worse overall (5-year survival: 74.45% versus 76.67%, hazard ratio: 1.09, 95% confidence interval: 0.90-1.33) or lung cancer-specific (5-year survival: 83.89% versus 86.11%, hazard ratio: 1.12, 95% confidence interval: 0.86-1.46) survival compared with lobectomy ($n = 1,085$) after adjusting for age, sex, lymph node quantity, and histology. Similar negative findings were identified when stratifying patients according to sex, age, histology, and number of evaluated lymph nodes. **CONCLUSIONS:** Segmentectomy may have survival outcomes not different than some patients who received lobectomy for pathological stage IA adenocarcinomas that are >10 and ≤20 mm in size. These results should be further confirmed via prospective randomised trials.

[Defining the Ideal Time Interval Between Planned Induction Therapy and Surgery for Stage IIIA Non-Small Cell Lung Cancer.](#)

Samson P1, Crabtree TD1, Robinson CG2, Morgensztern D3, Broderick S4, Krupnick AS1, Kreisel D1, Patterson GA1, Meyers B1, Puri V5. *Ann Thorac Surg.* 2017 Jan 19. pii: S0003-4975(16)31305-4. doi: 10.1016/j.athoracsur.2016.09.053. [Epub ahead of print]

BACKGROUND: Induction therapy leads to significant improvement in survival for selected patients with stage IIIA non-small cell lung cancer. The ideal time interval between induction therapy and surgery remains unknown. **METHODS:** Clinical stage IIIA non-small cell lung cancer patients receiving induction therapy and surgery were identified in the National Cancer Database. Delayed surgery was defined as greater than or equal to 3 months after starting induction therapy. A logistic regression model identified variables associated with delayed surgery. Cox proportional hazards modeling and Kaplan-Meier analysis were performed to evaluate variables independently associated with overall survival. **RESULTS:** From 2006 to 2010, 1,529 of 2,380 (64.2%) received delayed surgery. Delayed surgery patients were older (61.2 ± 10.0 years versus 60.3 ± 9.2 ; $p = 0.03$), more likely to be non-Caucasian (12.4% versus 9.7%; $p = 0.046$), and less likely to have private insurance (50% versus 58.2%; $p = 0.002$). Delayed surgery patients were also more likely to have a sublobar resection (6.3% versus 2.9%). On multivariate analysis, age greater than 68 years (odds ratio [OR], 1.37; 95% confidence interval [CI], 1.1 to 1.7) was associated with delayed surgery, whereas Caucasian race (OR, 0.75; 95% CI, 0.57 to 0.99) and private insurance status (OR, 0.82; 95% CI, 0.68 to 0.99) were associated with early surgery. Delayed surgery was associated with higher risk of long-term mortality (hazard ratio, 1.25; 95% CI, 1.07 to 1.47). **CONCLUSIONS:** Delayed surgery after induction therapy for stage IIIA lung cancer is associated with shorter survival, and is influenced by both social and physiologic factors. Prospective work is needed to further characterize the relationship between patient comorbidities and functional status with receipt of timely surgery.

[Video-Assisted Thoracic Surgery in Patients With Previous Sternotomy and Cardiac Surgery.](#)

Serna-Gallegos DR1, Merry HE, McKenna RJ Jr. *Innovations (Phila).* 2017 Jan/Feb;12(1):15-20. doi: 10.1097/IMI.0000000000000344.

OBJECTIVE: Although video-assisted thoracic surgery (VATS) lobectomy has become a standard approach for early-stage 1 lung cancer, concerns exist regarding potential damage to the heart or bypass

grafts when VATS is performed after cardiac surgery via median sternotomy. We could find only case reports regarding VATS lobectomy after sternotomy for cardiac surgery. Therefore, we reviewed our series of patients who underwent VATS anatomic resections after sternotomy for cardiac surgery.

METHODS: Between 1996 and 2010, there were 87 patients who underwent 88 pulmonary resections after sternotomy for coronary artery bypass grafting (64), valve replacement or repair (12), coronary artery bypass graft and valve replacement (6), and transplant (5). There were 10 women (11.5%) and 77 men (88.5%) with a mean age of 76.2 years. Diagnoses included lung cancer (83), pulmonary metastases (4), and benign disease (1). **RESULTS:** Dense adhesions between the lung and the mediastinum sometimes occur after cardiac surgery. Compared with the total series of 2684 VATS lobectomies, operations after sternotomy are associated with greater mortality (12, 0.4% vs 5, 5.7%), myocardial infarction (13, 0.5% vs 2, 2.3%), transfusion (45, 1.7% vs 12, 13.6%), conversion to thoracotomy (188, 7% vs 14, 15.9%). Injury occurred to the left main pulmonary artery (1, 1%) and internal mammary artery graft (1, 1%). There were no intraoperative deaths. **CONCLUSIONS:** Previous sternotomy for cardiac surgery does increase the risk for VATS lobectomy. Conversion to thoracotomy should be considered if dense adhesions are found. Techniques to reduce the risk for the heart are discussed.

PMID: 28106619 [PubMed - in process]

[The Role of Extent of Surgical Resection and Lymph Node Assessment for Clinical Stage I Pulmonary Lepidic Adenocarcinoma: An Analysis of 1991 Patients.](#) Cox ML1, Yang CJ1, Speicher PJ1, et al. J Thorac Oncol. 2017 Jan 8. pii: S1556-0864(17)30004-7. doi: 10.1016/j.jtho.2017.01.003. [Epub ahead of print]

BACKGROUND: This study examined the association of extent of lung resection, pathologic nodal evaluation, and survival for patients with clinical stage I (cT1-2N0M0) adenocarcinoma with lepidic histologic features in the National Cancer Data Base. **METHODS:** The association between extent of surgical resection and long-term survival for patients in the National Cancer Data Base with clinical stage I lepidic adenocarcinoma who underwent lobectomy or sublobar resection was evaluated using Kaplan-Meier and Cox proportional hazards regression analyses. **RESULTS:** Of the 1991 patients with cT1-2N0M0 lepidic adenocarcinoma who met the study criteria, 1544 underwent lobectomy and 447 underwent sublobar resection. Patients treated with sublobar resection were older, more likely to be female, and had higher Charlson/Deyo comorbidity scores, but they had smaller tumors and lower T status. Of the patients treated with lobectomy, 6% (n = 92) were upstaged because of positive nodal disease, with a median of seven lymph nodes sampled (interquartile range 4-10). In an analysis of the entire cohort, lobectomy was associated with a significant survival advantage over sublobar resection in univariate analysis (median survival 9.2 versus 7.5 years, p = 0.022, 5-year survival 70.5% versus 67.8%) and after multivariable adjustment (hazard ratio = 0.81, 95% confidence interval: 0.68-0.95, p = 0.011). However, lobectomy was no longer independently associated with improved survival when compared with sublobar resection (hazard ratio = 0.99, 95% confidence interval: 0.77-1.27, p = 0.905) in a multivariable analysis of a subset of patients in which only those patients who had undergone a sublobar resection including lymph node sampling were compared with patients treated with lobectomy. **CONCLUSIONS:** Surgeons treating patients with stage I lung adenocarcinoma with lepidic features should cautiously utilize sublobar resection rather than lobectomy, and they must always perform adequate pathologic lymph node evaluation.

[A randomized controlled trial comparing paravertebral block via the surgical field with thoracic epidural block using ropivacaine for post-thoracotomy pain relief.](#) Tamura T1,2, Mori S3, Mori A4, Ando M5, Yokota S1, Shibata Y2, Nishiwaki K6. J Anesth. 2017 Jan 23. doi: 10.1007/s00540-017-2307-5. [Epub ahead of print]

PURPOSE: We conducted a comparative study to evaluate analgesic efficacy between paravertebral block via the surgical field (PVB-sf), in which the catheter was inserted into the ventral side of the sympathetic trunk in the paravertebral space by a thoracic surgeon under thoracoscopic visualization, and epidural block (Epi) using ropivacaine for post-thoracotomy pain relief. **METHODS:** Lung cancer patients scheduled for lobectomy via thoracotomy were randomly allocated to receive either PVB-sf or Epi (n = 36 per group). Before thoracotomy closure, 0.375% ropivacaine was administered as a bolus (PVB-sf, 20 mL; Epi, 5 mL), followed by a 300-mL continuous infusion of 0.2% ropivacaine at 5 mL/h. Postoperative pain was assessed using a visual analog scale (VAS) score at various time points, including the primary endpoint of 2 h after ropivacaine bolus injection. Sensory block area, vital signs, serum ropivacaine concentrations, and side effects were also evaluated. **RESULTS:** The Epi group showed significantly lower VAS scores and blood pressure and a wider sensory block area than the PVB-sf group at all evaluation time points. While the mean serum ropivacaine concentration in the PVB-sf group was significantly higher than that in the Epi group until 1 h after injection of the ropivacaine bolus, there was no significant difference at any subsequent assessment point. The incidence of side effects was similar between the groups. **CONCLUSION:** The Epi was superior to PVB-sf for the management of post-thoracotomy pain in this patient cohort. The number of dermatomes anaesthetized by Epi was greater than that anaesthetized by PVB-sf. No difference in complication rates was observed between the two groups.

[Nationwide Assessment of Robotic Lobectomy for Non-Small Cell Lung Cancer.](#) Rajaram R1, Mohanty S2, Bentrem DJ3, Pavey ES4, Odell DD5, Bharat A6, Bilimoria KY7, DeCamp MM6. *Ann Thorac Surg.* 2017 Jan 18. pii: S0003-4975(16)31377-7. doi: 10.1016/j.athoracsur.2016.09.108. [Epub ahead of print]

BACKGROUND: Robotic lobectomy has been described for non-small cell lung cancer (NSCLC). Our objectives were to (1) evaluate the use of robotic lobectomy over time, (2) identify factors associated with its use, and (3) assess outcomes after robotic lobectomy compared with other surgical approaches. **METHODS:** Stage I to IIIA NSCLC patients were identified from the National Cancer Data Base (2010 to 2012). Trends in robotic lobectomy were assessed over time, and multivariable logistic regression models were developed to identify factors associated with its use. Propensity-matched cohorts were constructed to compare postoperative outcomes after robotic lobectomy with thoracoscopic and open lobectomy. **RESULTS:** Lobectomy was performed in 62,206 patients by open (n = 45,527), thoracoscopic (n = 12,990), or robotic (n = 3,689) procedures at 1,215 hospitals. Between 2010 and 2012, robotic lobectomy significantly increased, from 3.0% to 9.1% (p < 0.001). Academic (odds ratio, 1.55; 95% confidence interval, 1.04 to 2.33) and high-volume hospitals (odds ratio, 1.49; 95% confidence interval, 1.04 to 2.14) were associated with increased use of robotic lobectomy. Length of stay was shorter in robotic lobectomy compared with open lobectomy (6.1 vs 6.9 days; p < 0.001). Fewer lymph nodes (9.9 vs 10.9; p < 0.001) and 12 or more nodes were examined less frequently (32.0% vs 35.6%; p = 0.005) in robotic resections than in thoracoscopic resections. There was no difference between robotic and open or robotic and thoracoscopic lobectomy patients in margin positivity, 30-day readmission, and deaths at 30 and 90 days. **CONCLUSIONS:** Robotic lobectomies have significantly increased in stage I to IIIA NSCLC patients, with outcomes similar to other approaches. Additional studies are needed to determine if this technology offers potential advantages compared with video-assisted thoracoscopic operations.

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

[Effect of Adjuvant Chemotherapy after Complete Resection for Pathologic Stage IB Lung Adenocarcinoma in High-Risk Patients as Defined by a New Recurrence Risk Scoring Model.](#)

Jang HJ1, Cho S1,2, Kim K1,2, Jheon S1,2, Yang HC3, Kim DK4. *Cancer Res Treat.* 2017 Jan 18. doi: 10.4143/crt.2016.312. [Epub ahead of print]

PURPOSE: We conducted a retrospective analysis to determine if adjuvant chemotherapy prolongs overall survival in patients with pathologic stage IB lung adenocarcinoma who had undergone complete resection and were defined as high-risk by a newly developed recurrence risk scoring model.

MATERIALS AND METHODS: Patients who underwent curative resection for stage IB lung adenocarcinoma were analyzed with a newly developed recurrence risk scoring model and divided into a low-risk group and a high-risk group. The patients in the high-risk group were retrospectively divided into two groups based on whether they underwent adjuvant chemotherapy or observation. Recurrence-free survival and overall survival were compared between these two groups. **RESULTS:** A total of 328 patients who underwent curative resection between 2000 and 2009 were included in this study, of whom 110 (34%) received adjuvant chemotherapy and 218 (67%) underwent observation without additional treatment. According to our risk model, 167 patients (51%) were high-risk and 161 (49%) were low-risk. The 5-year recurrence-free survival rates and overall survival were 84.4% and 91.5% in low-risk patients and 53.9% and 74.7% in high-risk patients ($p < 0.001$). In high-risk patients, the 5-year overall survival rates were 77% among patients who underwent observation and 87% among those who underwent adjuvant chemotherapy ($p = 0.019$). **CONCLUSIONS:** Adjuvant chemotherapy prolonged overall survival among high-risk patients who had undergone complete resection for stage IB lung adenocarcinoma.

[First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer \(ASCEND-4\): a randomised, open-label, phase 3 study.](#) Soria JC1, Tan DS2, Chiari R3, et al. *Lancet*. 2017 Jan 23. pii: S0140-6736(17)30123-X. doi: 10.1016/S0140-6736(17)30123-X. [Epub ahead of print]

BACKGROUND: The efficacy of ceritinib in patients with untreated anaplastic lymphoma kinase (ALK)-rearranged non-small-cell lung cancer (NSCLC) is not known. We assessed the efficacy and safety of ceritinib versus platinum-based chemotherapy in these patients. **METHODS:** This randomised, open-label, phase 3 study in untreated patients with stage IIIB/IV ALK-rearranged non-squamous NSCLC was done in 134 centres across 28 countries. Eligible patients were assigned via interactive response technology to oral ceritinib 750 mg/day or platinum-based chemotherapy ([cisplatin 75 mg/m² or carboplatin AUC 5-6 plus pemetrexed 500 mg/m²] every 3 weeks for four cycles followed by maintenance pemetrexed); randomisation was stratified by World Health Organization performance status (0 vs 1-2), previous neoadjuvant or adjuvant chemotherapy, and presence of brain metastases as per investigator's assessment at screening. Investigators and patients were not masked to treatment assignment. The primary endpoint was blinded independent review committee assessed progression-free survival, based on all randomly assigned patients (the full analysis set). Efficacy analyses were done based on the full analysis set. All safety analyses were done based on the safety set, which included all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT01828099. **FINDINGS:** Between Aug 19, 2013, and May 11, 2015, 376 patients were randomly assigned to ceritinib (n=189) or chemotherapy (n=187). Median progression-free survival (as assessed by blinded independent review committee) was 16.6 months (95% CI 12.6-27.2) in the ceritinib group and 8.1 months (5.8-11.1) in the chemotherapy group (hazard ratio 0.55 [95% CI 0.42-0.73]; $p < 0.00001$). The most common adverse events were diarrhoea (in 160 [85%] of 189 patients), nausea (130 [69%]), vomiting (125 [66%]), and an increase in alanine aminotransferase (114 [60%]) in the ceritinib group and nausea (in 97 [55%] of 175 patients), vomiting (63 [36%]), and anaemia (62 [35%]) in the chemotherapy group. **INTERPRETATION:** First-line ceritinib showed a statistically significant and clinically meaningful improvement in progression-free survival versus chemotherapy in patients with advanced ALK-rearranged NSCLC. **FUNDING:** Novartis Pharmaceuticals Corporation.

[Association of Delayed Adjuvant Chemotherapy With Survival After Lung Cancer Surgery.](#)

Salazar MC1, Rosen JE1, Wang Z2, Arnold BN1, Thomas DC1, Herbst RS3, Kim AW1, Detterbeck FC1, Blasberg JD1, Boffa DJ1. JAMA Oncol. 2017 Jan 5. doi: 10.1001/jamaoncol.2016.5829. [Epub ahead of print]

IMPORTANCE: Adjuvant chemotherapy offers a survival benefit to a number of staging scenarios in non-small-cell lung cancer. Variable recovery from lung cancer surgery may delay a patient's ability to tolerate adjuvant chemotherapy, yet the urgency of chemotherapy initiation is unclear. **OBJECTIVE:** To assess differences in survival according to the time interval between non-small-cell lung cancer resection and the initiation of postoperative chemotherapy to determine the association between adjuvant treatment timing and efficacy. **DESIGN, SETTING, AND PARTICIPANTS:** This retrospective observational study examined treatment-naïve patients with completely resected non-small-cell lung cancer who received postoperative multiagent chemotherapy between 18 and 127 days after resection between January 2004 and December 2012. The study population was limited to patients with lymph node metastases, tumors 4 cm or larger, or local extension. Patients were identified from the National Cancer Database, a hospital-based tumor registry that captures more than 70% of incident lung cancer cases in the United States. The association between time to initiation of adjuvant chemotherapy and survival was evaluated using Cox models with restricted cubic splines. **EXPOSURES:** Adjuvant chemotherapy administered at different time points after surgery. **MAIN OUTCOMES AND MEASURES:** Effectiveness of adjuvant chemotherapy according to time to initiation after surgery. **RESULTS:** A total of 12 473 patients (median [interquartile range] age, 64 [57-70] years) were identified: 3073 patients (25%) with stage I disease; 5981 patients (48%), stage II; and 3419 patients (27%), stage III. A Cox model with restricted cubic splines identified the lowest mortality risk when chemotherapy was started 50 days postoperatively (95% CI, 39-56 days). Initiation of chemotherapy after this interval (57-127 days; ie, the later cohort) did not increase mortality (hazard ratio [HR], 1.037; 95% CI, 0.972-1.105; P = .27). Furthermore, in a Cox model of 3976 propensity-matched pairs, patients who received chemotherapy during the later interval had a lower mortality risk than those treated with surgery only (HR, 0.664; 95% CI, 0.623-0.707; P < .001). **CONCLUSIONS AND RELEVANCE:** In the National Cancer Database, adjuvant chemotherapy remained efficacious when started 7 to 18 weeks after non-small-cell lung cancer resection. Patients who recover slowly from non-small-cell lung cancer surgery may still benefit from delayed adjuvant chemotherapy started up to 4 months after surgery.

[A phase III randomised controlled trial of erlotinib vs gefitinib in advanced non-small cell lung cancer with EGFR mutations.](#)

Yang JJ1, Zhou Q1, Yan HH1, et al. Br J Cancer. 2017 Jan 19. doi: 10.1038/bjc.2016.456. [Epub ahead of print]

BACKGROUND: A phase III trial was conducted to compare the safety and efficacy of erlotinib with that of gefitinib in advanced non-small cell lung cancer harbouring epidermal growth factor receptor mutations in exon 19 or 21. **METHODS:** Eligible patients were randomised to receive erlotinib (150 mg per day) or gefitinib (250 mg per day) orally until disease progression or unacceptable toxicity. We aimed to determine whether erlotinib is superior to gefitinib in efficacy. The primary end point was progression-free survival. **RESULTS:** A total of 256 patients were randomised to receive erlotinib (N=128) or gefitinib (N=128). Median progression-free survival was not better with erlotinib than with gefitinib (13.0 vs 10.4 months, 95% confidence interval (CI) 0.62-1.05, P=0.108). The corresponding response rates and median overall survival were 56.3% vs 52.3% (P=0.530) and 22.9 vs 20.1 months (95% CI 0.63-1.13, P=0.250), respectively. There were no significant differences in grade 3/4 toxicities between the two arms (P=0.172). **CONCLUSIONS:** The primary end point was not met. Erlotinib was not significantly superior to gefitinib in terms of efficacy in advanced non-small cell lung cancer with epidermal growth factor receptor mutations in exon 19 or 21, and the two treatments had similar toxicities. British Journal of Cancer advance online publication 19 January 2017; doi:10.1038/bjc.2016.456 www.bjcancer.com.

Mixed Responses to Systemic Therapy Revealed Potential Genetic Heterogeneity and Poor Survival in Patients with Non-Small Cell Lung Cancer.

Dong ZY1,2, Zhai HR1,2, Hou QY3, Su J2, Liu SY2, Yan HH2, Li YS2, Chen ZY4, Zhong WZ2, Wu YL5,2. *Oncologist*. 2017 Jan;22(1):61-69. doi: 10.1634/theoncologist.2016-0150.

BACKGROUND: A subset of patients with non-small cell lung cancer (NSCLC) fosters mixed responses (MRs) to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) or chemotherapy. However, little is known about the clinical and molecular features or the prognostic significance and potential mechanisms. **METHODS:** The records of 246 consecutive patients with NSCLC receiving single-line chemotherapy or TKI treatment and who were assessed by baseline and interim positron emission tomography/computed tomography scans were collected retrospectively. The clinicopathological correlations of the MR were analyzed, and a multivariate analysis was performed to explore the prognostic significance of MR. **RESULTS:** The overall incidence of MR to systemic therapy was 21.5% (53/246) and predominated in patients with stage IIIB-IV, EGFR mutations and those who received TKI therapy ($p < .05$). Subgroup analyses based on MR classification (efficacious versus inefficacious) showed significant differences in subsequent treatment between the two groups ($p < .001$) and preferable progression-free survival (PFS) and overall survival (OS) in the efficacious MR group. Multivariate analyses demonstrated that the presence of MR was an independent unfavorable prognostic factor for PFS (hazard ratio [HR], 1.474; 95% confidence interval [CI], 1.018-2.134; $p = .040$) and OS (HR, 1.849; 95% CI, 1.190-2.871; $p = .006$) in patients with NSCLC. Induced by former systemic therapy, there were more T790M (18%), concomitant EGFR mutations (15%), and changes to EGFR wild type (19%) in the MR group among patients with EGFR mutations, which indicated higher incidence of genetic heterogeneity. **CONCLUSION:** MR was not a rare event in patients with NSCLC and tended to occur in those with advanced lung adenocarcinoma treated with a TKI. MR may result from genetic heterogeneity and is an unfavorable prognostic factor for survival. Further studies are imperative to explore subsequent treatment strategies. The *Oncologist* 2017;22:61-69

Implications for Practice: Tumor heterogeneity tends to produce mixed responses (MR) to systemic therapy, including TKI and chemotherapy; however, the clinical significance and potential mechanisms are not fully understood, and the subsequent treatment after MR is also a clinical concern. The present study systemically assessed patients by PET/CT and differentiated MR and therapies. The study identified a relatively high incidence of MR in patients with advanced NSCLC, particularly those treated with targeted therapies. An MR may be an unfavorable prognostic factor and originate from genetic heterogeneity. Further studies are imperative to explore subsequent treatment strategies.

Incorporating Erlotinib or Irinotecan Plus Cisplatin into Chemoradiotherapy for Stage III Non-small Cell Lung Cancer According to EGFR Mutation Status.

Lee Y1, Han JY1, Moon SH2, et al. *Cancer Res Treat*. 2017 Jan 6. doi: 10.4143/crt.2016.522. [Epub ahead of print]

PURPOSE: Concurrent chemoradiotherapy (CCRT) is the standard care for stage III non-small cell lung cancer (NSCLC) patients; however, a more effective regimen is needed to improve the outcome by better controlling occult metastases. We conducted two parallel randomized phase II studies to incorporate erlotinib or irinotecan-cisplatin (IP) into CCRT for stage III NSCLC depending on EGFR mutation status. **MATERIALS AND METHODS:** Patients with EGFR-mutant tumors were randomized to receive three cycles of erlotinib first and then either CCRT with erlotinib followed by erlotinib (arm A) or CCRT with IP only (arm B). Patients with EGFR unknown or wild-type tumors were randomized to receive either three cycles of IP before (arm C) or after CCRT with IP (arm D). **RESULTS:** Seventy-three patients were screened and the study was closed early because of slow accrual after 59 patients were randomized. Overall, there were seven patients in arm A, five in arm B, 22 in arm C, and 25 in arm D. The response rate was 71.4% and 80.0% for arm A and B, and 70.0% and 73.9% for arm C and D. The median overall

survival (OS) was 39.3 vs. 31.2 months for arm A and B (P= 0.442), and 16.3 vs. 25.3 months for arm C and D (P= 0.050). Patients with sensitive EGFR mutations had significantly longer OS than EGFR-wild patients (74.8 vs. 25.3 months, P= 0.034). There were no unexpected toxicities. **CONCLUSION:** Combined-modality treatment by molecular diagnostics is feasible in stage III NSCLC. EGFR-mutant patients appear to be a distinct subset with longer survival.

Randomized Phase II Study of Afatinib Plus Simvastatin Versus Afatinib Alone in Previously Treated Patients with Advanced Non-Adenocarcinomatous Non-Small Cell Lung Cancer.

Lee Y1, Lee KH2, Lee GK1, Lee SH1, Lim KY1, Joo J3, Go YJ1, Lee JS1, Han JY1. *Cancer Res Treat.* 2017 Jan 13. doi: 10.4143/crt.2016.546. [Epub ahead of print]

PURPOSE: This phase II study examined whether the addition of simvastatin to afatinib provides a clinical benefit compared with afatinib monotherapy in previously treated patients with non-adenocarcinomatous non-small cell lung cancer (NA-NSCLC). **MATERIALS AND METHODS:** Patients with advanced NA-NSCLC who progressed after one or two chemotherapy regimens were randomly assigned to a simvastatin (40 mg/day) plus afatinib (40 mg/day) (AS) arm or to an afatinib (A) arm. The primary endpoint was response rate (RR). **RESULTS:** Sixty-eight patients were enrolled (36 in the AS arm and 32 in the A arm). The RR was 5.7% (95% confidence interval [CI], 0.7-19.2%) for AS and 9.4% (95% CI, 2.0-25.0%) for A (P = 0.440). In arms AS and A, the median progression-free survival (PFS) was 1.0 vs. 3.6 months (P = 0.240) and the overall survival was 10.0 vs. 7.0 months (P = 0.930), respectively. Skin rash, stomatitis, and diarrhea were the most common adverse events in both arms. More grade 3 or 4 diarrhea was observed in arm A (18.8% vs. 5.6% in arm AS). In all patients, the median PFS for treatment including afatinib was not correlated with the status of EGFR mutation (P=0.122), EGFR fluorescence in situ hybridization (P=0.944), or EGFR immunohistochemistry (P=0.976). However, skin rash severity was significantly related to the risk of progression for afatinib (hazard ratio for skin rash grade ≥ 2 vs. grade < 2 , 0.44; 95% CI, 0.25-0.78; P = 0.005). **CONCLUSIONS:** There were no significant differences in the efficacy between AS and A arms in patients with NA-NSCLC.

NSCLC - RADIOTHERAPY

Stereotactic Ablative Radiation Therapy for Lung Oligometastases: Predictive Parameters of Early Response by 18FDG-PET/CT. Mazzola R1, Fiorentino A2, Di Paola G3, et al. *J Thorac Oncol.* 2017 Jan 24. pii: S1556-0864(16)33543-2. doi: 10.1016/j.jtho.2016.11.2234. [Epub ahead of print]

OBJECTIVES: The objective of this study was to investigate fludeoxyglucose F 18 positron emission tomography/computed tomography (18FDG-PET/CT) parameters as predictive of response after stereotactic ablative radiotherapy (SABR) for lung oligometastases. **METHODS:** The inclusion criteria of the current retrospective study were as follows: (1) lung oligometastases treated by SABR, (2) presence of 18FDG-PET/CT before and after SABR for at least two subsequent evaluations, (3) Karnofsky performance status higher than 80, and (4) life expectancy longer than 6 months. All patients were treated with a biologically equivalent dose of at least 100 Gy with an alpha/beta ratio of 10. The following metabolic parameters were semiquantitatively defined: maximum standardized uptake value (SUV_{max}), mean standardized uptake value (SUV_{mean}), metabolic tumor volume, and total lesion glycolysis. **RESULTS:** A total of 50 patients met the inclusion criteria, for a total of 70 lung metastases. The pre-SABR median SUV_{max} was 6.5 (range 4-17), the median SUV_{mean} was 3.7 (range 2.5-6.5), and the median metabolic tumor volume was 2.3 cm³ (0.2-31 cm³). The following metabolic parameters were significantly related to complete response at 6 months: SUV_{max} less than 5 (p < 0.001) and SUV_{mean} less than 3.5 (p = 0.03). Δ SUV_{max} at 3 to 6 months was +126% for lesions with in-field progression versus -26% for the remaining lesions (p = 0.002). Δ SUV_{mean} at 3 to 6 months was +15% for lesions with in-field progression versus -26% for the remaining metastases (p = 0.008). **CONCLUSIONS:** In the

current analysis, complete response from lung metastasis at 6 months after stereotactic body radiation therapy was significantly associated with both the maximum and mean values of pre-SABR 18FDG-PET/CT SUV. Longer-term trials are strongly advocated to improve the personalization of the monitoring of tumor response in patients with lung oligometastases and, consequently, monitoring of the cost-effectiveness of the health care.

[The efficacy and roles of combining temozolomide with whole brain radiotherapy in protection neurocognitive function and improvement quality of life of non-small-cell lung cancer patients with brain metastases.](#) Deng X1, Zheng Z1, Lin B1, et al. BMC Cancer. 2017 Jan 10;17(1):42. doi: 10.1186/s12885-016-3017-3.

BACKGROUND: Brain metastasis (BM) is a poor prognostic factor for non-small-cell lung cancer (NSCLC). The efficacy and roles of combining temozolomide (TMZ) with whole brain radiotherapy (WBRT) in protection neurocognitive function (NCF) and improvement quality of life (QOL) were investigated and compared with WBRT alone in the treatment of NSCLC patients with BM.

METHODS: A total of 238 NSCLC patients with BM were reviewed and categorized into WBRT plus TMZ (RCT) arm and WBRT alone (RT), respectively. The efficacy was evaluated with Pearson chi-square or Fisher's exact tests, Log-rank test and Cox proportional hazards model. NCF was assessed by using revised Hopkins Verbal Learning Test (HVLN-R), Controlled Oral Word Association (COWA) test and Trail-making Test (TMT). QOL was assessed by the Functional Assessment of Cancer Treatment-Lung (FACT-L) Chinese version 4.0 questionnaire. **RESULTS:** The average intracranial objective response (ORR) and disease control rate (DCR) for all the patients were 26.9 and 95.8%, respectively. The intracranial ORR and DCR for RCT and RT arm were 34.9% vs. 20.2% ($p = 0.01$) and 98.4% vs. 92.7% ($p = 0.03$), respectively. The median intracranial progression-free survival (PFS) and overall survival (OS) of NSCLC patients with BM were 5.2 and 7.3 months, respectively. The median PFS of RCT arm was significantly longer than that of RT arm (5.9 vs. 4.9 months, $p = 0.002$). The median OS of the RCT arm was also slightly longer than that of the RT arm (8.5 vs. 5.9 months), but without statistical significance ($p = 0.11$). Multivariate analysis indicated that TMZ was a significant factor for PFS. Statistically significant differences on NCF and QOL were observed between CRT and RT arms at 5 months. RCT showed a trend of toxicities increase compared with RT, however, the toxicities were tolerable and manageable. **CONCLUSIONS:** Adding TMZ to WBRT in the treatment of NSCLC patients with BM could improve the intracranial ORR, DCR, and median PFS compared with WBRT alone. Although no remarkable difference on median OS was found, adding TMZ could prevent NCF and QOL from worsening. The side effects increased by adding TMZ, but the difference was not statistical significance and toxicities were well tolerated.

[Dose-effect analysis of radiation induced rib fractures after thoracic SBRT.](#) Stam B1, van der Bijl E1, Peulen H1, Rossi MM1, Belderbos JS1, Sonke JJ2. Radiother Oncol. 2017 Jan 19. pii: S0167-8140(17)30009-9. doi: 10.1016/j.radonc.2017.01.004. [Epub ahead of print]

BACKGROUND AND PURPOSE: To determine a dose-effect relation for radiation induced rib fractures after stereotactic body radiation therapy (SBRT) in early stage non-small cell lung cancer (NSCLC). Automatic rib delineation has enabled the analysis of a large patient group. **MATERIAL AND METHODS:** Four-hundred and sixty-six patients with stage I/II NSCLC received SBRT with a median of 54Gy in 3 fractions. The optimal EQD2-corrected dose parameter to predict (a)symptomatic fractures was found using Cox regression. Three normal tissue complication probability (NTCP) models based on this optimal parameter were constructed: (1) at a median follow up (FU) of 26months, (2) for all data, with time to toxicity taken into account and (3) at a FU of 26months, excluding low dose ribs.

RESULTS: The median time to fracture was 22 (range 5-51) months. Maximum rib dose best predicted fractures. The TD50 (dose with 50% complication) of the second NTCP model was 375Gy. The TD50

was significantly higher for the other models indicating an under-estimation of the dose effect at the median follow-up time and/or when excluding low dose ribs. **CONCLUSIONS:** The risk of symptomatic rib fractures after SBRT was significantly correlated to dose, and was <5% at 26months when $D_{max} < 22.5\text{Gy}$.

Long-Term Results of a Trial of Concurrent Chemotherapy and Escalating Doses of Radiation for Unresectable Non-Small Cell Lung Cancer: NCCTG N0028 (ALLIANCE).

Schild SE1, Hillman SL2, Tan AD2, Ross HJ3, McGinnis WL4, Garces YA5, Graham DL6, Adjei AA7, Jett JR8; Mayo Clinic and North Central Cancer Treatment Group (NCCTG is now part of the ALLIANCE). J Thorac Oncol. 2017 Jan 12. pii: S1556-0864(17)30005-9. doi: 10.1016/j.jtho.2016.12.021. [Epub ahead of print]

INTRODUCTION OR HYPOTHESIS: This phase I/II trial was originally designed to determine the maximally tolerated dose (MTD) of thoracic radiotherapy (TRT) as part of a combined modality approach. This report includes the long-term outcome of patients treated on this study. The phase II portion was never completed as RTOG-0617 opened before it was concluded. **METHODS:** The MTD was defined as 74Gy in 37 fractions in this study. Twenty-five patients with unresectable non-small cell lung cancer (NSCLC) were treated with 2Gy daily fractions and concurrent weekly carboplatin and paclitaxel. Of these, twenty had stage III disease and 5 had stages I-II disease. **RESULTS:** Patients were followed until death or for a minimum of 5 years in survivors. Median and 5-year survival were 42.5 months and 20% for all patients, 52.9 months and 40% in patients with stages I/II disease, and 39.8 months and 15% in patients with stage III disease. **CONCLUSIONS:** The median survival of the stage III patients was quite favorable. We believe that this may have been due to a robust central review program of radiotherapy plans prior to treatment insuring compliance with protocol guidelines along with very low heart exposure to radiotherapy. Further improvements in 5-year survival will likely require research on both systemic therapy and TRT. Potential therapeutic modalities that may aid in these efforts include immunotherapy, targeted therapy, improved imaging, adaptive radiotherapy, simultaneous integrated boost techniques, novel dose-fractionation regimens, and charged particle therapy.

Long-term outcome of phase I/II prospective study of dose-escalated proton therapy for early-stage non-small cell lung cancer.

Chang JY1, Zhang W2, Komaki R2, et al. Radiother Oncol. 2017 Jan 27. pii: S0167-8140(16)34371-7. doi: 10.1016/j.radonc.2016.10.022. [Epub ahead of print]

PURPOSE: The aim of this phase I/II study was to assess the long-term clinical benefits and toxicities of proton beam therapy for medically inoperable early-stage non-small cell lung cancer (NSCLC).

PATIENTS AND METHODS: From June 2006 to September 2011, 35 patients with medically inoperable T1N0M0 (central or superior location, 12 patients) or T2-3N0M0 (any location, 23 patients) NSCLC were treated with 87.5Gy at 2.5Gy/fraction of proton therapy. Toxicities were scored according to the Common Terminology Criteria for Adverse Events, version 4.0. **RESULTS:** The median follow-up time was 83.1 months (95% CI: 69.2-97.1 months). For all 35 patients, the 1, 3, and 5-year overall survival rates were 85.7%, 42.9%, and 28.1%, respectively. The 5-year local recurrence-free, regional recurrence-free, and distant metastasis-free survival rates were 85.0%, 89.2%, and 54.4%, respectively. Different T stages had no effect on local and regional recurrence ($p=0.499$, $p=1.00$). However, with the increase in T stages, the distant metastasis rate increased significantly ($p=0.006$). The most common adverse effects were dermatitis (grade 2, 51.4%; grade 3, 2.9%) and radiation pneumonitis (grade 2, 11.4%; grade 3, 2.9%). Other grade 2 toxicities included esophagitis (2.9%), rib fracture (2.9%), heart toxicities (5.7%), and chest wall pain (2.9%). **CONCLUSIONS:** According to our long-term follow-up data, proton therapy with ablative doses is well tolerated and effective in medically inoperable early-stage NSCLC. Systemic therapy should be considered to reduce the rate of distant metastasis in cases of T2 and T3 lesions.

[Expression of Notch1 and Numb in small cell lung cancer.](#) Kikuchi H1, Sakakibara-Konishi J1, Furuta M1, et al. *Oncotarget*. 2017 Jan 2. doi: 10.18632/oncotarget.14411. [Epub ahead of print]

Notch signaling in tumorigenesis functions as an oncogene or tumor suppressor according to the type of malignancy. Numb represses intracellular Notch signaling. Previous studies have demonstrated that Notch signaling suppresses the proliferation of small cell lung cancer (SCLC) cell lines. However, in SCLC, the association between Notch1 and Numb expression and clinicopathological factors or prognosis has remained unclear. In this study, we evaluated the expression of Notch1 and Numb in SCLC. We immunohistochemically assessed 125 SCLCs that were surgically resected at 16 institutions participating in either the Hokkaido Lung Cancer Clinical Study Group Trial (HOT) or the Fukushima Investigative Group for Healing Thoracic Malignancy (FIGHT) between 2003 and 2013. Correlations between Notch1 or Numb expression and various clinicopathological features were evaluated. Notch1 expression was associated with ECOG performance status. Numb expression was associated with age, sex, and pathological histology (SCLC or Combined SCLC). Analysis of cellular biological expression did not demonstrate a significant correlation between the expression of Notch1 and of Numb. Multivariate Cox regression analysis showed that high Notch1 expression was an independent favorable prognostic factor for SCLC (hazard ratio = 0.503, P = 0.023). High Notch1 expression, but not Numb expression, is associated with favorable prognosis in SCLC.

[Capsaicin synergizes with camptothecin to induce increased apoptosis in human small cell lung cancers via the calpain pathway.](#) Friedman JR1, Perry HE1, Brown KC1, et al. *Biochem Pharmacol*.

2017 Jan 16. pii: S0006-2952(17)30019-9. doi: 10.1016/j.bcp.2017.01.004. [Epub ahead of print]

Small cell lung cancer (SCLC) is characterized by excellent initial response to chemotherapy and radiation therapy with a majority of the patients showing tumor shrinkage and even remission. However, the challenge with SCLC therapy is that patients inevitably relapse and subsequently do not respond to the first line treatment. Recent clinical studies have investigated the possibility of camptothecin-based combination therapy as first line treatment for SCLC patients. Conventionally, camptothecin is used for recurrent SCLC and has poor survival outcomes. Therefore, drugs which can improve the therapeutic index of camptothecin should be valuable for SCLC therapy. Extensive evidence shows that nutritional compounds like capsaicin (the spicy compound of chili peppers) can improve the anti-cancer activity of chemotherapeutic drugs in both cell lines and animal models. Statistical analysis shows that capsaicin synergizes with camptothecin to enhance apoptosis of human SCLC cells. The synergistic activity of camptothecin and capsaicin is observed in both classical and variant SCLC cell lines and, in vivo, in human SCLC tumors xenotransplanted on chicken chorioallantoic membrane (CAM) models. The synergistic activity of capsaicin and camptothecin are mediated by elevation of intracellular calcium and the calpain pathway. Our data foster hope for novel nutrition based combination therapies in SCLC.

[Italian, Multicenter, Phase III, Randomized Study of Cisplatin Plus Etoposide With or Without Bevacizumab as First-Line Treatment in Extensive-Disease Small-Cell Lung Cancer: The GOIRC-AIFA FARM6PMFJM Trial.](#) Tiseo M1, Boni L1, Ambrosio F1, et al. *J Clin Oncol*. 2017 Jan

30:JCO2016694844. doi: 10.1200/JCO.2016.69.4844. [Epub ahead of print]

PURPOSE: Considering promising results in phase II studies, a randomized phase III trial was designed to assess the efficacy of adding bevacizumab to first-line cisplatin plus etoposide for treatment of extensive-disease (ED) small-cell lung cancer (SCLC). **PATIENTS AND METHODS:** Treatment-naive patients with ED-SCLC were randomly assigned to receive either cisplatin plus etoposide (arm A) or the same regimen with bevacizumab (arm B) for a maximum of six courses. In the absence of progression, patients in arm B continued bevacizumab alone until disease progression or for a maximum of 18 courses.

The primary end point was overall survival (OS). **RESULTS:** Two hundred four patients were randomly assigned and considered in intent-to-treat analyses (103 patients in arm A and 101 patients in arm B). At a median follow-up of 34.9 months in arm A and arm B, median OS times were 8.9 and 9.8 months, and 1-year survival rates were 25% and 37% (hazard ratio, 0.78; 95% CI, 0.58 to 1.06; $P = .113$), respectively. A statistically significant effect of bevacizumab on OS in patients who received maintenance was seen (hazard ratio, 0.60; 95% CI, 0.40 to 0.91; $P = .011$). Median progression-free survival times were 5.7 and 6.7 months in arm A and arm B, respectively ($P = .030$). Regarding hematologic toxicity, no statistically significant differences were observed; for nonhematologic toxicity, only hypertension was more frequent in arm B (grade 3 or 4, 1.0% v 6.3% in arms A v B, respectively; $P = .057$). **CONCLUSION:** The addition of bevacizumab to cisplatin and etoposide in the first-line treatment of ED-SCLC had an acceptable toxicity profile and led to a statistically significant improvement in progression-free survival, which, however, did not translate into a statistically significant increase in OS. Further research with novel antiangiogenic agents, particularly in the maintenance setting, is warranted.

[Mathematical optimisation of the cisplatin plus etoposide combination for managing extensive-stage small-cell lung cancer patients.](#) Faivre C1, El Cheikh R1, Barbolosi D1, Barlesi F1,2. *Br J Cancer.* 2017 Jan;116(3):344-348. doi: 10.1038/bjc.2016.439. Epub 2017 Jan 12.

BACKGROUND: Small-cell lung cancer (SCLC) represents one of the most aggressive forms of lung cancer. Despite the fair sensitivity of SCLC to chemotherapy and radiotherapy, the current standard treatment regimens have modest survival rates and are associated with potential life-threatening adverse events. Therefore, research into new optimised regimens that increase drug efficacy while respecting toxicity constraints is of primary importance. **METHODS:** A PK/PD model for the combination of cisplatin and etoposide to treat extensive-stage SCLC patients was generated. The model takes into consideration both the efficacy of the drugs and their haematological toxicity. Using optimisation techniques, the model can be used to propose new regimens. **RESULTS:** Three new regimens with varying timing for combining cisplatin and etoposide have been generated that respect haematological toxicity constraints and achieve better or similar tumour regression. The proposed regimens are: (1) Protocol OP1: etoposide 80 mg m⁻² over 1 h D1, followed by a long infusion 12 h later (over 3 days) of 160 mg m⁻² plus cisplatin 80 mg m⁻² over 1 h D1, D1-D1 21 days; (2) Protocol OP2: etoposide 80 mg m⁻² over 1 h D1, followed by a long infusion 12 h later (over 4 days) of 300 mg m⁻² plus cisplatin 100 mg m⁻² over 1 h D1, D1-D1 21 days; and (3) Protocol OP3: etoposide 40 mg m⁻² over 1 h, followed by a long infusion 6 h later (3 days) of 105 mg m⁻² plus cisplatin 50 mg m⁻² over 1 h, D1-D1 14 days. **CONCLUSIONS:** Mathematical modelling can help optimise the design of new cisplatin plus etoposide regimens for managing extensive-stage SCLC patients.

[Efficacy and safety of angiogenesis inhibitors in small-cell lung cancer.](#) Lin H1,2, Li L1, Luo S1, Zhou S1, Shen R1, Yang H1, Chen H1, Xie X1. *Oncotarget.* 2017 Jan 3;8(1):1141-1155. doi: 10.18632/oncotarget.13588.

OBJECTIVE: The purpose of this study was to investigate the efficacy and safety of angiogenesis inhibitors for small-cell lung cancer (SCLC). **METHODS:** Totally, 16 controlled trials (1898 cases) involving angiogenesis inhibitors plus chemotherapy (ACT group) versus chemotherapy alone group (CT group) were identified from PubMed, EMBASE, Cochrane Library and Wanfang Data before March 2016. **RESULTS:** Compared with CT group, ACT group obtained a significant benefit on objective response rate (ORR) (RR = 1.34; 95% CI = 1.19-1.51; $P < 0.00001$) and a trend of prolonging progression-free survival (PFS) (HR = 0.86; 95% CI = 0.73-1.01; $P = 0.07$) without improving overall survival (OS) (HR = 1.05; 95% CI = 0.94-1.17; $P = 0.36$). Remarkably, subgroup analysis showed that the antibodies targeting VEGF significantly prolonged PFS (HR = 0.76; 95% CI = 0.64-0.90; $P = 0.001$). With regard to toxicity, there was no significant difference in severe adverse events (AEs, Grade \geq 3)

between two groups except that gastrointestinal symptom, hypertension, metabolic disorders, neurology and pain were higher in ACT group. **CONCLUSION:** Compared with chemotherapy alone, antibodies targeting VEGF plus chemotherapy significantly improved ORR and prolonged PFS with an acceptable toxicity profile for patients with SCLC. Therefore, angiogenesis inhibitors, especially antibodies targeting VEGF, combining with chemotherapy may be a potential promising strategy in managing SCLC.

Prophylactic cranial irradiation after definitive chemoradiotherapy for limited-stage small cell lung cancer: Do all patients benefit? Farooqi AS1, Holliday EB1, Allen PK1, Wei X1, Cox JD1, Komaki R2. *Radiother Oncol.* 2017 Jan 7. pii: S0167-8140(16)34398-5. doi: 10.1016/j.radonc.2016.11.012. [Epub ahead of print]

PURPOSE: Prophylactic cranial irradiation (PCI) can improve overall survival (OS) and suppress brain metastases (BM) in patients with limited-stage small cell lung cancer (LS-SCLC) after complete response to primary therapy. However, PCI can be toxic. We sought to identify characteristics of patients who may not benefit from PCI. **METHODS:** We identified 658 patients who received chemoradiotherapy at MD Anderson in 1986-2012; 364 received PCI and 294 did not. Median follow-up time was 21.2 months (range 1.2-240.8 months). Cox proportional hazards regression, competing-risk regression, and Kaplan-Meier analyses were used to identify factors influencing OS and BM. **RESULTS:** PCI reduced risks of death [HR 0.73, 95% CI 0.61-0.88, P=0.001] and BM [HR 0.54, 95% CI 0.39-0.76, P<0.001]. Having tumors ≥ 5 cm increased the risk of BM [HR 1.77, 95% CI 1.22-2.55, P=0.002] but not death [HR 1.16, 95% CI 0.96-1.40, P=0.114]. Among patients ≥ 70 years with ≥ 5 -cm tumors, PCI did not improve OS [2-year rates 39.4% vs 40.9%, P=0.739]. **CONCLUSIONS:** PCI remains standard therapy after complete response to chemoradiotherapy for LS-SCLC. However, older patients may be at risk from comorbidity or extracranial disease. Further work is warranted to identify patients who may not benefit from PCI.

The Biological Effects of Dickkopf1 on Small Cell Lung Cancer Cells and Bone Metastasis. Pang H, Ma N, Jiao M, Shen W, Xin B, Wang T, Zhang F, Liu L, Zhang H. *Oncol Res.* 2017 Jan 2;25(1):35-42. doi: 10.3727/096504016X14719078133249.

The bone is among the most common sites of metastasis in patients with lung cancer. Over 30%-40% of lung cancers can develop bone metastasis, and no effective therapeutic methods exist in clinic cases. Wnt/ β -catenin signaling and Dickkopf1 (DKK1) play important roles in the progression of lung cancer, which preferentially metastasizes to the skeleton. However, the role of DKK1 in osteotropism of small cell lung cancer (SCLC) remains to be elucidated. This study aimed to define the role of DKK1 in SCLC bone metastasis and investigate the underlying mechanisms. Our results demonstrated that the expression level of DKK1 was dramatically higher in bone metastatic SCLC cells (SBC-5 cell line) compared with that in cells without bone metastatic ability (SBC-3 cell line). Therefore, we hypothesized that DKK1 was involved in the bone metastasis of SCLC. We then suppressed the DKK1 expression in SBC-5 cells by RNAi and found that downregulation of DKK1 can inhibit cell proliferation, colony formation, cell migration, and invasion, but increase the apoptosis rate. Downregulation of DKK1 did not affect the cell cycle progression of SBC-5 cells in vitro. In vivo, downregulated DKK1 in SBC-5 cells resulted in attenuated bone metastasis. These results indicated that DKK1 may be an important regulator in bone metastases of SCLC, and targeting DKK1 may be an effective method to prevent and treat skeleton metastases in SCLC cases.

Correlation between the Ki-67 proliferation index and response to radiation therapy in small cell lung cancer. Ishibashi N1, Maebayashi T2, Aizawa T2, Sakaguchi M2, Nishimaki H3, Masuda S3. *Radiat Oncol.* 2017 Jan 13;12(1):16. doi: 10.1186/s13014-016-0744-1.

BACKGROUND: In the breast cancer, the decision whether to administer adjuvant therapy is increasingly influenced by the Ki-67 proliferation index. In the present retrospective study, we

investigated if this index could predict the therapeutic response to radiation therapy in small cell lung cancer (SCLC). **METHODS:** Data from 19 SCLC patients who received thoracic radiation therapy were included. Clinical staging was assessed using the TNM classification system (UICC, 2009; cstage IIA/IIB/IIIA/IIIB = 3/1/7/8). Ki-67 was detected using immunostained tumour sections and the Ki-67 proliferation index was determined using e-Count software. Radiation therapy was administered at total doses of 45-60 Gy. A total of 16 of the 19 patients received chemotherapy. **RESULTS:** Patients were divided into two groups, one with a Ki-67 proliferation index $\geq 79.77\%$ (group 1, 8 cases) and the other with a Ki-67 proliferation index $< 79.77\%$ (group 2, 11 cases). Following radiation therapy, a complete response (CR) was observed in six cases from group 1 (75.0%) and three cases from group 2 (27.3%). The Ki-67 proliferation index was significantly correlated with the CR rate ($P = 0.05$), which was significantly higher in group 1 than in group 2 ($P = 0.04$). The median survival time was 516 days for all patients, and the survival rates did not differ significantly between groups 1 and 2. **CONCLUSIONS:** Our study is the first to evaluate the correlation between the Ki-67 proliferation index and SCLC tumour response to radiation therapy. Our findings suggest that a high Ki-67 proliferation index might represent a predictive factor for increased tumour radiosensitivity.

PALLIATIVE AND SUPPORTIVE CARE

[Coping Well with Advanced Cancer: A Serial Qualitative Interview Study with Patients and Family Carers.](#) Walshe C1, Roberts D2, Appleton L3, Calman L4, Large P5, Lloyd-Williams M6, Grande G2. PLoS One. 2017 Jan 20;12(1):e0169071. doi: 10.1371/journal.pone.0169071. eCollection 2017.

OBJECTIVES: To understand successful strategies used by people to cope well when living with advanced cancer; to explore how professionals can support effective coping strategies; to understand how to support development of effective coping strategies for patients and family carers. **DESIGN:** Qualitative serial (4-12 week intervals) interview study with people with advanced cancer and their informal carers followed by focus groups. The iterative design had a novel focus on positive coping strategies. Interview analysis focused on patients and carers as individuals and pairs, exploring multiple dimensions of their coping experiences. Focus group analysis explored strategies for intervention development.

PARTICIPANTS: 26 people with advanced (stage 3-4) breast, prostate, lung or colorectal cancer, or in receipt of palliative care, and 24 paired nominated informal/family carers. **SETTING:** Participants recruited through outpatient clinics at two tertiary cancer centres in Merseyside and Manchester, UK, between June 2012 and July 2013. **RESULTS:** 45 patient and 41 carer interviews were conducted plus 4 focus groups (16 participants). People with advanced cancer and their informal/family carers develop coping strategies which enable effective management of psychological wellbeing. People draw from pre-diagnosis coping strategies, but these develop through responding to the experience of living with advanced cancer. Strategies include being realistic, indulgence, support, and learning from others, which enabled participants to regain a sense of wellbeing after emotional challenge. Learning from peers emerged as particularly important in promoting psychological wellbeing through the development of effective 'everyday', non-clinical coping strategies. **CONCLUSIONS:** Our findings challenge current models of providing psychological support for those with advanced cancer which focus on professional intervention. It is important to recognise, enable and support peoples' own resources and coping strategies. Peer support may have potential, and could be a patient-centred, cost effective way of managing the needs of a growing population of those living with advanced cancer.

[Using Perceived Self-efficacy to Improve Fatigue and Fatigability In Postsurgical Lung Cancer Patients: A Pilot Randomized Controlled Trial.](#) Hoffman AJ1, Brintnall RA, Given BA, von Eye A, Jones LW, Brown JK. Cancer Nurs. 2017 Jan/Feb;40(1):1-12.

BACKGROUND: Fatigue remains a prevalent and debilitating symptom in persons with non-small cell lung cancer (NSCLC). Exercise has been shown to be effective in reducing fatigue, yet interventions are limited for postsurgical NSCLC patients. To date, while surgery is offered as a standard curative treatment for NSCLC, no formal guidelines exist for postsurgical rehabilitation. **OBJECTIVE:** This study focuses on the design and testing of a postsurgical intervention for NSCLC patients to promote perceived self-efficacy for fatigue self-management targeting cancer-related fatigue (CRF) severity and its associated fatigability through exercise. **METHODS:** A 2-arm randomized controlled trial was used to examine the impact of a 6-week rehabilitative CRF self-management exercise intervention on 37 NSCLC participants compared with 35 control group participants receiving usual care from diagnosis to 6 weeks' postsurgical hospital discharge. **RESULTS:** We exceeded goals for recruitment (66%), retention (97%), adherence (93%), and acceptability. Our 6-week exercise intervention demonstrated preliminary efficacy in significantly reducing CRF severity and fatigability as compared with usual care, with mean CRF levels restored to levels lower than presurgery. Likewise, the exercise group's functional performance (physical and mental health scores) exceeded usual care. Furthermore, no adverse events were reported; participants had a mean age of 67 years and a mean of 8 comorbid conditions. **CONCLUSIONS:** An exercise intervention for postsurgical NSCLC patients is feasible, safe, and highly acceptable showing positive changes in CRF self-management. **IMPLICATIONS FOR PRACTICE:** To advance practice, testing of the effectiveness of this health-promoting self-management exercise intervention in a larger-scale randomized controlled trial is needed.

[Preparation for the end of life and life completion during late-stage lung cancer: An exploratory analysis.](#) Adorno G1, Wallace C2. Palliat Support Care. 2017 Jan 18:1-11. doi: 10.1017/S1478951516001012. [Epub ahead of print]

OBJECTIVE: Our aim was to explore preparation for the end of life (EoL) and life closure among persons with advanced metastatic lung cancer. Understanding quality of life through the lens of preparation and completion is important since the trajectory of lung cancer can be relatively short, often leading to application of cancer-directed therapies near death without the opportunity for advance planning or palliative care. Clinical research is needed to understand the kinds of distress specific to older adults with advanced lung cancer that are amendable to palliative care interventions. **METHOD:** We employed an exploratory cross-sectional design to examine psychosocial and existential concerns among a purposive sample (N = 30) of advanced lung cancer patients using the "end-of-life preparation" and "life completion" subscales of the Quality of Life at the End of Life (QUAL-E) questionnaire. Nonparametric methods were employed to analyze preparation, completion, global quality of life (QoL), and the associations among depressive symptoms, preparation, completion, and global QoL. **RESULTS:** Higher scores on life completion were associated with better global QoL, and with items related to transcendence, communicative acts, and interpersonal relationships demonstrating important contributions. The perception of being a future burden on family members was the greatest concern within the preparation domain. Depressive symptoms were not associated with preparation, completion, or global QoL. **SIGNIFICANCE OF RESULTS:** Psychosocial and existential issues contribute to QoL at the EoL among older adults with late-stage lung cancer during cancer-directed therapy, concurrent care, and hospice. The role of preparation, especially self-perceived burden, merits further research early on in the oncological setting. The preparation and life completion subscales of the QUAL-E are feasible clinical tools for facilitating dyadic communication about sensitive topics in the palliative care setting.

[Inflammatory pathway genes associated with inter-individual variability in the trajectories of morning and evening fatigue in patients receiving chemotherapy.](#)

Wright F1, Hammer M2, Paul SM3, et al. Cytokine. 2017 Jan 19;91:187-210. doi: 10.1016/j.cyto.2016.12.023. [Epub ahead of print]

Fatigue, a highly prevalent and distressing symptom during chemotherapy (CTX), demonstrates diurnal and interindividual variability in severity. Little is known about the associations between variations in genes involved in inflammatory processes and morning and evening fatigue severity during CTX. The purposes of this study, in a sample of oncology patients (N=543) with breast, gastrointestinal (GI), gynecological (GYN), or lung cancer who received two cycles of CTX, were to determine whether variations in genes involved in inflammatory processes were associated with inter-individual variability in initial levels as well as in the trajectories of morning and evening fatigue. Patients completed the Lee Fatigue Scale to determine morning and evening fatigue severity a total of six times over two cycles of CTX. Using a whole exome array, 309 single nucleotide polymorphisms SNPs among the 64 candidate genes that passed all quality control filters were evaluated using hierarchical linear modeling (HLM). Based on the results of the HLM analyses, the final SNPs were evaluated for their potential impact on protein function using two bioinformational tools. The following inflammatory pathways were represented: chemokines (3 genes); cytokines (12 genes); inflammasome (11 genes); Janus kinase/signal transducers and activators of transcription (JAK/STAT, 10 genes); mitogen-activated protein kinase/jun amino-terminal kinases (MAPK/JNK, 3 genes); nuclear factor-kappa beta (NFkB, 18 genes); and NFkB and MAP/JNK (7 genes). After controlling for self-reported and genomic estimates of race and ethnicity, polymorphisms in six genes from the cytokine (2 genes); inflammasome (2 genes); and NFkB (2 genes) pathways were associated with both morning and evening fatigue. Polymorphisms in six genes from the inflammasome (1 gene); JAK/STAT (1 gene); and NFkB (4 genes) pathways were associated with only morning fatigue. Polymorphisms in three genes from the inflammasome (2 genes) and the NFkB (1 gene) pathways were associated with only evening fatigue. Taken together, these findings add to the growing body of evidence that suggests that morning and evening fatigue are distinct symptoms.

[Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab.](#) Cappelli LC1, Gutierrez AK1, Baer AN1, ET AL. *Ann Rheum Dis.* 2017 Jan;76(1):43-50. doi: 10.1136/annrheumdis-2016-209595. Epub 2016 Jun 15.

OBJECTIVES: Immune checkpoint inhibitors (ICIs) targeting the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) pathways have demonstrated survival improvements in multiple advanced cancers, but also cause immune-related adverse events (IRAEs). IRAEs with clinical features similar to rheumatic diseases have not been well described. We report patients with inflammatory arthritis and sicca syndrome secondary to ICIs. **METHODS:** We report patients evaluated in the Johns Hopkins Rheumatology clinics from 2012 to 2016 identified as having new rheumatological symptoms in the context of treatment with ipilimumab (anti-CTLA-4) and/or nivolumab (anti-PD-1) for solid tumours. **RESULTS:** We identified 13 patients who received ICIs and developed rheumatological IRAEs. Mean age was 58.7 years. Cancer types included melanoma, non-small cell lung cancer, small cell lung cancer and renal cell carcinoma. ICI regimens included nivolumab or ipilimumab as monotherapy (n=5), or combination nivolumab and ipilimumab (n=8). Nine of 13 patients developed an inflammatory arthritis, 4 with synovitis confirmed on imaging (3 ultrasound, 1 MRI) and 4 with inflammatory synovial fluid. Four patients developed sicca syndrome with severe salivary hypofunction. Other IRAEs included: pneumonitis, colitis, interstitial nephritis and thyroiditis. Antinuclear antibodies were positive in 5 out of 13 patients. All 13 patients were treated with corticosteroids with varying response. Two patients were treated with methotrexate and antitumor necrosis factor therapy for inflammatory arthritis. **CONCLUSIONS:** As ICIs are increasingly used for a range of malignancies, new cases of rheumatic IRAEs are likely to emerge. Further research is required to understand mechanisms, determine risk factors and develop management algorithms for rheumatic IRAEs.

Reactive Oxygen Species/Nitric Oxide Mediated Inter-Organ Communication in Skeletal Muscle Wasting Diseases.

Leitner LM1, Wilson RJ2, Yan Z2,3, Gödecke A1. *Antioxid Redox Signal*. 2017 Jan 4. doi: 10.1089/ars.2016.6942. [Epub ahead of print]

SIGNIFICANCE: Cachexia is defined as a complex metabolic syndrome that is associated with underlying illness and a loss of muscle with or without loss of fat mass. This disease is associated with a high incidence with chronic diseases such as heart failure, cancer, chronic obstructive pulmonary disease (COPD), and acquired immunodeficiency syndrome (AIDS), among others. Since there is currently no effective treatment available, cachectic patients have a poor prognosis. Elucidation of the underlying mechanisms is, therefore, an important medical task. Recent Advances: There is accumulating evidence that the diseased organs such as heart, lung, kidney, or cancer tissue secrete soluble factors, including Angiotensin II, myostatin (growth differentiation factor 8 [GDF8]), GDF11, tumor growth factor beta (TGF β), which act on skeletal muscle. There, they induce a set of genes called atrogenes, which, among others, induce the ubiquitin-proteasome system, leading to protein degradation. Moreover, elevated reactive oxygen species (ROS) levels due to modulation of NADPH oxidases (Nox) and mitochondrial function contribute to disease progression, which is characterized by loss of muscle mass, exercise resistance, and frailty. **CRITICAL ISSUES:** Although substantial progress was achieved to elucidate the pathophysiology of cachexia, effective therapeutic strategies are urgently needed. **FUTURE DIRECTIONS:** With the identification of key components of the aberrant inter-organ communication leading to cachexia, studies in mice and men to inhibit ROS formation, induction of anti-oxidative superoxide dismutases, and upregulation of muscular nitric oxide (NO) formation either by pharmacological tools or by exercise are promising approaches to reduce the extent of skeletal muscle wasting.

Distress is Interdependent in Patients and Caregivers with Newly Diagnosed Incurable Cancers.

Jacobs JM1,2, Shaffer KM3,4, Nipp RD5, et al. *Ann Behav Med*. 2017 Jan 17. doi: 10.1007/s12160-017-9875-3. [Epub ahead of print]

BACKGROUND: Individuals with advanced, incurable cancer often experience high physical and psychological symptom burden. Family and friend caregivers are at risk for emotional distress. **PURPOSE:** The aim of the study is to investigate the interrelationship of distress in patient-caregiver dyads at the time of newly diagnosed incurable cancer. **METHODS:** From May 2011 to July 2015, within 8 weeks of diagnosis of advanced lung or noncolorectal gastrointestinal cancer, 350 patients and 275 family caregivers were enrolled in a randomized controlled trial of early palliative care. Actor-partner interdependence modeling was used to examine relationships between dyad's self-reported anxiety and depressive symptoms on the Hospital Anxiety and Depression Scale at baseline. **RESULTS:** Comparing patients with caregivers, patients reported more depressive symptoms (M diff = .84; $t[274] = 3.17$, $p = .002$, $d = .22$) and caregivers reported more anxiety symptoms (M diff = 1.62, $t[274] = 4.91$, $p < .001$, $d = .39$). Dyads' anxiety symptoms were positively associated, as were depressive symptoms ($r_s = .21$, $p_s \leq .001$). Actor-partner interdependence modeling showed that patients' anxiety symptoms were positively associated with their own depressive symptoms, with an equal effect for caregivers (actor effect $\beta_s = 0.52$, $p_s < .001$). Patients' own anxiety was concurrently positively associated with their caregivers' depressive symptoms, with an equal effect for caregivers to patients (partner effect $\beta_s = 0.08$, $p_s = .008$). **CONCLUSIONS:** In the context of newly diagnosed incurable cancer, caregivers experience more pronounced anxiety, while patients report greater depressive symptoms. Findings indicate that anxiety and depressive symptoms are interrelated among dyads facing newly diagnosed incurable disease. Results emphasize the importance of addressing distress in both patients and caregivers. Future research should discern when dyadic versus individual psychosocial interventions would be optimal.

[A Home-based Exercise Intervention for Non-Small Cell Lung Cancer Patients Post-Thoracotomy.](#)

Hoffman AJ, Brintnall RA. *Semin Oncol Nurs*. 2017 Feb;33(1):106-117. doi: 10.1016/j.soncn.2016.11.011. Epub 2017 Jan 3.

OBJECTIVES: There are no evidenced-based rehabilitative guidelines for postsurgical non-small cell lung cancer (NSCLC) patients. This qualitative study provides evidence on the acceptability of an effective postsurgical exercise intervention targeting the self-management of cancer-related fatigue to fill this gap. **DATA SOURCES:** Qualitative perspective of 37 individuals randomized to a 6-week exercise program following hospital discharge post-thoracotomy for NSCLC. **CONCLUSION:** Postsurgical NSCLC participants found this rehabilitative exercise intervention highly acceptable because it removed traditional barriers to exercise. **IMPLICATION FOR NURSING PRACTICE:** A highly acceptable and effective solution for meeting the unmet rehabilitative support needs of NSCLC patients has broader implications for extension to other vulnerable, aging, deconditioned populations.

COMPLEMENTARY & ALTERNATIVE THERAPY

[A comparison of the effects of medical Qigong and standard exercise therapy on symptoms and quality of life in patients with advanced cancer.](#)

Vanderbyl BL1, Mayer MJ2, Nash C1, Tran AT1,3, Windholz T1, Swanson T1, Kasymjanova G3, Jagoe RT4,5. *Support Care Cancer*. 2017 Jan 19. doi: 10.1007/s00520-017-3579-x. [Epub ahead of print]

PURPOSE: Patients with advanced cancer frequently experience anxiety, depression and poor quality of life (QOL), as well as physical symptoms such as fatigue and weakness. Physical exercise has potential to help control these symptoms but the optimal training prescription is still not clear. We performed a study comparing medical Qigong (QG) and standard endurance and strength training (SET) in patients with advanced stage non-small cell lung (NSCLC) and gastrointestinal (GI) cancers. **METHODS:** A randomized, cross-over study was performed in patients with advanced NSCLC and GI cancers receiving or eligible for chemotherapy. Patients received supervised QG or SET twice-weekly for 6 weeks. Psychological functioning, QOL, symptoms and physical functioning were assessed before and after each intervention period. **RESULTS:** Nineteen patients completed both interventions. Comparing interventions revealed no difference between QG and SET on change in anxiety or depression scores or QOL. However, SET treatment was better at improving perceived strength ($P = 0.05$) and walking distance ($P = 0.02$). The order in which interventions were performed had a significant impact on the improvement in certain symptoms (sleep quality, breathlessness, $P < 0.05$), QOL ($P = 0.01$) and walking distance ($P = 0.008$). In all cases, the beneficial effects of the exercise interventions were markedly reduced during the second interval. **CONCLUSIONS:** QG and SET are equivalent in their impact on many aspects of psychological function in cancer patients. However, SET leads to greater improvements in exercise capacity and helps reduce some symptoms. The reduction in beneficial effect of SET on exercise function when offered as the second intervention is a new finding that warrants further study.

[Pomegranate for Prevention and Treatment of Cancer: An Update.](#)

Sharma P1, McClees SF2, Afaq F3,4. *Molecules*. 2017 Jan 24;22(1). pii: E177. doi: 10.3390/molecules22010177. Cancer is the second leading cause of death in the United States, and those who survive cancer may experience lasting difficulties, including treatment side effects, as well as physical, cognitive, and psychosocial struggles. Naturally-occurring agents from dietary fruits and vegetables have received considerable attention for the prevention and treatment of cancers. These natural agents are safe and cost efficient in contrast to expensive chemotherapeutic agents, which may induce significant side effects. The pomegranate (*Punica granatum* L.) fruit has been used for the prevention and treatment of a multitude of diseases and ailments for centuries in ancient cultures. Pomegranate exhibits strong antioxidant activity and is a rich source of anthocyanins, ellagitannins, and hydrolysable tannins. Studies have shown that the

pomegranate fruit as well as its juice, extract, and oil exert anti-inflammatory, anti-proliferative, and anti-tumorigenic properties by modulating multiple signaling pathways, which suggest its use as a promising chemopreventive/chemotherapeutic agent. This review summarizes preclinical and clinical studies highlighting the role of pomegranate in prevention and treatment of skin, breast, prostate, lung, and colon cancers.

Bu-Zhong-Yi-Qi Decoction, the Water Extract of Chinese Traditional Herbal Medicine, Enhances Cisplatin Cytotoxicity in A549/DDP Cells through Induction of Apoptosis and Autophagy.

Yu N1, Xiong Y2, Wang C3. Biomed Res Int. 2017;2017:3692797. doi: 10.1155/2017/3692797. Epub 2017 Jan 5.

Cisplatin is one of the most active cytotoxic agents for non-small cell lung cancer (NSCLC) treatment. However, the development of cisplatin resistance is common. Bu-Zhong-Yi-Qi decoction (BZYQD), a Chinese traditional herbal medicine, is widely used for the enhancement of antitumor effect in other medications. In this study, we evaluated the effect and drug-resistance reversal mechanism of BZYQD combined with cisplatin on cisplatin-resistant A549/DDP cells. Our results showed that BZYQD exhibited direct cytotoxic and chemosensitizing effects. Cotreatment with BZYQD and cisplatin induced intrinsic apoptotic pathways which were measured by condensed nuclear chromatin, Annexin V/PI apoptosis assay, and apoptosis related proteins expression. In addition, cotreatment with BZYQD and cisplatin also activated autophagy, as indicated by an increase in LC3 puncta, classical autophagosomes and/or autolysosomes, and an accumulation of LC3-II and ATG7 protein. Finally, cotreatment with BZYQD and cisplatin resulted in the generation of ROS and scavenging ROS by NAC almost completely suppressing cell death. These results suggest that cotreatment with BZYQD and cisplatin might reverse cisplatin resistance by inducing ROS accumulation, which activates apoptosis and autophagy by oxidative stress. The combination of BZYQD and cisplatin may represent a novel approach in treatment for NSCLC and thus offer a new target for chemotherapy.

MISCELLANEOUS WORKS

Differences in Access to and Use of Electronic Personal Health Information Between Rural and Urban Residents in the United States.

Greenberg AJ1,2, Haney D3, Blake KD2, Moser RP2, Hesse BW2. J Rural Health. 2017 Jan 11. doi: 10.1111/jrh.12228. [Epub ahead of print]

PURPOSE: The increase in use of health information technologies (HIT) presents new opportunities for patient engagement and self-management. Patients in rural areas stand to benefit especially from increased access to health care tools and electronic communication with providers. We assessed the adoption of 4 HIT tools over time by rural or urban residency. **METHODS:** Analyses were conducted using data from 7 iterations of the National Cancer Institute's Health Information National Trends Survey (HINTS; 2003-2014). Rural/urban residency was based on the USDA's 2003 Rural-Urban Continuum Codes. Outcomes of interest included managing personal health information online; whether providers maintain electronic health records (EHRs); e-mailing health care providers; and purchasing medicine online. Bivariate analyses and logistic regression were used to assess relationships between geography and outcomes, controlling for sociodemographic characteristics. **FINDINGS:** In total, 6,043 (17.6%, weighted) of the 33,749 respondents across the 7 administrations of HINTS lived in rural areas. Rural participants were less likely to report regular access to Internet (OR = 0.70, 95% CI = 0.61-0.80). Rural respondents were neither more nor less likely to report that their health care providers maintained EHRs than were urban respondents; however, they had decreased odds of managing personal health information online (OR = 0.59, 95% CI = 0.40-0.78) and e-mailing health care providers (OR = 0.62, 95% CI = 0.49-0.77). **CONCLUSIONS:** The digital divide between rural and urban residents extends to HIT. Additional

investigation is needed to determine whether the decreased use of HIT may be due to lack of Internet connectivity or awareness of these tools.

[Proportion of Never-Smoker Non-Small Cell Lung Cancer Patients at Three Diverse Institutions.](#)

Pelosof L1, Ahn C1, Gao A1, Horn L1, Madrigales A1, Cox J1, McGavic D1, Minna JD1, Gazdar AF1, Schiller J2. *J Natl Cancer Inst.* 2017 Jan 28;109(7). pii: djw295. doi: 10.1093/jnci/djw295. Print 2017 Jan.

BACKGROUND: Approximately 10% to 15% of lung cancer cases in the United States occur in never smokers, but there has been much debate about whether this rate is increasing. To determine whether the proportion of never smokers among lung cancer cases is increasing, we conducted a retrospective study using registries from The University of Texas Southwestern Medical Center, Parkland Hospital, and Vanderbilt University. **METHODS:** Registries were queried for demographic information from 1990 to 2013 including sex, age, stage, and self-reported smoking history. Ten thousand five hundred ninety-three non-small cell lung cancer (NSCLC) case patients and 1510 small cell lung cancer (SCLC) case patients were captured, and logistic regression analysis was performed. All statistical tests were two-sided. **RESULTS:** The proportion of never-smoker NSCLC patients increased from 8.0% in the years 1990 to 1995 to 14.9% in 2011 to 2013 ($P < .001$). This increase was also observed using multivariable logistic regression after controlling for sex, stage at diagnosis, and race/ethnicity. The percentage of never smokers among SCLC case patients (1.5% in 1990-1995 to 2.5% in 2011-2013, $P = .36$) or squamous cell NSCLC case patients did not statistically significantly change during this period. **CONCLUSIONS:** This study demonstrates an increasing proportion of NSCLC patients who have never smoked in a large, diverse patient population between 1990 and 2013. Given that this increase appears independent of sex, stage, and race/ethnicity and also occurred in our county hospital, this trend is unlikely due to changes in referral patterns and suggests that the actual incidence of lung cancer in never smokers is increasing.

[Dyadic Perceptions of the Decision Process in Families Living With Lung Cancer.](#) Miller LM1, Sullivan DR2, Lyons KS2. *Oncol Nurs Forum.* 2017 Jan 1;44(1):108-115.

PURPOSE/OBJECTIVES: To use dyadic analyses to identify determinants of patients' and family members' perceptions of the positive and negative aspects of the decision-making process in families living with lung cancer. **DESIGN:** Cross-sectional study. **SETTING:** Community setting in Greater Portland, Oregon. **SAMPLE:** 109 family care dyads (patient and family member) recruited from a statewide cancer registry. **METHODS:** Surveys were completed in-person, separately, and privately by each member of the family care dyad. Secondary analysis was completed using multilevel modeling. **MAIN RESEARCH VARIABLES:** Negative and positive aspects of the decision process. **FINDINGS:** Level 1 data revealed significant variability across care dyads' positive or negative perceptions of the decision-making process. Level 2 results for negative perceptions of decision making indicated that patient and family member perceptions were significantly associated with their own depressive symptoms and feelings of not being listened to by others. Level 2 results for positive perceptions of decision making indicated that patient and family member perceptions were significantly inversely associated with their own feelings of not being listened to and being in nonspousal relationships. In addition, family members' perceptions were more positive when the patients were older. **CONCLUSIONS:** This study highlighted the complexity of the decision-making process in families with lung cancer, and underscored the importance of the care dyad feeling listened to by family members in the context of life-threatening illnesses. **IMPLICATIONS FOR NURSING:** Nurses assisting families with decisions about lung cancer should be aware of the dynamics of the care dyad and how the decision process is perceived by patients and their family members.

[Increasing Rates of No Treatment in Advanced-Stage Non-Small Cell Lung Cancer Patients: A Propensity-Matched Analysis.](#)

David EA1, Daly ME2, Li CS3, Chiu CL4, Cooke DT5, Brown LM5, Melnikow J6, Kelly K7, Canter RJ8. J Thorac Oncol. 2017 Jan 18. pii: S1556-0864(16)33476-1. doi: 10.1016/j.jtho.2016.11.2221. [Epub ahead of print]

INTRODUCTION: Variation in treatment and survival outcomes for NSCLC is high among patients with stage III or IV disease, but patients with untreated NSCLC have not been critically analyzed to evaluate for improvable outcomes. We evaluated treatment trends and their association with oncologic outcomes for NSCLC, hypothesizing that there are a substantial number of untreated patients who are similar to patients who undergo treatment. **METHODS:** Linear regression was used to calculate trends in utilization of treatment. Kaplan-Meier and Cox regression modeling were used to determine predictors of receiving treatment. Propensity matching was used to compare survival among subsets of treated versus untreated patients. **RESULTS:** Patients with primary NSCLC were identified from the National Cancer Data base from 1998 to 2012, and 21% of patients (190,539) received no treatment. For stage IIIA and IV, the proportion of untreated patients increased over the study period by 0.21% and 0.4%, respectively ($p = 0.003$ and $p < 0.0001$). Regardless of stage, untreated patients had significantly shorter overall survival (OS) ($p < 0.0001$). Propensity-matched analyses of 6144 stage IIIA patient pairs treated with chemoradiation versus no treatment confirmed shorter OS for untreated patients (median 16.5 versus 6.1 months, $p < 0.0001$). For 19,046 stage IV patient pairs treated with chemotherapy versus no treatment, similar results were obtained (median OS 9.3 versus 2.0 months, $p < 0.0001$). **CONCLUSIONS:** The proportion of untreated patients with stage IIIA and IV disease is increasing. Survival outcomes among patients with advanced-stage disease are superior with treatment, independent of selection bias. The benefits and risks of treatment should be carefully assessed before choosing to forego treatment.