Caring Ambassadors Lung Cancer Program

Literature Review, February 2016

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

The Microenvironment of Lung Cancer and Therapeutic Implications. Mittal V1,2,3, El Rayes T4,5,6,7, Narula N8, McGraw TE5,6,9, Altorki NK5,6, Barcellos-Hoff MH10. Adv Exp Med Biol. 2016;890:75-110. doi: 10.1007/978-3-319-24932-2_5.

The tumor microenvironment (TME) represents a milieu that enables tumor cells to acquire the hallmarks of cancer. The TME is heterogeneous in composition and consists of cellular components, growth factors, proteases, and extracellular matrix. Concerted interactions between genetically altered tumor cells and genetically stable intratumoral stromal cells result in an "activated/reprogramed" stroma that promotes carcinogenesis by contributing to inflammation, immune suppression, therapeutic resistance, and generating premetastatic niches that support the initiation and establishment of distant metastasis. The lungs present a unique milieu in which tumors progress in collusion with the TME, as evidenced by regions of aberrant angiogenesis, acidosis and hypoxia. Inflammation plays an important role in the pathogenesis of lung cancer, and pulmonary disorders in lung cancer patients such as chronic obstructive pulmonary disease (COPD) and emphysema, constitute comorbid conditions and are independent risk factors for lung cancer. The TME also contributes to immune suppression, induces epithelial-to-mesenchymal transition (EMT) and diminishes efficacy of chemotherapies. Thus, the TME has begun to emerge as the "Achilles heel" of the disease, and constitutes an attractive target for anti-cancer therapy. Drugs targeting the components of the TME are making their way into clinical trials. Here, we will focus on recent advances and emerging concepts regarding the intriguing role of the TME in lung cancer progression, and discuss future directions in the context of novel diagnostic and therapeutic opportunities.

The p70S6K Specific Inhibitor PF-4708671 Impedes Non-Small Cell Lung Cancer Growth. Qiu ZX1, Sun RF2, Mo XM3, Li WM1. PLoS One. 2016 Jan 15;11(1):e0147185. doi: 10.1371/journal.pone.0147185. eCollection 2016.

BACKGROUND: As a serine/threonine protein kinase, p70S6K plays an important role in tumor cells. Evidence has revealed overexpression of p70S6K and phosphorylated p70S6K (p-p70S6K) in various tumor tissues, with these proteins identified as independent prognostic markers in non-small cell lung cancer (NSCLC). In this study, we explored the role of the p70S6K specific inhibitor PF-4708671 in

NSCLC. **METHODS:** Three NSCLC cell lines (A549, SK-MES-1, and NCI-H460) were treated with PF-4708671 at five different concentrations, including 0.1μM, 0.3μM, 1μM, 3μM and 10μM, and protein levels were determined by Western-blot. Then, PF-4708671's effects were assessed both in vitro (cell proliferation, apoptosis, cell cycle distribution, and invasion) and in vivo. **RESULTS:** The expression levels of p-p70S6K and the downstream effector S6 were significantly reduced by PF-4708671. Diametrically opposite, the downstream protein levels of BAD, Caspase3 and ERK had increased after treatment with PF-4708671. In addition, PF-4708671 drastically inhibited cell proliferation and invasion ability in A549, SK-MES-1 and NCI-H460 cells in vitro, causing cell cycle arrest in G0-G1 phase. Limited effects of PF-4708671 were observed on apoptosis in the three NSCLC cell lines assessed. Importantly, PF-4708671 could inhibit tumorigenesis in nude mice in vivo. **CONCLUSION:** These findings demonstrated that the p70S6K specific inhibitor PF-4708671 has inhibitory effects on NSCLC tumorigenesis in vitro and in vivo. Therefore, P70S6K should be considered a new potential therapeutic target, and PF-470867 may be used as targeted drug for cancer treatment.

The Role of Cancer Stem Cells in Recurrent and Drug-Resistant Lung Cancer. Suresh R1, Ali S2, Ahmad A3, Philip PA2, Sarkar FH4,5. Adv Exp Med Biol. 2016;890:57-74. doi: 10.1007/978-3-319-24932-2_4.
Lung cancer is the leading cause of cancer-related deaths worldwide with a 5-year overall survival rate of less than 20 %. Considering the treatments currently available, this statistics is shocking. A possible explanation for the disconnect between sophisticated treatments and the survival rate can be related to the post-treatment enrichment of Cancer Stem Cells (CSCs), which is one of a sub-set of drug resistant tumor cells with abilities of self-renewal, cancer initiation, and further maintenance of tumors. Lung CSCs have been associated with resistance to radiation and chemotherapeutic treatments. CSCs have also been implicated in tumor recurrence because CSCs are not typically killed after conventional therapy. Investigation of CSCs in determining their role in tumor recurrence and drug-resistance relied heavily on the use of specific markers present in CSCs, including CD133, ALDH, ABCG2, and Nanog. Yet another cell type that is also associated with increased resistance to treatment is epithelial-to-mesenchymal transition (EMT) phenotypic cells. Through the processes of EMT, epithelial cells lose their epithelial phenotype and gain mesenchymal properties, rendering EMT phenotypic cells acquire drug-resistance. In this chapter, we will further discuss the role of microRNAs (miRNAs) especially because miRNA-based therapies are becoming attractive target with respect to therapeutic resistance and CSCs. Finally, the potential role of the natural agents and synthetic derivatives of natural compounds with anti-cancer activity, e.g. curcumin, CDF, and BR-DIM is highlighted in overcoming therapeutic resistance, suggesting that the above mentioned agents could be important for better treatment of lung cancer in combination therapy.

Serum Biomarkers Associated with Clinical Outcomes Fail to Predict Brain Metastases in Patients with Stage IV Non-Small Cell Lung Cancers. Li BT1,2, Lou E3, Hsu M4, et al. PLoS One. 2016 Jan 5;11(1):e0146063. doi: 10.1371/journal.pone.0146063. eCollection 2016.
BACKGROUND: Lung cancers account for the majority of brain metastases which pose major therapeutic challenges. Biomarkers prognosticating for the development of brain metastases in patients with non-small cell lung cancers (NSCLC) may improve personalized care. Six serum proteomic biomarkers were previously investigated at Memorial Sloan Kettering but their associations with brain metastases were unknown. **METHODS:** Serum NSE, CYFRA 21-1, ProGRP, SCC-Ag, TIMP1, and HE4 by ELISA-based proteomic assays were prospectively collected from consecutive patients with stage IV NSCLC. Pre-treatment serum biomarker levels as well as age, histology, and epidermal growth factor receptor (EGFR) mutation status were evaluated for association with the baseline presence of brain metastases using logistic regression and multivariable analysis. For patients without brain metastases at

baseline, the cumulative incidence of subsequent brain metastases were compared according to baseline biomarkers and clinical factors using Gray's test. **RESULTS:** A total of 118 patients were enrolled, 31 (26%; 95% CI 0.19-0.35) had brain metastases at baseline and a further 26 (22%; 95% CI 0.15-0.30) developed brain metastases subsequently. Pre-treatment serum biomarker levels were available in 104 patients. There was no significant association between the six serum biomarkers and the baseline presence or subsequent development of brain metastases. Age younger than 65 years was the only clinical factor significantly associated with brain metastasis at baseline (OR 3.00; 95% CI 1.22-7.34, P = 0.02) by multivariable analysis. A trend toward increased cumulative incidence of subsequent brain metastases was observed in patients with EGFR mutation (p = 0.2), but this was not statistically significant possibly due to small sample size. **CONCLUSIONS:** Serum NSE, CYFRA 21-1, Pro-GRP, SCC-Ag, TIMP1, and HE4 are not significantly associated with brain metastases. Our methods taking into account follow-up time may be applied to independent datasets to identify a patient cohort with a higher biologic propensity for developing brain metastases. Such information may be useful for the study of agents targeting the development of brain metastases.

PDL1 Regulation by p53 via miR-34. Cortez MA1, Ivan C1, Valdecanas D1, et al. J Natl Cancer Inst. 2015 Nov 17;108(1). pii: djv303. doi: 10.1093/jnci/djv303. Print 2016 Jan.
BACKGROUND: Although clinical studies have shown promise for targeting PD1/PDL1 signaling in non-small cell lung cancer (NSCLC), the regulation of PDL1 expression is poorly understood. Here, we show that PDL1 is regulated by p53 via miR-34. **METHODS:** p53 wild-type and p53-deficient cell lines (p53(-/-) and p53(+/+) HCT116, p53-inducible H1299, and p53-knockdown H460) were used to determine if p53 regulates PDL1 via miR-34. PDL1 and miR-34a expression were analyzed in samples from patients with NSCLC and mutated p53 vs wild-type p53 tumors from The Cancer Genome Atlas for Lung Adenocarcinoma (TCGA LUAD). We confirmed that PDL1 is a direct target of miR-34 with western blotting and luciferase assays and used a p53(R172HΔ)g/+K-ras(LA1/+) syngeneic mouse model (n = 12) to deliver miR-34a-loaded liposomes (MRX34) plus radiotherapy (XRT) and assessed PDL1 expression and tumor-infiltrating lymphocytes (TILs). A two-sided t test was applied to compare the mean between different treatments. **RESULTS:** We found that p53 regulates PDL1 via miR-34, which directly binds to the PDL1 3' untranslated region in models of NSCLC (fold-change luciferase activity to control group, mean for miR-34a = 0.50, SD = 0.2, P < .001; mean for miR-34b = 0.52, SD = 0.2, P = .006; and mean for miR-34c = 0.59, SD = 0.14, and P = .006). Therapeutic delivery of MRX34, currently the subject of a phase I clinical trial, promoted TILs (mean of CD8 expression percentage of control group = 22.5%, SD = 1.9%; mean of CD8 expression percentage of MRX34 = 30.1%, SD = 3.7%, P = .016, n = 4) and reduced CD8(+)PD1(+) cells in vivo (mean of CD8/PD1 expression percentage of control group = 40.2%, SD = 6.2%; mean of CD8/PD1 expression percentage of MRX34 = 20.3%, SD = 5.1%, P = .001, n = 4). Further, MRX34 plus XRT increased CD8(+) cell numbers more than either therapy alone (mean of CD8 expression percentage of MRX34 plus XRT to control group = 44.2%, SD = 8.7%, P = .004, n = 4). Finally, miR-34a delivery reduced the numbers of radiation-induced macrophages (mean of F4-80 expression percentage of control group = 52.4%, SD = 1.7%; mean of F4-80 expression percentage of MRX34 = 40.1%, SD = 3.5%, P = .008, n = 4) and T-regulatory cells. **CONCLUSIONS:** We identified a novel mechanism by which tumor immune evasion is regulated by p53/miR-34/PDL1 axis. Our results suggest that delivery of miRNAs with standard therapies, such as XRT, may represent a novel therapeutic approach for lung cancer.

SCREENING, DIAGNOSIS AND STAGING

Emerging Biomarkers in Personalized Therapy of Lung Cancer. Cagle PT1, Raparia K2, Portier BP3. Adv Exp Med Biol. 2016;890:25-36. doi: 10.1007/978-3-319-24932-2_2.
The two clinically validated and Food and Drug Administration approved lung cancer predictive biomarkers (epidermal growth factor receptor mutations and anaplastic lymphoma kinase (ALK) translocations) occur in only about 20 % of lung adenocarcinomas and acquired resistance develops to first generation drugs. Several other oncogenic drivers for lung adenocarcinoma have emerged as potentially druggable targets with new predictive biomarkers. Oncologists are requesting testing for ROS1 translocations which predict susceptibility to crizotinib, already approved for ALK positive lung cancers. Other potential biomarkers which are currently undergoing clinical trials are RET, MET, HER2 and BRAF. Detection of these biomarkers includes fluorescent in situ hybridization and/or reverse transcriptase polymerase chain reaction (ROS1, RET, HER2), mutation analysis (BRAF) and immunohistochemistry (MET). Screening by immunohistochemistry may be useful for some biomarkers (ROS1, BRAF). Targeted next generation sequencing techniques may be useful as well. These five biomarkers are under consideration for inclusion in revised lung cancer biomarker guidelines by the College of American Pathologists, International Association for the Study of Lung Cancer and Association for Molecular Pathology.

Limitations of PET/CT in the Detection of Occult N1 Metastasis in Clinical Stage I(T1-2aN0) Non-Small Cell Lung Cancer for Staging Prior to Stereotactic Body Radiotherapy. Akthar AS1, Ferguson MK2, Koshy M1, Vigneswaran WT3, Malik R4. Technol Cancer Res Treat. 2016 Jan 20. pii: 1533034615624045. [Epub ahead of print]
PURPOSE/OBJECTIVES: Patients receiving stereotactic body radiotherapy for stage I non-small cell lung cancer are typically staged clinically with positron emission tomography-computed tomography. Currently, limited data exist for the detection of occult hilar/peribronchial (N1) disease. We hypothesize that positron emission tomography-computed tomography underestimates spread of cancer to N1 lymph nodes and that future stereotactic body radiotherapy patients may benefit from increased pathologic evaluation of N1 nodal stations in addition to N2 nodes. **MATERIALS/METHODS:** A retrospective study was performed of all patients with clinical stage I (T1-2aN0) non-small cell lung cancer (American Joint Committee on Cancer, 7th edition) by positron emission tomography-computed tomography at our institution from 2003 to 2011, with subsequent surgical resection and lymph node staging. Findings on positron emission tomography-computed tomography were compared to pathologic nodal involvement to determine the negative predictive value of positron emission tomography-computed tomography for the detection of N1 nodal disease. An analysis was conducted to identify predictors of occult spread. **RESULTS:** A total of 105 patients with clinical stage I non-small cell lung cancer were included in this study, of which 8 (7.6%) patients were found to have occult N1 metastasis on pathologic review yielding a negative predictive value for N1 disease of 92.4%. No patients had occult mediastinal nodes. The negative predictive value for positron emission tomography-computed tomography in patients with clinical stage T1 versus T2 tumors was 72 (96%) of 75 versus 25 (83%) of 30, respectively (P = .03), and for peripheral versus central tumor location was 77 (98%) of 78 versus 20 (74%) of 27, respectively (P = .0001). The negative predictive values for peripheral T1 and T2 tumors were 98% and 100%, respectively; while for central T1 and T2 tumors, the rates were 85% and 64%, respectively. Occult lymph node involvement was not associated with primary tumor maximum standard uptake value, histology, grade, or interval between positron emission tomography-computed tomography and surgery. **CONCLUSION:** Our results support pathologic assessment of N1 lymph nodes in patients with stage Inon-small cell lung cancer considered for stereotactic body radiotherapy, with the greatest benefit in

patients with central and T2 tumors. Diagnostic evaluation with endoscopic bronchial ultrasound should be considered in the evaluation of stereotactic body radiotherapy candidates.

Translating New Lung Cancer Screening Guidelines into Practice: The Experience of One Community Hospital. Ledford CJ1, Gawrys BL2, Wall JL2, Saas PD2, Seehusen DA2. J Am Board Fam ed. 2016 Jan-Feb;29(1):152-5. doi: 10.3122/jabfm.2016.01.150120.
INTRODUCTION: In December 2013 the US Preventive Services Task Force issued a recommendation for lung cancer screening with annual low-dose computed tomography (LDCT). As screening guidelines emerge and change, this creates an environment for studying the translation of these guidelines into practice. This study assessed how these guidelines were implemented in a community hospital setting and the resulting radiologic findings. **METHODS:** This observational study examined the radiologic outcomes of LDCT lung cancer screening guidelines and the resulting notification. **RESULTS:** During the first year after publication of the guidelines, 94 screening LDCT scans were ordered. Of these, 21 (22.3%) did not meet the criteria outlined by the US Preventive Services Task Force. Among the 72 cases that did met published criteria, 65.3% of scans detected nodules, and among the remaining 35.6%, half had another clinically significant finding. **DISCUSSION:** This study shows that new lung cancer screening guidelines, as implemented at a community hospital, resulted in radiologic findings that required follow-up in more than half of patients. Clinicians must be aware of these potential incidental findings when talking to patients about the decision to order screenings.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Women in Thoracic Surgery: 30 Years of History. Antonoff MB1, David EA2, Donington JS3, Colson YL4, Litle VR5, Lawton JS6, Burgess NL7. Ann Thorac Surg. 2016 Jan;101(1):399-409. doi: 10.1016/j.athoracsur.2015.11.014.
Women in Thoracic Surgery was founded in 1986, with 2016 marking its 30th anniversary. Reflecting back on the last 3 decades of history, accomplishments, and enormous strides in our field, we review the past, present, and future of this organization. Although women still constitute a small minority of practicing surgeons in our field today, opportunities currently abound for women in thoracic surgery. Owing much to the early female pioneers in the field and to the support of male sponsors and our national societies, Women in Thoracic Surgery has grown and prospered, as have its members and the global community of female thoracic surgeons as a whole. In celebration of our 30th anniversary, we share with the readership the rich history of Women in Thoracic Surgery and its goals for the future.

Nodal Upstaging Is More Common with Thoracotomy than with VATS During Lobectomy for Early-Stage Lung Cancer: An Analysis from the National Cancer Data Base. Medbery RL1, Gillespie TW2, Liu Y3, et al. J Thorac Oncol. 2016 Feb;11(2):222-33. doi: 10.1016/j.jtho.2015.10.007. Epub 2016 Jan 11.
INTRODUCTION: Questions remain regarding differences in nodal evaluation and upstaging between thoracotomy (open) and video-assisted thoracic surgery (VATS) approaches to lobectomy for early-stage lung cancer. Potential differences in nodal staging based on operative approach remain the final significant barrier to widespread adoption of VATS lobectomy. The current study examines differences in nodal staging between open and VATS lobectomy. **METHODS:** The National Cancer Data Base was queried for patients with clinical stage T2N0M0 or lower lung cancer who underwent lobectomy in 2010-2011. Propensity score matching was performed to compare the rate of nodal upstaging in VATS with that in open approaches. Additional subgroup analysis was performed to assess whether rates of upstaging

differed by specific clinical setting. **RESULTS:** A total of 16,983 lobectomies were analyzed; 4935 (29.1%) were performed using VATS. Nodal upstaging was more frequent in the open group (12.8% versus 10.3%; $p < 0.001$). In 4437 matched pairs, nodal upstaging remained more common for open approaches. For a subgroup of patients who had seven lymph or more nodes examined, propensity matching revealed that nodal upstaging remained more common after an open approach than after VATS (14.0% versus 12.1%; $p = 0.03$). For patients who were treated in an academic/research facility, however, the difference in nodal upstaging between an open and VATS approach was no longer significant (12.2% versus 10.5%, $p = 0.08$). **CONCLUSIONS:** For early-stage lung cancer, nodal upstaging was observed more frequently with thoracotomy than with VATS. However, nodal upstaging appears to be affected by facility type, which may be a surrogate for expertise in minimally invasive surgical procedures.

The Society of Thoracic Surgeons Composite Score for Rating Program Performance for Lobectomy for Lung Cancer. Kozower BD1, O'Brien SM2, Kosinski AS2, et al. Ann Thorac Surg. 2016 Jan 16. pii: S0003-4975(15)01753-1. doi: 10.1016/j.athoracsur.2015.10.081. [Epub ahead of print]
BACKGROUND: The Society of Thoracic Surgeons (STS) has developed multidimensional composite quality measures for common cardiac surgery procedures. This first composite measure for general thoracic surgery evaluates STS participant performance for lobectomy in lung cancer patients.
METHODS: The STS lobectomy composite score is composed of two outcomes: risk-adjusted mortality; and any-or-none, risk-adjusted major complications. General Thoracic Surgery Database data were included from 2011 to 2014 to provide adequate sample size, and 95% Bayesian credible intervals were used to determine "star ratings." The STS participants were also compared with national benchmarks (including non-STS participants) using the National Inpatient Sample. Comparisons of discharge mortality, postoperative length of stay, and percent of stage I lung cancers resected using minimally invasive approaches are not included in star ratings but will be reported to participants in STS feedback reports. **RESULTS:** The study population included 20,657 lobectomy patients from 231 participating centers. Operative mortality was 1.5%, major complication rate was 9.6%, and median postoperative length of stay was 4 days. Risk-adjusted mortality and major complication rates varied threefold from highest performing (three-star) to lowest performing (one-star) programs. Approximately 5% of participants were one-star, 7% were three-star, and 88% were two-star programs. **CONCLUSIONS:** The STS has developed the first general thoracic surgery quality composite measure to compare programs performing lobectomy for lung cancer. This measure will be used for quality assessment and provider feedback, and will be made available for voluntary public reporting.

Limited thoracotomy for segmentectomy: a comparison of postoperative pain with thoracoscopic lobectomy. Nomori H1, Cong Y2, Sugimura H2. Surg Today. 2016 Jan 18. [Epub ahead of print]
PURPOSES: To assess whether a video-assisted thoracoscopic surgery (VATS) procedure is superior to limited thoracotomy (LT) for segmentectomy; postoperative pain was compared between VATS-lobectomy (VATS-L) and LT-segmentectomy (LT-S). Widely opened anterolateral thoracotomy segmentectomy (WT-S) was used as a control. **METHODS:** This study was a retrospective analysis of prospectively collected data for 220 consecutive patients with stage I NSCLC treated between 2012 and 2015 at a single institute using VATS-L ($n = 58$), LT-S ($n = 93$), or WT-S ($n = 69$). Pain scores from postoperative days (POD) 1-4 were measured using a visual analog scale three times a day. Chronic pain was assessed by the need for analgesics at 1, 2, and 3 months postoperatively. **RESULTS:** No significant differences in pain from POD 1 to 4 were observed between VATS-L and LT-S, whereas WT-S showed significantly higher pain scores than these two procedures ($p = 0.0001$-0.02). Chronic pain did not differ significantly among the procedures. **CONCLUSION:** Postoperative pain does not differ significantly between VATS-L and LT-S. LT may be preferable to VATS for segmentectomy to identify the anatomy, dissect the hilar nodes, and establish surgical margins.

Prevention of Atrial Fibrillation in High-risk Patients Undergoing Lung Cancer Surgery: The PRESAGE Trial. Cardinale D1, Sandri MT, Colombo A, et al. Ann Surg. 2016 Jan 13. [Epub ahead of print]

OBJECTIVE: We performed a prospective, randomized clinical study to assess whether prophylactic treatment with metoprolol or losartan, initiated soon after lung cancer surgery in patients with elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, reduces the incidence of postoperative atrial fibrillation. **BACKGROUND:** Postoperative atrial fibrillation is a well recognized complication after lung cancer surgery, with an incidence as high as 30%. Perioperative increase of NT-proBNP has been demonstrated to be a strong independent predictor of postoperative atrial fibrillation in this setting. **METHODS:** NT-proBNP concentration was measured 24 hours before surgery and soon after surgery in 1116 patients. Three hundred twenty (29%) patients showed a high NT-proBNP value and were enrolled: 108 were assigned to the metoprolol group, 102 to the losartan group, and 110 to the control group. **RESULTS:** Overall, the incidence of postoperative atrial fibrillation was 20% (n = 64); it was significantly lower in the metoprolol and losartan groups compared with the control group [6%, 12%, and 40%, respectively; relative risk 0.19, 95% confidence intervals (CIs), 0.09-0.37; P < 0.001 in the metoprolol group; and 0.29, 95% CI, 0.16-0.52; P < 0.001 in the losartan group). No significant difference was found when the metoprolol and losartan groups were directly compared (P = 0.21). **CONCLUSIONS:** A prophylactic treatment with metoprolol or losartan, initiated soon after lung cancer surgery in patients with high NT-proBNP levels, significantly reduced the occurrence of postoperative atrial fibrillation.

NSCLC - CHEMOTHERAPY

Benefit-Risk Summary of Nivolumab for Patients With Metastatic Squamous Cell Lung Cancer After Platinum-Based Chemotherapy: A Report From the US Food and Drug Administration. Kazandjian D1, Khozin S1, Blumenthal G1, et al. JAMA Oncol. 2016 Jan 1;2(1):118-22. doi: 10.1001/jamaoncol.2015.3934.

IMPORTANCE: Metastatic squamous non-small-cell lung cancer (SQ NSCLC) is a serious and life-threatening malignant condition with unmet medical need. In late December 2014, the US Food and Drug Administration (FDA) obtained the data monitoring committee report of a planned interim analysis of a trial in second-line SQ NSCLC (CM017) that demonstrated an overall survival benefit for patients treated with nivolumab compared with docetaxel. **OBSERVATIONS:** In that trial, 272 patients with metastatic SQ NSCLC patients had been randomized to receive nivolumab (n = 135) or docetaxel (n = 137). Median overall survival was 9.2 months for patients randomized to nivolumab and 6.0 months for those randomized to docetaxel (hazard ratio, 0.59; 95% CI, 0.44-0.79; P < .001). The safety of nivolumab was evaluated in a single-arm trial of 117 patients in previously treated metastatic SQ NSCLC and was consistent with the safety profile in melanoma, with rare but serious immune-mediated adverse events managed with corticosteroids and dose interruption. **CONCLUSIONS AND RELEVANCE:** The FDA granted nivolumab traditional approval on March 4, 2015, for treatment of metastatic SQ NSCLC with progression during or after platinum-based chemotherapy. The approval provides an important treatment option for these patients, affecting routine care and clinical trials.

Adjuvant Chemotherapy Improves the Probability of Freedom From Recurrence in Patients With Resected Stage IB Lung Adenocarcinoma. Hung JJ1, Wu YC1, Chou TY2, Jeng WJ3, Yeh YC2, Hsu WH4. Ann Thorac Surg. 2016 Jan 12. pii: S0003-4975(15)01747-6. doi: 10.1016/j.athoracsur.2015.10.075. [Epub ahead of print]

BACKGROUND: The benefit of adjuvant chemotherapy remains controversial for patients with stage IB non-small-cell lung cancer (NSCLC). This study investigated the effect of adjuvant chemotherapy and the predictors of benefit from adjuvant chemotherapy in patients with stage IB lung adenocarcinoma. **METHODS:** A total of 243 patients with completely resected pathologic stage IB lung adenocarcinoma were included in the study. Predictors of the benefits of improved overall survival (OS) or probability of freedom from recurrence (FFR) from platinum-based adjuvant chemotherapy in patients with resected stage IB lung adenocarcinoma were investigated. **RESULTS:** Among the 243 patients, 70 (28.8%) had received platinum-based doublet adjuvant chemotherapy. A micropapillary/solid-predominant pattern (versus an acinar/papillary-predominant pattern) was a significantly worse prognostic factor for probability of FFR ($p = 0.033$). Although adjuvant chemotherapy (versus surgical intervention alone) was not a significant prognostic factor for OS ($p = 0.303$), it was a significant prognostic factor for a better probability of FFR ($p = 0.029$) on multivariate analysis. In propensity-score-matched pairs, there was no significant difference in OS between patients who received adjuvant chemotherapy and those who did not ($p = 0.386$). Patients who received adjuvant chemotherapy had a significantly better probability of FFR than those who did not ($p = 0.043$). For patients with a predominantly micropapillary/solid pattern, adjuvant chemotherapy ($p = 0.033$) was a significant prognostic factor for a better probability of FFR on multivariate analysis. **CONCLUSIONS:** Adjuvant chemotherapy is a favorable prognostic factor for the probability of FFR in patients with stage IB lung adenocarcinoma, particularly in those with a micropapillary/solid-predominant pattern.

Treatment of recurrent and platinum-refractory stage IV non-small cell lung cancer with nanoparticle albumin-bound paclitaxel (nab-paclitaxel) as a single agent. Saxena A1, Schneider BJ2,3, Christos PJ4, Audibert LF2,5, Cagney JM2,6, Scheff RJ2. Med Oncol. 2016 Feb;33(2):13. doi: 10.1007/s12032-015-0728-2. Epub 2016 Jan 9.
The role of single-agent nab-paclitaxel in relapsed or platinum-refractory advanced non-small cell lung cancer (NSCLC) has not been well reported in Western populations. We reviewed our own institution's experience using nab-paclitaxel in these settings. We analyzed the records of stage IV NSCLC patients with relapsed or platinum-refractory disease treated with single-agent nab-paclitaxel at Weill Cornell Medical College between October 2008 and December 2013. The primary endpoint of the study was treatment failure-free survival (TFFS), defined as the time from the start of nab-paclitaxel therapy to discontinuation of the drug for any reason. The best overall response was recorded for each patient, and overall response and disease control rates were calculated. Thirty-one stage IV NSCLC patients received a median of 4 cycles (range 1-40) of nab-paclitaxel. Dose reduction or drug discontinuation due to toxicity occurred in 10 patients, mainly because of grade 2/3 fatigue or peripheral neuropathy. The overall response rate was 16.1 %, and the disease control rate was 64.5 %. Median TFFS was 3.5 months (95 % CI 1.3-5.3 months). No statistically significant difference in TFFS based on line of therapy or prior taxane exposure was identified. There was a statistically significant decrease in TFFS for patients with non-adenocarcinoma histology, although there were only five patients in this group. There was a trend toward reduction in the risk of treatment failure with increasing age. One patient remained on nab-paclitaxel therapy for over 3 years. Single-agent nab-paclitaxel was well tolerated and demonstrated efficacy in advanced NSCLC patients with relapsed or platinum-refractory disease. Further prospective clinical trials with nab-paclitaxel in these settings are warranted.

Effectiveness of bevacizumab exposure beyond disease progression in patients with non-small-cell lung cancer: analyses of the ARIES observational cohort study. Leon L1, Kosty M2, Jahanzeb M3, et al. Pharmacoepidemiol Drug Saf. 2016 Jan 8. doi: 10.1002/pds.3948. [Epub ahead of print]
PURPOSE: Bevacizumab used in combination with first-line chemotherapy confers an overall survival (OS) benefit for patients with non-squamous non-small-cell lung cancer (NSCLC). This analysis from the

ARIES observational cohort study (OCS) was initiated to evaluate the effect of bevacizumab use beyond disease progression (BBP) on clinical outcomes in patients with NSCLC receiving first-line treatment with bevacizumab and chemotherapy. **METHODS:** The ARIES OCS prospectively enrolled patients from 2006 to 2009 in the United States who had advanced non-squamous NSCLC, received bevacizumab with chemotherapy in the first-line setting, and survived progressive disease (PD). A dichotomous landmark analysis examined post-PD OS (ppOS) in patients who received BBP versus no BBP within 30 days post PD. A time-dependent Cox model assessed the effect of cumulative BBP exposure on ppOS. **RESULTS:** The ARIES OCS enrolled 1967 patients with first-line NSCLC; 1358 patients had first PD and were alive at the 30-day landmark (351 patients with BBP and 1007 patients with no BBP). The landmark analysis showed that BBP was associated with a lower risk of death (BBP versus No-BBP); hazard ratio [HR], 0.75; 95% confidence interval 0.65-0.86. In the cumulative exposure analysis of 1461 patients who had PD, HRs for ppOS decreased by approximately 4% for each additional 21-day interval of bevacizumab received. Protocol-specified bevacizumab-select adverse events occurred in 14% of BBP patients. **CONCLUSIONS:** BBP was associated with a lower risk of death in patients with NSCLC treated with first-line bevacizumab and chemotherapy.

Volumetric Tumor Response and Progression in EGFR-mutant NSCLC Patients Treated with Erlotinib or Gefitinib. Nishino M1, Dahlberg SE2, Fulton LE3, Digumarthy SR4, Hatabu H5, Johnson BE6, Sequist LV3. Acad Radiol. 2016 Jan 8. pii: S1076-6332(15)00517-6. doi: 10.1016/j.acra.2015.11.005. [Epub ahead of print]
RATIONALE AND OBJECTIVES: The aims of this study were to investigate the association between 8-week tumor volume decrease and survival in an independent cohort of epidermal growth factor receptor (EGFR)-mutant advanced non-small cell lung cancer (NSCLC) patients treated with first-line erlotinib or gefitinib, and to assess the rate of their volumetric tumor growth after the volume nadir. **MATERIALS AND METHODS:** In patients with advanced NSCLC harboring sensitizing EGFR mutations treated with first-line erlotinib or gefitinib, computed tomography (CT) tumor volumes of dominant lung lesions were analyzed for (1) the association with survival, and (2) the volumetric tumor growth rate after the volume nadir. **RESULTS:** In 44 patients with the 8-week follow-up CT, the 8-week tumor volume decrease (%) was significantly associated with longer overall survival when fitted as a continuous variable in a Cox model ($P = 0.01$). The growth rate of the logarithm of tumor volume (logeV), obtained using a linear mixed-effects model adjusting for time since baseline, was 0.096/month (SE: 0.013/month; 95% confidence interval [CI]: 0.071-0.12/month), which was similar to the rate of 0.12/month (SE: 0.015/month; 95%CI: 0.090-0.15/month) observed in the previous report. **CONCLUSIONS:** The 8-week tumor volume decrease was validated as a marker for longer survival in the independent cohort of EGFR-mutant NSCLC patients treated with first-line erlotinib or gefitinib. The volumetric tumor growth rate after the nadir in this cohort was similar to that of the previous cohort, indicating the reproducibility of the observation among different patient cohorts.

NSCLC - RADIOTHERAPY

Radiotherapy effects on brain/bone metastatic adenocarcinoma lung cancer and the importance of EGFR mutation test. Qu BL, Cai BN, Yu W, Liu F, Huang YR, Ju ZJ, Wang XS, Ou GM, Feng LC. Neoplasma. 2016;63(1):158-62. doi: 10.4149/neo_2016_019.
This study proposed to retrospectively analyze the efficacy of radiotherapy on brain/bone metastases in patients with stage IV lung adenocarcinoma and to evaluate the correlation between overall survival after radiotherapy and other factors including metastatic sites and EGFR mutation status. 115 patients with Stage IV lung adenocarcinoma admitted to our center from March, 2011 to December, 2013 were enrolled. They presented with metastases to no other solid organs except the bone or brain and had

received no prior treatment. 50 patients received EGFR mutation test with 32 detected as EGFR mutant and 18 wild-type. Patients with brain metastases were treated with 40 Gy whole brain irradiation (WBI) in 2 Gy fractions; patients with bone metastases were treated with 30 Gy local irradiation in 3 Gy fractions or 40 Gy in 2 Gy fractions. All the patients received systemic therapy during or after radiotherapy and 68 received targeted therapy.The median overall survival of patients with solitary brain metastases, solitary bone metastases or combined brain and bone metastases were 8.50 months, 8.50 months and 9.50 months respectively, revealing no significant difference (p=0.57). The median overall survival of patients with EGFR mutations was 10.25 months, longer than the 8.75 months of patients without EGFR mutations, revealing no significant difference (p=0.57). The median overall survival of EGFR mutant patients with solitary bone metastases, solitary brain metastases or combined brain and bone metastases were 7.50 months, 10.50 months and 11.50 months respectively, revealing no significant difference (p=0.91). 36 patients with untested EGFR mutation status received EGFR-TKI. Among EGFR mutant patients, 10 didn't receive targeted therapy; 8 were administered Erlotinib and 14 Gefitinib with median overall survival of 10.25 months and 14.5 months, showing no significant difference (p=0.11) between the two drugs. When patients with stage IV lung adenocarcinoma have been treated by early radiotherapy, the overall survival doesn't correlate with metastatic sites. Radiotherapy could extend survival for EGFR mutant patients with stage IV lung adenocarcinoma. EGFR mutation test should be performed before treatment of the disease.

Changes in Treatment Patterns and Overall Survival in Patients With Early-Stage Non-Small Cell Lung Cancer in the United States After the Incorporation of Stereotactic Ablative Radiation Therapy: A Population-based Analysis. Haque W1, Szeja S, Tann A, Kalra S, Teh BS. Am J Clin Oncol. 2016 Jan 14. [Epub ahead of print]

PURPOSE: Technologic developments have made radiation therapy (RT) more effective and have introduced new treatment options, such as stereotactic ablative radiation therapy (SABR). This study sought to determine changes in practice patterns for treatment of stage IA non-small cell lung cancer (NSCLC) after the introduction of SABR into the United States. This population-based study also examined changes in survival during this time period for all patients and specifically for patients treated with RT, surgery, or observation. **METHODS:** We included patients in the Surveillance, Epidemiology, and End Results database diagnosed with stage IA NSCLC diagnosed between 2004 and 2012. Changes in treatment patterns were assessed. Outcomes were compared across 2 time periods: 2004 to 2008 (pre-SABR) and 2009 to 2012 (post-SABR). Kaplan-Meier and Cox regression were performed to compare overall survival (OS) for patients treated with surgery, RT, or observation. **RESULTS:** A total of 32,249 patients met the specified criteria. Comparing patients diagnosed in 2004 to those diagnosed in 2012, RT use increased from 13% to 29% (P<0.001), surgery use decreased from 76% to 61% (P<0.001), and patients observed decreased from 11% to 10% (P=0.3). There was no significant OS improvement in all patients or those patients who were observed; there were significant improvements in OS for patients treated with RT (hazard ratio=0.768; 95% confidence interval, 0.711-0.829) and those patients treated with surgery (hazard ratio=0.9; 95% confidence interval, 0.855-0.962). **CONCLUSIONS:** There has been an increase in RT utilization and decrease in surgical utilization after the incorporation of SABR by radiation oncologists within the United States. In addition, there has been an improvement in OS for patients treated with definitive RT for early-stage NSCLC between 2004 and 2012 that may be associated with increased utilization of SABR.

Patient outcomes of monotherapy with hypofractionated three-dimensional conformal radiation therapy for stage T2 or T3 non-small cell lung cancer: a retrospective study. Sakaguchi M1, Maebayashi T2, Aizawa T3, Ishibashi N4, Fukushima S5, Abe O6, Saito T7. Radiat Oncol. 2016 Jan 19;11(1):3. doi: 10.1186/s13014-016-0582-1.

BACKGROUND: Hypofractionated three-dimensional conformal radiation therapy (3D-CRT) is a treatment option for patients with early-stage non-small cell lung cancer (NSCLC) who are medically unable to tolerate surgery and who are not amenable to treatment with stereotactic body radiotherapy. This study assessed the efficacy and safety of 3D-CRT as a monotherapy in patients with localized stage T2 or T3 NSCLC. **METHODS:** This retrospective study consisted of 29 patients (20 males) aged 56-89 years (median, 76 years) with histologically confirmed NSCLC who underwent 3D-CRT between 2005 and 2014. **RESULTS:** The median duration of patient observation was 17.0 months (range, 1.0-64.0 months). Complete and partial responses occurred in 13.8 and 44.8 % of patients, respectively, and the overall response rate was 58.2 %. Meanwhile, the 1- and 3-year survival rates were 65.8 and 33.8 %, respectively. In T2 NSCLC, the median survival time (MST) was 12 months, and the 1- and 3-year survival rates were 62.4 and 21.4 %, respectively. In T3 NSCLC, the MST was 17 months, and the 1- and 3-year survival rates were 72.9 and 48.6 %, respectively. Severe toxicities (Common Terminology Criteria Grade 3) were not observed. The mean biologically effective dose required to improve local control exceeded 80 Gy (range, 67.2-96.0 Gy). **CONCLUSION:** These findings support a role for 3D-CRT as a treatment option for patients who refuse or could not tolerate surgical therapy with early-stage NSCLC. Although this was a small, retrospective study, it may form the basis for future, larger controlled studies on 3D-CRT as a monotherapy for NSCLC.

Fractures of thoracic vertebrae in patients with locally advanced non-small cell lung carcinoma treated with intensity modulated radiotherapy. Uyterlinde W1, Chen C2, Belderbos J2, Sonke JJ2, Lange C3, de Bois J2, van den Heuvel M1. Radiother Oncol. 2016 Jan 16. pii: S0167-8140(15)00616-7. doi: 10.1016/j.radonc.2015.11.011. [Epub ahead of print]

PURPOSE: To report on the incidence of vertebral fractures in patients treated with Intensity Modulated Radiotherapy (IMRT) for locally advanced non-small cell lung carcinoma (NSCLC) and to analyse the association with clinical and dosimetric parameters. **PATIENTS AND METHODS:** Between 2007 and 2012, 524 patients treated with ⩾51Gy were retrospectively analysed for the incidence of vertebral fractures (VF). Clinical parameters were assessed. In addition, a case control study in 50 patients was performed to study the association between the radiotherapy dose and fractured vertebrae. **RESULTS:** Three hundred and thirty-six patients were eligible for analyses. Twenty-eight patients (8%) were observed with VF at a median follow up of 12months. Age was significantly higher in the group with VF ($p<0.01$). After balancing age, the mean vertebrae dose was most significantly associated with fractures of the vertebrae ($p<0.01$). **CONCLUSION:** VF was observed in 8% of the patients with locally advanced NSCLC. RT dose was associated with the occurrence of thoracic vertebral fractures.

Longitudinal Brain Changes Associated with Prophylactic Cranial Irradiation in Lung Cancer. Simó M1, Vaquero L2, Ripollés P2, et al. J Thorac Oncol. 2016 Jan 21. pii: S1556-0864(16)00330-0. doi: 10.1016/j.jtho.2015.12.110. [Epub ahead of print]

INTRODUCTION: The toxic effects of prophylactic cranial irradiation (PCI) and platinum-based chemotherapy on cognition in lung cancer population have not yet been well-established. In the present study we examined the longitudinal neuropsychological and brain structural changes observed in lung cancer patients under these treatments. **MATERIAL AND METHODS:** Twenty-two small-cell lung cancer (SCLC) patients that underwent platinum-based chemotherapy and PCI were compared to two control groups: an age and education-matched healthy control group (HC, n=21) and a non-small-cell lung cancer group (NSCLC, n=13) that underwent platinum-based chemotherapy. All groups were evaluated using a neuropsychological battery and multimodal structural magnetic resonance imaging (MRI: T1-weighted and diffusion-tensor imaging, DTI) at baseline (prior to PCI for SCLC and to chemotherapy for NSCLC) and at 3 months following treatment. Voxel-based morphometry (T1-VBM)

and Tract-based Spatial Statistics (DTI-TBSS) were used to analyze gray matter (GM) and white matter (WM) microstructure changes. A Quality of Life Questionnaire (QLQ-C30) was also completed. **RESULTS:** SCLC patients exhibited cognitive deterioration over time in verbal fluency. Structural MRI showed GM decreases at 3 months in SCLC compared to both control groups in right subcortical regions and the bilateral insular cortex and superior temporal gyrus. Additionally, SCLC showed GM decreases over time in the aforementioned regions plus the right parahippocampal gyrus and hippocampus, together with changes in the WM microstructure of the entire corpus callosum. These findings however had a limited impact on QLQ-30. NSCLC showed no cognitive or brain structural differences following chemotherapy. **CONCLUSION:** This longitudinal study documents moderate neuropsychological deficits together with notable brain-specific structural changes (GM and WM) in SCLC following chemotherapy and PCI, suggesting that chemotherapy and especially PCI are associated with the development of cognitive and structural brain toxic effects.

Radiobiological impact of dose calculation algorithms on biologically optimized IMRT lung stereotactic body radiation therapy plans.
Liang X1, Penagaricano J2, Zheng D3, Morrill S4, Zhang X5, Corry P6, Griffin RJ7, Han EY8, Hardee M9, Ratanatharathorn V10. Radiat Oncol. 2016 Jan 22;11(1):10. doi: 10.1186/s13014-015-0578-2.
BACKGROUND: The aim of this study is to evaluate the radiobiological impact of Acuros XB (AXB) vs. Anisotropic Analytic Algorithm (AAA) dose calculation algorithms in combined dose-volume and biological optimized IMRT plans of SBRT treatments for non-small-cell lung cancer (NSCLC) patients. **METHODS:** Twenty eight patients with NSCLC previously treated SBRT were re-planned using Varian Eclipse (V11) with combined dose-volume and biological optimization IMRT sliding window technique. The total dose prescribed to the PTV was 60 Gy with 12 Gy per fraction. The plans were initially optimized using AAA algorithm, and then were recomputed using AXB using the same MUs and MLC files to compare with the dose distribution of the original plans and assess the radiobiological as well as dosimetric impact of the two different dose algorithms. The Poisson Linear-Quadatric (PLQ) and Lyman-Kutcher-Burman (LKB) models were used for estimating the tumor control probability (TCP) and normal tissue complication probability (NTCP), respectively. The influence of the model parameter uncertainties on the TCP differences and the NTCP differences between AAA and AXB plans were studied by applying different sets of published model parameters. Patients were grouped into peripheral and centrally-located tumors to evaluate the impact of tumor location. **RESULTS:** PTV dose was lower in the re-calculated AXB plans, as compared to AAA plans. The median differences of PTV(D95%) were 1.7 Gy (range: 0.3, 6.5 Gy) and 1.0 Gy (range: 0.6, 4.4 Gy) for peripheral tumors and centrally-located tumors, respectively. The median differences of PTV(mean) were 0.4 Gy (range: 0.0, 1.9 Gy) and 0.9 Gy (range: 0.0, 4.3 Gy) for peripheral tumors and centrally-located tumors, respectively. TCP was also found lower in AXB-recalculated plans compared with the AAA plans. The median (range) of the TCP differences for 30 month local control were 1.6 % (0.3 %, 5.8 %) for peripheral tumors and 1.3 % (0.5 %, 3.4 %) for centrally located tumors. The lower TCP is associated with the lower PTV coverage in AXB-recalculated plans. No obvious trend was observed between the calculation-resulted TCP differences and tumor size or location. AAA and AXB yield very similar NTCP on lung pneumonitis according to the LKB model estimation in the present study. **CONCLUSION:** AAA apparently overestimates the PTV dose; the magnitude of resulting difference in calculated TCP was up to 5.8 % in our study. AAA and AXB yield very similar NTCP on lung pneumonitis based on the LKB model parameter sets we used in the present study.

Forecasting the impact of stereotactic ablative radiotherapy for early-stage lung cancer on the thoracic surgery workforce†. Edwards JP1, Datta I2, Hunt JD3, Stefan K4, Ball CG2, Dixon E2, Grondin SC5. Eur J Cardiothorac Surg. 2016 Jan 21. pii: ezv421. [Epub ahead of print]

OBJECTIVES: To predict variation in thoracic surgery workforce requirements with the introduction of stereotactic ablative radiotherapy (SABR) for the treatment of early-stage non-small-cell lung cancer (NSCLC). **METHODS:** Using Canadian census microdata and the Canadian Community Health Survey, a microsimulation model representing the national population was developed. The demand component simulates the incidence of lung cancer, incorporating the impact of computed tomography (CT) screening for high-risk individuals (>30 pack-year smoking history; age 55-74 years). The supply component simulates the number of thoracic surgeons. SABR was introduced into the model to predict changes in the number of operable NSCLC cases per thoracic surgeon, modelling 30, 60 and 90% compliance with SABR for Stage IA and then for both Stage IA and IB NSCLC. **RESULTS:** In the absence of SABR, the volume of operative NSCLC per surgeon increases by a peak of 49.4% (by 2027) and then gradually declines to the present day volume by 2049. More dramatic decreases are seen with increasing compliance with SABR for Stage IA/IB NSCLCs. If the number of new surgeons entering the workforce per year were reduced by 33%, the operative volume per surgeon would increase by a peak of 57.1% (30% Stage IA SABR compliance) and would decrease by up to 49.1% (90% Stage IA SABR compliance). **CONCLUSIONS:** With the implementation of SABR for treatment of early NSCLC, there would be a decrease in operative volume. The impact would depend on the stage of NSCLC for which SABR is recommended and on compliance. A national strategy for thoracic surgery workforce planning is necessary, given the complex interaction of CT screening and the treatment of medically operable early NSCLC with SABR.

A comparison between accelerated hypofractionation and stereotactic ablative radiotherapy (SABR) for early-stage non-small cell lung cancer (NSCLC): Results of a propensity score-matched analysis. Chiang A1, Thibault I2, Warner A3, et al. Radiother Oncol. 2016 Jan 18. pii: S0167-8140(16)00005-0. doi: 10.1016/j.radonc.2015.12.026. [Epub ahead of print]
BACKGROUND AND PURPOSE: Stereotactic ablative radiotherapy (SABR) has become standard for inoperable early-stage non-small cell lung cancer (NSCLC). However, there is no randomized evidence demonstrating benefit over more fractionated radiotherapy. We compared accelerated hypofractionation (AH) and SABR using a propensity score-matched analysis. **MATERIALS AND METHODS:** From 1997-2007, 119 patients (T1-3N0M0 NSCLC) were treated with AH (48-60Gy, 12-15 fractions). Prior to SABR, this represented our institutional standard. From 2008-2012, 192 patients (T1-3N0M0 NSCLC) were treated with SABR (48-52Gy, 4-5 fractions). A total of 114 patients (57 per cohort) were matched (1:1 ratio, caliper: 0.10) using propensity scores. **RESULTS:** Median follow-up (range) for the AH cohort was 36.3 (2.5-109.1) months, while that for the SABR group was 32.5 (0.3-62.6)months. Three-year overall survival (OS) and local control (LC) rates were 49.5% vs. 72.4% [p=0.024; hazard ratio (HR): 2.33 (1.28, 4.23), p=0.006] and 71.9% vs. 89.3% [p=0.077; HR: 5.56 (1.53, 20.2), p=0.009], respectively. On multivariable analysis, tumour diameter and PET staging were predictive for OS, while the only predictive factor for LC was treatment cohort. **CONCLUSIONS:** OS and LC were improved with SABR, although OS is more closely related to non-treatment factors. This represents one of the few studies comparing AH to SABR for early-stage lung cancer.

SMALL CELL LUNG CANCER - SCLC

Clinical Correlation of Extensive-Stage Small Cell Lung Cancer Genomics. Dowlati A1, Lipka MB1, McColl K1, et al. Ann Oncol. 2016 Jan 22. pii: mdw005. [Epub ahead of print]
BACKGROUND: Genomic studies in small cell lung cancer (SCLC) lag far behind those performed in non-small cell lung cancer (NSCLC). To date, most SCLC studies have evaluated patients with surgically resectable disease. Here we sought to evaluate the genomic mutation spectrum of 'every-day' SCLC patient tumors with extensive stage disease (ES-SCLC) and to correlate mutations with the main clinical

outcomes of response to chemotherapy, progression-free (PFS) and overall (OS) survival. **PATIENTS AND METHODS:** A total of 50 SCLC patient tumors were examined in this study; targeted exome sequencing was obtained on 42 patients and whole-exome sequencing on 8 patients. Mutated genes were correlated with clinical outcomes using Kaplan-Meier methods (PFS, OS) and logistic regression (chemo-response). RB1 protein expression was detected by either western blotting of cultured cell lysates or IHC of tumor specimens. **RESULTS:** In all, 39 patients had ES-SCLC; 15 patients had either primary refractory/ resistant disease and 21 patients had sensitive disease. The two most frequently mutated genes were TP53 (86%) and RB1 (58%); other frequently mutated genes (>10% patients) were involved in epigenetic regulation as well as the mTOR pathway. We identified a number of low frequency, targetable mutations, including RICTOR, FGFR1, KIT, PTCH1 and RET. Using multivariate analysis, RB1 was the only significant factor (p=0.038) in predicting response to first line chemotherapy, with an odds ratio of 5.58 comparing mutant RB1 to wild-type. Patients with mutant RB1 had both better OS (11.7 vs. 9.1 months p=0.04) and PFS (11.2 vs. 8.6 months, p =0.06) compared to patients with wild-type RB1. Interestingly, about 25% of SCLC cell lines and tumor specimens expressed RB1 protein, possibly representing the subgroup with wild-type RB1. **CONCLUSION:** We found that SCLC tumors harboring no mutation in RB1 had a poor response to chemotherapy.

Target Identification in Small Cell Lung Cancer via Integrated Phenotypic Screening and Activity-Based Protein Profiling. Li J1, Fang B2, Kinose F1, Bai Y1, Kim JY1, Chen YA3, Rix U4, Koomen JM5, Haura EB6. Mol Cancer Ther. 2016 Jan 15. [Epub ahead of print]

To overcome hurdles in identifying key kinases in small cell lung cancer (SCLC), we integrated a target-agnostic phenotypic screen of kinase inhibitors with target identification using activity-based protein profiling (ABPP) in which a desthiobiotin-ATP probe was used. We screened 21 SCLC cell lines with known c-MYC amplification status for alterations in viability using a chemical library of 235 small-molecule kinase inhibitors. One screen hit compound was interrogated with ABPP, and, through this approach, we reidentified Aurora kinase B as a critical kinase in MYC-amplified SCLC cells. We next extended the platform to a second compound that had activity in SCLC cell lines lacking c-MYC amplification and identified TANK-binding kinase 1, a kinase that affects cell viability, polo-like kinase-1 signaling, G2-M arrest, and apoptosis in SCLC cells lacking MYC amplification. These results demonstrate that phenotypic screening combined with ABPP can identify key disease drivers, suggesting that this approach, which combines new chemical probes and disease cell screens, has the potential to identify other important targets in other cancer types.

Feasibility study of chemoradiotherapy followed by amrubicin and cisplatin for limited-disease small cell lung cancer. Sekine I1, Sumi M2, Satouchi M3, et al. Cancer Sci. 2016 Jan 7. doi: 10.1111/cas.12875. [Epub ahead of print]

To evaluate the feasibility of amrubicin plus cisplatin (AP) following chemoradiotherapy for limited-disease small-cell lung cancer, chemo-naïve patients aged 20 -70 years with a performance status of 0 or 1 and normal organ functions were treated with etoposide 100 mg/m2 on days 1-3, cisplatin 80 mg/m2 on day 1 and concurrent thoracic radiotherapy at 45Gy/30 fractions (EP-TRT), followed by 3 cycles of amrubicin 40 mg/m2 on days 1-3 and cisplatin 60 mg/m2 on day 1 every 3 weeks. The EP-TRT could be completed in 21 patients (15 males and six females with a median age of 62 years). Of these, 18 (86%), one and two patients received three, two and one cycles of AP, respectively. Sixteen (76%) patients required a granulocyte-colony stimulating factor (G-CSF) support. Grade 3/4 neutropenia occurred in all patients. Grade 3 febrile neutropenia was observed in nine patients, lasting for 1 day in five patients. The incidences of grade 3/4 thrombocytopenia and anemia were 43% and 24%, respectively. Grade 3 infection and anorexia occurred in two and three patients, respectively. The response rate was 95%. The median (95% confidence interval [CI]) progression-free survival (PFS) was 41.9 (0-102) months, and the 5-year

PFS rate (CI) was 41.9% (20.4-63.4%). The median overall survival (OS) has not been reached yet, and the 5-year OS rate (CI) was 57.8% (35.2-80.4%). In conclusions, EP-TRT followed by AP therapy was well-tolerated, although a large number of patients required G-CSF support.

Prognostic Factors and Skeletal-Related Events in Patients with Small Cell Lung Cancer with Bone Metastases at the Time of Diagnosis. Kang EJ1, Lee SY, Kim HJ, et al. Oncology. 2016 Jan 20. [Epub ahead of print]
BACKGROUND/OBJECTIVE: The aim of this study was to evaluate the characteristics and prognostic factors of small cell lung cancer (SCLC) with bone metastases. We also investigated the characteristics and predictive factors of skeletal-related events (SREs) in these patients. **MATERIALS AND ETHODS:** Sixty-one patients who were first diagnosed with SCLC with bone metastases at our institution were included in this retrospective analysis. RESULTS: The overall survival (OS) of patients with bone metastases was shorter than that of patients without bone metastases (4.13 vs. 6.17 months, p = 0.015). Poor Eastern Cooperative Oncology Group (ECOG) performance status (PS; ≥2) and higher serum alkaline phosphatase (ALP; above upper normal limit × 2) were independent poor prognostic factors (p = 0.027 for ECOG PS, p = 0.002 for ALP). More than 1 SRE occurred in 21 patients (34.4%). Cervical spine metastasis, thoracic spine metastasis, pelvic bone metastasis, more than 5 bone metastatic regions and higher serum lactate dehydrogenase were correlated with the occurrence of SREs. Thoracic spinal metastasis was a strong predictive factor for the occurrence of SREs (odds ratio = 5.475; 95% CI: 1.080-27.755). **CONCLUSION:** Our study demonstrates the poor prognosis of SCLC patients with bone metastases. Physicians should treat SCLC patients with bone metastases with caution.

Transformation to SCLC after Treatment with the ALK Inhibitor Alectinib. Fujita S1, Masago K2, Katakami N2, Yatabe Y3. J Thorac Oncol. 2016 Jan 2. pii: S1556-0864(15)00275-0. doi: 10.1016/j.jtho.2015.12.105. [Epub ahead of print]
We report an anaplastic lymphoma receptor tyrosine kinase gene (ALK)-positive patient who showed a paradoxical response to the ALK inhibitor alectinib; the primary lesion increased in size, whereas other metastatic lesions decreased markedly. A biopsy of the primary lesion confirmed an ALK rearrangement; however, the tumor had transformed histologically into small cell lung cancer. The lack of reports of small cell lung cancer transformation in ALK-positive patients implies that this outcome was unusual; this patient was treated with alectinib, which is more selective and has a greater inhibitory effect than crizotinib. This case may reveal resistance mechanisms that differ according to the agent used for treatment.

Protocol for the CONVERT trial-Concurrent ONce-daily VErsus twice-daily RadioTherapy: an international 2-arm randomised controlled trial of concurrent chemoradiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited stage small cell lung cancer (LS-SCLC) and good performance status. Faivre-Finn C1, Falk S2, Ashcroft L2, et al. BMJ Open. 2016 Jan 20;6(1):e009849. doi: 10.1136/bmjopen-2015-009849.
INTRODUCTION: Concurrent ONce-daily VErsus twice-daily RadioTherapy (CONVERT) is the only multicentre, international, randomised, phase III trial open in Europe and Canada looking at optimisation of chemoradiotherapy (RT) in limited stage small cell lung cancer (LS-SCLC). Following on from the Turrisi trial of once-daily versus twice-daily (BD) concurrent chemoradiotherapy, there is a real need for a new phase III trial using modern conformal RT techniques and investigating higher once-daily radiation dose. This trial has the potential to define a new standard chemo-RT regimen for patients with LS-SCLC and good performance status. **METHODS AND ANALYSIS:** 447 patients with histologically or cytologically proven diagnosis of SCLC were recruited from 74 centres in eight countries between 2008 and 2013. Patients were randomised to receive either concurrent twice-daily RT(45 Gy in 30 twice-daily

fractions over 3 weeks) or concurrent once-daily RT(66 Gy in 33 once-daily fractions over 6.5 weeks) both starting on day 22 of cycle 1. Patients are followed up until death. The primary end point of the study is overall survival and secondary end points include local progression-free survival, metastasis-free survival, acute and late toxicity based on the Common Terminology Criteria for Adverse Events V.3.0, chemotherapy and RTdose intensity. **ETHICS AND DISSEMINATION:** The trial received ethical approval from NRES Committee North West-Greater Manchester Central (07/H1008/229). There is a trial steering committee, including independent members and an independent data monitoring committee. Results will be published in a peer-reviewed journal and presented at international conferences.

Role of Adjuvant Therapy in a Population-Based Cohort of Patients With Early-Stage Small-Cell Lung Cancer. Yang CJ1, Chan DY1, Speicher PJ1, et al. J Clin Oncol. 2016 Jan 19. pii: JCO638171. [Epub ahead of print]
PURPOSE: Data on optimal adjuvant therapy after complete resection of small-cell lung cancer (SCLC) are limited, and in particular, there have been no studies evaluating the role of adjuvant chemotherapy, with or without prophylactic cranial irradiation, relative to no adjuvant therapy for stage T1-2N0M0 SCLC. This National Cancer Data Base analysis was performed to determine the potential benefits of adjuvant chemotherapy with and without prophylactic cranial irradiation in patients who undergo complete resection for early-stage small-cell lung cancer. **PATIENTS AND METHODS:** Overall survival of patients with pathologic T1-2N0M0 SCLC who underwent complete resection in the National Cancer Data Base from 2003 to 2011, stratified by adjuvant therapy regimen, was evaluated using Kaplan-Meier and Cox proportional hazards analysis. Patients treated with induction therapy and those who died within 30 days of surgery were excluded from analysis. **RESULTS:** Of 1,574 patients who had pT1-2N0M0 SCLC during the study period, 954 patients (61%) underwent complete R0 resection with a 5-year survival of 47%. Adjuvant therapy was administered to 59% of patients (n = 566), including chemotherapy alone (n = 354), chemoradiation (n = 190, including 99 patients who underwent cranial irradiation), and radiation alone (n = 22). Compared with surgery alone, adjuvant chemotherapy with or without radiation was associated with significantly improved survival. In addition, multivariable Cox modeling demonstrated that treatment with adjuvant chemotherapy (hazard ratio [HR], 0.78; 95% CI, 0.63 to 0.95) or chemotherapy with radiation directed at the brain (HR, 0.52; 95% CI, 0.36 to 0.75) was associated with improved survival when compared with no adjuvant therapy. **CONCLUSION:** Patients with pT1-2N0M0 SCLC treated with surgical resection alone have worse outcomes than those who undergo resection with adjuvant chemotherapy alone or chemotherapy with cranial irradiation.

PALLIATIVE AND SUPPORTIVE CARE

Analysis of the psychological impact of cancer-related symptoms on patients with non-small cell lung cancer. Walker MS1, Pohl GM2, Houts AC1, Peltz G2,3, Miller PJ1, Schwartzberg LS1,4, Stepanski EJ1, Marciniak M2,5. Psychooncology. 2016 Jan 20. doi: 10.1002/pon.4071. [Epub ahead of print]
BACKGROUND: Patients with non-small cell lung cancer (NSCLC) experience adverse physical symptoms because of cancer, cancer treatment, and comorbidities. The relations among Cancer-Related Symptoms, Functional Impairment, and Psychological Symptoms in patients with NSCLC is not well understood. **METHODS:** Retrospective analysis of patient-reported symptoms with the 38-item Patient Care Monitor survey, collected in routine clinical care for 1138 patients with NSCLC at eight US community oncology practices. Study sample was randomly split, and structural equation models examined the direct and mediated effects of Cancer-Related Symptoms and Functional Impairment on

symptoms of acute distress (Distress) and depression (Despair) in the training sample. The training model was cross validated in testing sample. Results are presented for the full model using the entire sample. **RESULTS:** Patients were 48.3% female, with mean age of 66.0 years. The most common comorbidities were anemia (60.8%) and respiratory disease (24.5%). Severity of Cancer-Related Symptoms was strongly and positively related to Functional Impairment and Psychological Symptoms in both training and testing models. The modeled effect of Functional Impairment on Distress and Despair was significant in the overall model using the total sample, and significant or near-significant in the training and testing models. The mediated effect of Cancer-Related Symptoms by Functional Impairment tended to be weaker than its direct modeled effect on Distress and Despair. **CONCLUSIONS:** Despite prior research suggesting that Functional Impairment plays a larger role than symptom burden in depression in NSCLC, the independent modeled effects of Functional Impairment were no greater than the direct modeled effects of Cancer-Related Symptoms.

In Their Own Words: A Qualitative Study of the Psychosocial Concerns of Post-treatment and Long-term Lung Cancer Survivors. Rohan EA1, Boehm J1, Allen KG1,2, Poehlman J3. J Psychosoc Oncol. 2016 Jan 14:0. [Epub ahead of print]
While lung cancer is the deadliest type of cancer, survival rates are improving. To address the dearth of literature about the concerns of lung cancer survivors, we conducted 21 in-depth interviews with lung cancer survivors that focused on experiences during diagnosis, treatment, and long-term survivorship. Emergent themes included: feeling blamed for having caused their cancer, being stigmatized as "throwaways," and long-term survivors' experiencing surprise that they're still alive, given poor overall survival rates. Finally, survivors desired increased public support. It is imperative for healthcare and public health professionals to learn more about needs of this population

Correlation between patient quality of life in palliative care and burden of their family caregivers: a prospective observational cohort study. Krug K1, Miksch A2, Peters-Klimm F3, Engeser P4, Szecsenyi J5. BMC Palliat Care. 2016 Jan 15;15(1):4. doi: 10.1186/s12904-016-0082-y.
BACKGROUND: Family caregivers play a key role in palliative care at home, and understanding the interdependencies in the constellation of patient, family caregivers and service providers is important. As few longitudinal studies have examined the influence of patient quality of life (QoL) in palliative care on burden of family caregivers, the aim of this study was to identify correlations between changing patient QoL and changing burden of family caregivers that need consideration in patient management.
METHODS: Palliative patients with cancer in primary care evaluated their QoL (Quality of Life Questionnaire Core 15 Palliative Care, QLQ-C15-PAL). They were assessed monthly for an interval of 6 months or until death of the patient. Family caregivers reported the burden they perceived while supporting the patient (Short form of the Burden Scale for Family Caregivers, BSFC). Longitudinal data were analysed for all patients with at least 3 available assessments, considering the most recent data for participants with more than 3 assessments. Changes in patient QoL were analysed using the Friedman test. In a stepwise regression analysis, influences of change in patient QoL on changing caregiver burden were investigated. **RESULTS:** One hundred patients (63 men, 37 women; average age: 68 years) were enrolled in the study. The most common primary diagnoses were colon, lung or breast cancer. In 58 cases, assessments were available from both patients and caregivers. Patients reported overall quality of life increasing towards end of life, although reporting that physical functioning deteriorated. Symptoms of pain and fatigue bothered patients most. Caregiver burden was moderate and on average did not change over time. In a stepwise regression model, the difference in emotional functioning and the difference in dyspnoea showed an influence on the development of caregiver burden (explained variance of 19.3 %).
CONCLUSIONS: Patients' dyspnoea, feelings of depression and anxiety impacted on the perceived burden of family caregivers, but are manageable symptoms. Our results corroborate the need of regular

assessment of patients' needs taking into account caregiver burden. In this way, general practice teams can intervene early and may more likely meet patients' needs in the end of life care process.

"I Told Myself to Stay Positive" Perceptions of Coping Among Latinos With a Cancer Diagnosis Living in the United States. Carrion IV1, Nedjat-Haiem F2, Macip-Billbe M3, Black R3. Am J Hosp Palliat Care. 2016 Jan 12. pii: 1049909115625955. [Epub ahead of print]
PURPOSE: This study contributes to the sparse body of literature examining perceptions of coping among Latino men and women with a cancer diagnosis living in the United States. There are currently 50 million Latinos in the United States and, by 2050, projected to grow to 128 million. Although some research indicates that Latinos have unique sociocultural beliefs that influence their cancer care, very little is known about their perceptions of coping after being diagnosed with cancer. We examined Latino men and women's perceptions of coping to understand the meaning of their experience with cancer METHOD: Using criterion sampling technique, 60 immigrant and migrant Latino men and women diagnosed with cancer within the past 5 years were recruited from community-based organizations, clinics, and churches. The study consisted of 60- to 90-minute semistructured interviews asking open-ended questions pertaining to coping. The qualitative design facilitated an understanding of coping within the participants' social and cultural contexts. **RESULTS:** Median age of the participants was 55 years. Among the women, 80% had breast cancer; 12% had ovarian cancer; and 8% had throat, thyroid, stomach, or skin cancers. Among the men, 94% had prostate cancer and 6% had brain, colorectal, or lung cancers. Emerging themes associated with the development of coping strategies involved positive reframing, family support, religion and spirituality, and support from health care providers. The term "positive reframing" relates to finding meaning and positive emotions that help sustain the coping process, despite having a cancer diagnosis. In addition, when medical and helping professionals provided tangible support, participants engaged in meaning-based coping. **CONCLUSION:** This study provides insights regarding the existing coping strategies which Latinos utilize and provides clinician-tangible information pertaining to participant's engagement in meaning-based coping. Family support facilitated coping among the Latino men and women. The role of religion and spirituality in the lives of the participants enabled them to cope with the cancer diagnosis. Future research is necessary to examine coping strategies regarding specific cancers at end of life.

Family Perspectives on Aggressive Cancer Care Near the End of Life. Wright AA1, Keating NL2, Ayanian JZ3, et al. JAMA. 2016 Jan 19;315(3):284-92. doi: 10.1001/jama.2015.18604.
IMPORTANCE: Patients with advanced-stage cancer are receiving increasingly aggressive medical care near death, despite growing concerns that this reflects poor-quality care. **OBJECTIVE:** To assess the association of aggressive end-of-life care with bereaved family members' perceptions of the quality of end-of-life care and patients' goal attainment. **DESIGN, SETTING, AND PARTICIPANTS:** Interviews with 1146 family members of Medicare patients with advanced-stage lung or colorectal cancer in the Cancer Care Outcomes Research and Surveillance study (a multiregional, prospective, observational study) who died by the end of 2011 (median, 144.5 days after death; interquartile range, 85.0-551.0 days). **EXPOSURES:** Claims-based quality measures of aggressive end-of-life care (ie, intensive care unit [ICU] admission or repeated hospitalizations or emergency department visits during the last month of life; chemotherapy ≤2 weeks of death; no hospice or ≤3 days of hospice services; and deaths occurring in the hospital). **MAIN OUTCOMES AND MEASURES:** Family member-reported quality rating of "excellent" for end-of-life care. Secondary outcomes included patients' goal attainment (ie, end-of-life care congruent with patients' wishes and location of death occurred in preferred place).
RESULTS: Of 1146 patients with cancer (median age, 76.0 years [interquartile range, 65.0-87.0 years]; 55.8% male), bereaved family members reported excellent end-of-life care for 51.3%. Family members reported excellent end-of-life care more often for patients who received hospice care for longer than 3

days (58.8% [352/599]) than those who did not receive hospice care or received 3 or fewer days (43.1% [236/547]) (adjusted difference, 16.5 percentage points [95% CI, 10.7 to 22.4 percentage points]). In contrast, family members of patients admitted to an ICU within 30 days of death reported excellent end-of-life care less often (45.0% [68/151]) than those who were not admitted to an ICU within 30 days of death (52.3% [520/995]) (adjusted difference, -9.4 percentage points [95% CI, -18.2 to -0.6 percentage points]). Similarly, family members of patients who died in the hospital reported excellent end-of-life care less often (42.2% [194/460]) than those who did not die in the hospital (57.4% [394/686]) (adjusted difference, -17.0 percentage points [95% CI, -22.9 to -11.1 percentage points]). Family members of patients who did not receive hospice care or received 3 or fewer days were less likely to report that patients died in their preferred location (40.0% [152/380]) than those who received hospice care for longer than 3 days (72.8% [287/394]) (adjusted difference, -34.4 percentage points [95% CI, -41.7 to -27.0 percentage points]). **CONCLUSIONS AND RELEVANCE:** Among family members of older patients with fee-for service Medicare who died of lung or colorectal cancer, earlier hospice enrollment, avoidance of ICU admissions within 30 days of death, and death occurring outside the hospital were associated with perceptions of better end-of-life care. These findings are supportive of advance care planning consistent with the preferences of patients.

Physical activity interests and preferences of cancer patients with brain metastases: a cross-sectional survey. Lowe SS1, Danielson B2, Beaumont C3, Watanabe SM4, Courneya KS5. BMC Palliat Care. 2016 Jan 19;15(1):7. doi: 10.1186/s12904-016-0083-x.
BACKGROUND: Physical activity has been shown to positively impact cancer-related fatigue, physical functioning and quality of life outcomes in early stage cancer patients, however its role at the end stage of cancer has yet to be determined. Brain metastases are amongst the most common neurological complications of advanced cancer, with significant deterioration in fatigue and quality of life. The purpose of the present study was to examine the physical activity interests and preferences of cancer patients with brain metastases initiating palliative whole brain radiotherapy. **METHODS:** Thirty-one patients aged 18 years or older, cognitively intact, diagnosed with brain metastases, and with Palliative Performance Scale scores of greater than 30 %, were recruited from a multidisciplinary outpatient brain metastases clinic. An interviewer-administered survey was used to assess physical activity interests and preferences of participants who were embarking upon palliative whole brain radiotherapy. **RESULTS:** 87 % (n = 27) of participants felt that physical activity was important, however there was limited interest in participating in a structured program at the onset of palliative whole brain radiotherapy. Lung cancer diagnosis was associated with being less interested in participating in a physical activity program, and feeling less able to participate in a physical activity program at the onset of palliative whole brain radiotherapy.
CONCLUSIONS: Cancer patients with brain metastases demonstrate limited interest and varied preferences for physical activity during palliative whole brain radiotherapy. Additional pilot work with this patient population is needed before physical activity interventions can be tested in clinical research.

COMPLEMENTARY & ALTERNATIVE THERAPY

In vitro antimicrobial and anti-proliferative activities of plant extracts from Spathodea campanulata, Ficus bubu, and Carica papaya. Mbosso Teinkela JE1,2,3, Assob Nguedia JC4, et al. Pharm Biol. 2016 Jan 22:1-10. [Epub ahead of print]
CONTEXT: African medicinal plants represent a prominent source of new active substances. In this context, three plants were selected for biological investigations based on their traditional uses.
OBJECTIVE: The antimicrobial and anti-proliferative features of three plants used for medicinal purpose were evaluated. **MATERIALS AND METHODS:** The antimicrobial activities of methanol extracts of Ficus bubu Warb. (Moraceae) stem bark and leaves, of Spathodea campanulata P. Beauv.

(Bignoniaceae) flowers, as well as those of Carica papaya Linn. (Caricaceae) latex, were determined using the microbroth dilution method against a set of bacteria and fungi pathogens including: Enterococcus faecalis, Staphylococcus aureus, S. saprophyticus, S. epidermididis, Escherichia coli, Klebsiella pneumonia, Salmonella typhimurium, Candida albicans, and Trichophyton rubrum. The tested concentrations of extracts ranged from 2500.0 to 2.4 µg/mL and MIC values were evaluated after 24 h incubation at 37 °C. Subsequently, MTT assay was used to estimate anti-proliferative activity of these methanol extracts and of F. bubu latex on three human cancer cell lines (U373 glioblastoma, A549 NSCLC, and SKMEL-28 melanoma). **RESULTS**: The methanol extract of F. bubu stem bark exhibited the highest antimicrobial activity against C. albicans with a MIC value of 9.8 µg/mL, while the F. bubu latex and the methanol extract of F. bubu leaves induced significant anti-proliferative activity against lung (IC50 values of 10 and 14 µg/mL, respectively) and glioma (IC50 values of 13 and 16 µg/mL, respectively) cancer cells. **CONCLUSION:** These results indicate that effective drugs could be derived from the three studied plants.

Morinda citrifolia edible leaf extract enhanced immune response against lung cancer. Lim SL1, Goh YM2, Noordin MM2, Rahman HS1, Othman HH2, Abu Bakar NA1, Mohamed S1. Food Funct. 2016 Jan 14. [Epub ahead of print]
Lung cancer causes 1.4 million deaths annually. In the search for functional foods as complementary therapies against lung cancer, the immuno-stimulatory properties of the vegetable Morinda citrifolia leaves were investigated and compared with the anti-cancer drug erlotinib. Lung tumour-induced BALB/c mice were fed with 150 mg kg-1 or 300 mg kg-1 body weight of the leaf extract, or erlotinib (50 mg kg-1 body-weight) for 21 days. The 300 mg kg-1 body weight extract significantly (and dose-dependently) suppressed lung tumour growth; the extract worked more effectively than the 50 mg kg-1 body weight erlotinib treatment. The extract significantly increased blood lymphocyte counts, and spleen tissue B cells, T cells and natural killer cells, and reduced the epidermal growth factor receptor (EGFR) which is a lung adenocarcinoma biomarker. The extract also suppressed the cyclooxygenase 2 (COX2) inflammatory markers, and enhanced the tumour suppressor gene (phosphatase and tensin homolog, PTEN). It inhibited tumour growth cellular gene (transformed mouse 3T3 cell double minute 2 (MDM2), V-raf-leukemia viral oncogene 1 (RAF1), and mechanistic target of rapamycin (MTOR)) mRNA expression in the tumours. The extract is rich in scopoletin and epicatechin, which are the main phenolic compounds. The 300 mg kg-1Morinda citrifolia leaf 50% ethanolic extract showed promising potential as a complementary therapeutic dietary supplement which was more effective than the 50 mg kg-1 erlotinib in suppressing lung adenocarcinoma. Part of the mechanisms involved enhancing immune responses, suppressing proliferation and interfering with various tumour growth signalling pathways.

Chinese Herbal Medicine for Improving Quality of Life Among Nonsmall Cell Lung Cancer Patients: Overview of Systematic Reviews and Network Meta-Analysis. Wu X1, Chung VC, Lu P, Poon SK, et al. Medicine (Baltimore). 2016 Jan;95(1):e2410. doi: 10.1097/MD.0000000000002410.
For patients with nonsmall cell lung cancer (NSCLC) receiving chemotherapy, current clinical evidence has indicated add-on benefit of Chinese herbal medicine (CHM) in improving quality of life (QoL). However, the relative performance among different CHM is unknown.The aim of this overview of systematic reviews (SRs) and network meta-analyses (NMA) is to evaluate the comparative effectiveness of different CHM.Seven electronic databases including both international databases and Chinese databases were searched.SRs focus on randomized controlled trials (RCTs) with comparison of CHM plus chemotherapy against chemotherapy alone on QoL among NSCLC patients were considered eligible.Data from RCTs were extracted for random effect pairwise meta-analyses. Pooled relative risk (RR) with 95% confidence interval (CI) was used to quantify the impact of CHM on QoL. NMA was used to explore the most effective CHM for improving QoL when used with chemotherapy.From 14 SRs, 61 RCTs (n=4247)

assessing 11 different CHM were included. Result from pairwise meta-analyses showed 6 CHM (Kang-lai-te injection, Shei-qi-fu-zheng injection, Compound ku-shen injection, Kang-ai injection, Zi-jin-long tablet, and Shen-fu injection) has significant beneficial effect on QoL among NSCLC patients when used with chemotherapy, even after adjustment for publication bias. Pooled RR varied from 1.38 (95% CI: 1.11-1.72, I=0.0%, Kang-lai-te injection) to 3.36 (95% CI: 1.30-8.66, I=0.0%, Zi-jin-long tablet). One trial comparing Hai-shen-su (a protein extract from Tegillarca granosa L.) plus chemotherapy with chemotherapy also demonstrated beneficial effect of combined treatment (RR=3.13, 95% CI: 1.41-6.98). Results from NMA showed no differences on the comparative effectiveness among CHM, but Hai-shen-su plus chemotherapy has the highest probability (62.3%) of being the best option for improving QoL.Use of CHM on top of chemotherapy can significantly improve QoL in NSCLC patients. Although Hai-shen-su showed the highest probability of being the best add-on to chemotherapy, the effectiveness of all 11 CHM reviewed appeared to be similar. In the future, rigorous placebo controlled trials with proper blinding are needed to confirm the effectiveness of CHM.

MISCELLANEOUS WORKS

Lung Cancer in Never Smokers. Rivera GA1, Wakelee H2. Adv Exp Med Biol. 2016;893:43-57. doi: 10.1007/978-3-319-24223-1_3.
Lung cancer is predominantly associated with cigarette smoking; however, a substantial minority of patients with the disease have never smoked. In the US it is estimated there are 17,000-26,000 annual deaths from lung cancer in never smokers, which as a separate entity would be the seventh leading cause of cancer mortality. Controversy surrounds the question of whether or not the incidence of lung cancer in never-smokers is increasing, with more data to support this observation in Asia. There are several factors associated with an increased risk of developing lung cancer in never smokers including second hand smoke, indoor air pollution, occupational exposures, and genetic susceptibility among others. Adenocarcinoma is the most common histology of lung cancer in never smokers and in comparison to lung cancer in smokers appears less complex with a higher likelihood to have targetable driver mutations.

Epidemiology of Lung Cancer. Schwartz AG1, Cote ML2. Adv Exp Med Biol. 2016;893:21-41. doi: 10.1007/978-3-319-24223-1_2.
Lung cancer continues to be one of the most common causes of cancer death despite understanding the major cause of the disease: cigarette smoking. Smoking increases lung cancer risk 5- to 10-fold with a clear dose-response relationship. Exposure to environmental tobacco smoke among nonsmokers increases lung cancer risk about 20 %. Risks for marijuana and hookah use, and the new e-cigarettes, are yet to be consistently defined and will be important areas for continued research as use of these products increases. Other known environmental risk factors include exposures to radon, asbestos, diesel, and ionizing radiation. Host factors have also been associated with lung cancer risk, including family history of lung cancer, history of chronic obstructive pulmonary disease and infections. Studies to identify genes associated with lung cancer susceptibility have consistently identified chromosomal regions on 15q25, 6p21 and 5p15 associated with lung cancer risk. Risk prediction models for lung cancer typically include age, sex, cigarette smoking intensity and/or duration, medical history, and occupational exposures, however there is not yet a risk prediction model currently recommended for general use. As lung cancer screening becomes more widespread, a validated model will be needed to better define risk groups to inform screening guidelines.

Transforming Cancer Prevention through Precision Medicine and Immune-oncology. Kensler TW1, Spira A2, Garber JE3, et al. Cancer Prev Res (Phila). 2016 Jan;9(1):2-10. doi: 10.1158/1940-6207.CAPR-15-0406.

We have entered a transformative period in cancer prevention (including early detection). Remarkable progress in precision medicine and immune-oncology, driven by extraordinary recent advances in genome-wide sequencing, big-data analytics, blood-based technologies, and deep understanding of the tumor immune microenvironment (TME), has provided unprecedented possibilities to study the biology of premalignancy. The pace of research and discovery in precision medicine and immunoprevention has been astonishing and includes the following clinical firsts reported in 2015: driver mutations detected in circulating cell-free DNA in patients with premalignant lesions (lung); clonal hematopoiesis shown to be a premalignant state; molecular selection in chemoprevention randomized controlled trial (RCT; oral); striking efficacy in RCT of combination chemoprevention targeting signaling pathway alterations mechanistically linked to germline mutation (duodenum); molecular markers for early detection validated for lung cancer and showing promise for pancreatic, liver, and ovarian cancer. Identification of HPV as the essential cause of a major global cancer burden, including HPV16 as the single driver of an epidemic of oropharyngeal cancer in men, provides unique opportunities for the dissemination and implementation of public health interventions. Important to immunoprevention beyond viral vaccines, genetic drivers of premalignant progression were associated with increasing immunosuppressive TME; and Kras vaccine efficacy in pancreas genetically engineered mouse (GEM) model required an inhibitory adjuvant (Treg depletion). In addition to developing new (e.g., epigenetic) TME regulators, recent mechanistic studies of repurposed drugs (aspirin, metformin, and tamoxifen) have identified potent immune activity. Just as precision medicine and immune-oncology are revolutionizing cancer therapy, these approaches are transforming cancer prevention. Here, we set out a brief agenda for the immediate future of cancer prevention research (including a "Pre-Cancer Genome Atlas" or "PCGA"), which will involve the inter-related fields of precision medicine and immunoprevention - pivotal elements of a broader domain of personalized public health. Cancer Prev Res; 9(1); 2-10. ©2016 AACR.

Survival among Never-Smokers with Lung Cancer in the Cancer Care Outcomes Research and Surveillance Study. Clément-Duchêne C1,2, Stock S3, Xu X4, et al. Ann Am Thorac Soc. 2016 Jan;13(1):58-66. doi: 10.1513/AnnalsATS.201504-241OC.

RATIONALE: Differences in patient characteristics and outcomes have been observed among current, former, and never-smokers with lung cancer, but most prior studies included few never-smokers and were not prospective. **OBJECTIVES:** We used data from a large, prospective study of lung cancer care and outcomes in the United States to compare characteristics of never-smokers and smokers with lung cancer and to examine survival among the never-smokers. **METHODS:** Smoking status at diagnosis was determined by self-report and survival was determined from medical records and cancer registries, with follow-up through June 2010 or later. Cox regression was used to examine the association between smoking and survival, and to identify predictors of survival among never-smokers. **MEASUREMENTS AND MAIN RESULTS:** Among 3,410 patients with lung cancer diagnosed between September 1, 2003 and October 14, 2005 who completed a baseline patient survey, there were 274 never-smokers (8%), 1,612 former smokers (47%), 1,496 current smokers or smokers who quit recently (44%), and 28 with missing information about smoking status (<1%). Never-smokers appeared more likely than former and current/recent smokers to be female and of Asian or Hispanic race/ethnicity, and to have adenocarcinoma histology, fewer comorbidities, private insurance, and higher income and education. Compared with never-smokers, the adjusted hazard of death from any cause was 29% higher among former smokers (hazard ratio, 1.29; 95% confidence interval, 1.08-1.55), and 39% higher among current/recent smokers (hazard ratio, 1.39; 95% confidence interval, 1.16-1.67). Factors predicting worse overall survival among never-smokers included Hispanic ethnicity, severe comorbidity, undifferentiated histology, and regional or distant stage. Never-smoking Hispanics appeared more likely to have regional or advanced disease at diagnosis and less likely to undergo surgical resection, although these differences were not statistically significant. **CONCLUSIONS:** Never-smokers with lung cancer are more likely than ever-smokers to be

female, Asian or Hispanic, and more advantaged socioeconomically, suggesting possible etiologic differences in lung cancer by smoking status. Among never-smokers, Hispanics with lung cancer had worse survival than non-Hispanic whites.