



Caring Ambassadors Lung Cancer Program Literature Review, January 2012

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BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Antitumor Activity of Sorafenib in Human Cancer Cell Lines with Acquired Resistance to EGFR and VEGFR Tyrosine Kinase Inhibitors. Morgillo F, Martinelli E, Troiani T, Orditura M, De Vita F, Ciardiello F. PLoS One. 2011;6(12):e28841. Epub 2011 Dec 9.

<http://www.ncbi.nlm.nih.gov/pubmed/22174910>

Treatment of non small cell lung cancer (NSCLC) and colorectal cancer (CRC) have substantially changed in the last years with the introduction of epidermal growth factor receptor (EGFR) inhibitors in the clinical practice. The understanding of mechanisms which regulate cells sensitivity to these drugs is necessary for their optimal use. An in vitro model of acquired resistance to two tyrosine kinase inhibitors (TKI) targeting the EGFR, erlotinib and gefitinib, and to a TKI targeting EGFR and VEGFR, vandetanib, was developed by continuously treating the human NSCLC cell line CALU-3 and the human CRC cell line HCT116 with escalating doses of each drug. MTT, western blot analysis, migration, invasion and anchorage-independent colony forming assays were conducted in vitro and experiments with established xenografts in athymic nude mice were performed in vivo in sensitive, wild type (WT) and TKI-resistant CALU-3 and HCT116 cell lines. As compared to WT CALU-3 and HCT116 human cancer cells, TKI-resistant cell lines showed a significant increase in the levels of activated, phosphorylated AKT, MAPK, and of survivin. Considering the role of RAS and RAF as downstream signals of both the EGFR and VEGFR pathways, we treated resistant cells with sorafenib, an inhibitor of C-RAF, B-RAF, c-KIT, FLT-3, RET, VEGFR-2, VEGFR-3, and PDGFR- β . Sorafenib reduced the activation of MEK and MAPK and caused an inhibition of cell proliferation, invasion, migration, anchorage-independent growth in vitro and of tumor growth in vivo of all TKI-resistant CALU-3 and HCT116 cell lines. These data suggest that resistance to EGFR inhibitors is predominantly driven by the RAS/RAF/MAPK pathway and can be overcome by treatment with sorafenib.

Overexpression of GLUT1 correlates with Kras mutations in lung carcinomas. Sasaki H, Shitara M, Yokota K, Hikosaka Y, Moriyama S, Yano M, Fujii Y. Mol Med Report. 2011 Dec 22. doi: 10.3892/mmr.2011.736. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22200795>

Glucose is the major source of energy for cells, and glucose transporter 1 (GLUT1) is the most common glucose transporter. GLUT1 has been found to be aberrantly expressed in several tumor types. From the results of the microarray and serial analysis of gene expression (SAGE), GLUT1 transcript expression was found to be higher in clones with mutant Kras alleles. We hypothesized that GLUT1 overexpression might be correlated with clinicopathological features of Japanese lung cancers. Immunohistochemistry for GLUT1 was performed in 283 surgically treated non-small cell lung cancer (NSCLC) cases from Nagoya City University Hospital. Thirty-six Kras mutant carcinoma cases were included. GLUT1 overexpression was found in 138 (48.8%) lung cancer patients. The GLUT1 overexpression status was significantly correlated with gender (women 31.9% vs. men 54.5%, $P < 0.0001$), smoking status (never smoker 31.4% vs. smoker 59.4%, $P < 0.0001$) and pathological subtypes (adenocarcinoma 36.4% vs. non adenocarcinoma 74.5%, $P < 0.0001$). In addition, the GLUT1 overexpression status was significantly correlated with gene mutation status, including EGFR (mutation-positive 23.4% vs. -negative 58.3%, $P < 0.0001$) and Kras (mutation-positive 66.7% vs. -negative 46.6%, $P = 0.038$). The survival of patients with GLUT1 overexpression ($n = 137$, 50 were deceased) was significantly worse when compared to the patients with normal expression of GLUT1 ($n = 142$, 31 were deceased) (Log-rank test, $P = 0.0009$). Thus, GLUT-1 overexpression correlates with an aggressive phenotype of lung carcinoma.

Number of Circulating Endothelial Progenitor Cells and Intratumoral Microvessel Density in Non-small Cell Lung Cancer Patients: Differences in Angiogenic Status between Adenocarcinoma Histologic Subtypes. Maeda R, Ishii G, Ito M, et al. J Thorac Oncol. 2011 Dec 22. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22198428>

INTRODUCTION: Angiogenesis plays a significant role in tumor progression. This study examined the association between the number of circulating endothelial progenitor cells (EPCs), intratumoral microvessel density (MVD) (both of which may be markers for neovascularization), and lung cancer histological types, particularly adenocarcinoma histological subtypes. **METHODS:** A total of 83 stage I non-small cell lung cancer (NSCLC) patients underwent complete tumor resection between November 2009 and July 2010. The number of EPCs from the pulmonary artery of the resected lungs was measured by assaying CD34/vascular endothelial growth factor receptor 2 positive cells, and the MVD was assessed immunohistochemically in tumor specimens by staining for CD34. **RESULTS:** A statistically significant correlation between the number of EPCs from pulmonary artery and intratumoral MVD was found ($p < 0.001$). No statistically significant differences in the number of EPCs and the MVD were observed between the adenocarcinomas and the squamous cell carcinomas. Among the adenocarcinoma histological subtypes, a higher number of EPCs and MVD were found significantly more frequently in solid adenocarcinomas than in nonsolid adenocarcinomas ($p < 0.001$ and $p = 0.011$, respectively). In addition, solid adenocarcinomas showed higher levels of vascular endothelial growth factor using quantitative real-time polymerase chain reaction in the tumor tissue samples than in the nonsolid adenocarcinomas ($p = 0.005$). **CONCLUSION:** The higher number of circulating EPCs and the MVD of solid adenocarcinoma may indicate the presence of differences in the tumor angiogenic status between early-stage adenocarcinoma histological subtypes. Among adenocarcinoma patients, patients with solid adenocarcinoma may be the best candidates for antiangiogenic therapies.

Role of Insulin-Like Growth Factor-1 Signaling Pathway in Cisplatin-Resistant Lung Cancer Cells. Sun Y, Zheng S, Torossian A, et al. Int J Radiat Oncol Biol Phys. 2011 Dec 22. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22197230>

PURPOSE: The development of drug-resistant phenotypes has been a major obstacle to cisplatin use in non-small-cell lung cancer. We aimed to identify some of the molecular mechanisms that underlie cisplatin resistance using microarray expression analysis. **METHODS AND MATERIALS:** H460 cells were treated with cisplatin. The differences between cisplatin-resistant lung cancer cells and parental H460 cells were studied using Western blot, MTS, and clonogenic assays, in vivo tumor implantation, and microarray analysis. The cisplatin-R cells were treated with human recombinant insulin-like growth factor (IGF) binding protein-3 and siRNA targeting IGF-1 receptor. **RESULTS:** Cisplatin-R cells illustrated greater expression of the markers CD133 and aldehyde dehydrogenase, more rapid in vivo tumor growth, more resistance to cisplatin- and etoposide-induced apoptosis, and greater survival after treatment with cisplatin or radiation than the parental H460 cells. Also, cisplatin-R demonstrated decreased expression of insulin-like growth factor binding protein-3 and increased activation of IGF-1 receptor signaling compared with parental H460 cells in the presence of IGF-1. Human recombinant IGF binding protein-3 reversed cisplatin resistance in cisplatin-R cells and targeting of IGF-1 receptor using siRNA resulted in sensitization of cisplatin-R-cells to cisplatin and radiation. **CONCLUSIONS:** The IGF-1 signaling pathway contributes to cisplatin-R to cisplatin and radiation. Thus, this pathway represents a potential target for improved lung cancer response to treatment.

Expression and Clinical Significance of Ezrin in Non-Small-Cell Lung Cancer. Zhang XQ, Chen GP, Wu T, Yan JP, Zhou JY. Clin Lung Cancer. 2011 Dec 1. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22137559>

BACKGROUND: Ezrin is known to regulate cellular survival, adhesion, migration, and invasion and has been identified as 1 of the key components of tumor progression and metastasis. The purpose of this study was to evaluate the clinicopathologic and prognostic significance of ezrin expression in non-small-cell lung cancer (NSCLC). **MATERIALS AND METHODS:** We investigated the expression pattern of ezrin immunohistochemically in 89 paraffin samples of NSCLC between January 1998 and December 2006 and conducted survival analyses. In addition, 73 frozen specimens (including tumorous and precancerous tissues) of NSCLC and 28 frozen specimens of benign pneumonic diseases collected between January 2009 and December 2009 were analyzed by Western blot and reverse transcriptase-polymerase chain reaction (RT-PCR). **RESULTS:** In 89 paraffin samples, ezrin was expressed in 40 cases, either in the cytoplasm or on the membrane. Ezrin-positive expression was significantly associated with increased tumor stage and lymph node (LN) metastasis. The positive rate of cytoplasm expression was significantly associated with LN metastasis. Importantly, ezrin-positive expression independently predicted inferior overall survival (OS) and disease-free survival (DFS). In 73 frozen specimens of NSCLC and 28 frozen specimens of benign pneumonic diseases, the ezrin mRNA, protein, and phospho-ezrin protein expressions in tumorous tissues were higher than they were in precancerous tissues and benign pneumonic tissues. **CONCLUSION:** These results suggested that high-level ezrin expression contributed to NSCLC progression and that phosphorylation and subcellular translocation of ezrin might be the important mechanisms. Ezrin might be a potential prognostic marker of progression in NSCLC.

DIAGNOSIS, MOLECULAR TESTING AND STAGING

Carcinoembryonic antigen (CEA) as tumor marker in lung cancer. Grunnet M, Sorensen JB. Lung Cancer. 2011 Dec 6. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22153832>

The use of CEA as a prognostic and predictive marker in patients with lung cancer is widely debated. The aim of this review was to evaluate the results from studies made on this subject. Using the search words "CEA", "tumor markers in lung cancer", "prognostic significance", "diagnostic significance" and "predictive significance", a search was carried out on PubMed. Exclusion criteria was articles never

published in English, articles before 1981 and articles evaluating tumor markers in lung cancer not involving CEA. Initially 217 articles were found, and 34 were left after selecting those relevant for the present study. Four of these included both Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC) patients, and 31 dealt solely with NSCLC patients. Regarding SCLC no studies showed that serum level of CEA was a prognostic marker for overall survival (OS). The use of CEA serum level as a prognostic marker in NSCLC was investigated in 23 studies and the use of CEA plasma level in two. In 18 (17 serum, 1 plasma) of these studies CEA was found to be a useful prognostic marker for either OS, recurrence after surgery or/and progression free survival (PFS) in NSCLC patients. Interestingly, an overweight of low stage (stage I-II) disease and adenocarcinoma (AC) patients were observed in this group. The remaining 7 studies (6 serum, 1 plasma) contained an overweight of patients with squamous carcinoma (SQ). One study found evidence for that a tumor marker index (TMI), based on preoperative CEA and CYFRA21-1 serum levels, is useful as a prognostic marker for OS in NSCLC. Six studies evaluated the use of CEA as a predictive marker for risk of recurrence and risk of death in NSCLC patients. Four of these studies found, that CEA was useful as a predictive marker for risk of recurrence and risk of death measured over time. No studies found CEA levels useful as a diagnostic marker for lung cancer. With regard to NSCLC the level of CEA measured in tumor tissue in NSCLC patients, were not of prognostic, diagnostic or predictive significance for OS or recurrence after treatment. In one study CEA level was measured in Pleural Lavage Fluid (PLF) it was here found to be useful as prognostic markers for overall survival (OS) after surgery. In conclusion serum level of CEA carries prognostic and predictive information of risk of recurrence and of death in NSCLC independent of treatment or study design. The observation that TMI index could be a potential prognostic marker for OS in NSCLC is interesting. Future studies may benefit from evaluating more than one marker at a time, which may possibly create a more precise index for prognosis and recurrence in lung cancer, than is possible by the use of single biomarkers.

Diffusion weighted MRI and 18F-FDG PET/CT in non-small cell lung cancer (NSCLC): Does the apparent diffusion coefficient (ADC) correlate with tracer uptake (SUV)? Regier M, Derlin T, Schwarz D, et al. Eur J Radiol. 2011 Dec 22. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22197090>

INTRODUCTION: To investigate the potential correlation of the apparent diffusion coefficient assessed by diffusion-weighted MRI (DWI) and glucose metabolism determined by the standardized uptake value (SUV) at 18F-FDG PET/CT in non-small cell lung cancer (NSCLC). **MATERIALS AND METHODS:** 18F-FDG PET/CT and DWI (TR/TE, 2000/66ms; b-values, 0 and 500s/mm²) were performed in 41 consecutive patients with histologically verified NSCLC. Analysing the PET-CT data calculation of the mean (SUV(mean)) and maximum (SUV(max)) SUV was performed. By placing a region-of-interest (ROI) encovering the entire tumor mean (ADC(mean)) and minimum ADC (ADC(min)) were determined by two independent radiologists. Results of 18F-FDG PET-CT and DWI were compared on a per-patient basis. For statistical analysis Pearson's correlation coefficient, Bland-Altman and regression analysis were assessed. **RESULTS:** Data analysis revealed a significant inverse correlation of the ADC(min) and SUV(max) ($r=-0.46$; $p=0.032$). Testing the correlation of the ADC(min) and SUV(max) for each histological subtype separately revealed that the inverse correlation was good for both adenocarcinomas ($r=-0.47$; $p=0.03$) and squamouscell carcinomas ($r=-0.71$; $p=0.002$), respectively. No significant correlation was found for the comparison of ADC(min) and SUV(mean) ($r=-0.29$; $p=0.27$), ADC(mean) vs. SUV(mean) ($r=-0.28$; $p=0.31$) or ADC(mean) vs. SUV(max) ($r=-0.33$; $p=0.23$). The κ -value of 0.88 indicated a good agreement between both observers. **CONCLUSION:** This preliminary study is the first to verify the relation between the SUV and the ADC in NSCLC. The significant inverse correlation of these two quantitative imaging approaches points out the association of metabolic activity and tumor cellularity. Therefore, DWI with ADC measurement might represent a new prognostic marker in NSCLC.

The management impact of clinically significant incidental lesions detected on staging FDG PET-CT in patients with non-small cell lung cancer (NSCLC): An analysis of 649 cases. Lin M, Ambati C. Lung Cancer. 2011 Dec 27. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22206598>

To evaluate FDG PET-CT in the detection of unexpected pre-malignancy or second malignancy at the initial staging of patients with histologically proven non-small cell lung cancer (NSCLC) and its impact on management. **METHODS:** Staging FDG PET-CT scans acquired between February 2006 and July 2010 in 649 patients (M=389; F=260) with NSCLC were reviewed for the presence of unexpected pre-malignancy or second primary. A "True-Positive" lesion represented a second primary or pre-malignant lesion. A "False-Positive" lesion was due to benign causes or an atypical site of metastasis from NSCLC. **RESULTS:** 77 (12%) patients were identified on PET-CT as having a potential pre-malignancy or second primary. 39 out of 77 (51%) patients had diagnostic verification where histopathology served as reference standard in 33 patients (85%) and the rest had endoscopy and progress PET-CT scans. 20 patients (3.1%) had a second primary (n=11) or pre-malignant lesions comprising dysplastic colorectal polyps (n=9), and additional therapy and/or management change for the index tumour was instigated in 17 patients (85%). In patients with a second primary, 3 (27%) patients had a high impact change in management from an initial curative intent to palliative. **CONCLUSION:** Staging FDG PET-CT is highly valuable in identifying second primary cancers or pre-malignant lesions in patients with NSCLC. When a second primary is detected on PET-CT, there is a high impact change in management in 27% of patients.

Crizotinib and Testing for ALK. Shaw AT, Solomon B, Kenudson MM. J Natl Compr Canc Netw. 2011 Dec 1;9(12):1335-41.

<http://www.ncbi.nlm.nih.gov/pubmed/22157554>

Crizotinib was recently approved by the US FDA for the treatment of advanced non-small cell lung cancer (NSCLC) harboring the ALK (anaplastic lymphoma kinase) gene rearrangement. To ensure identification of patients most likely to benefit, the FDA approved crizotinib concurrently with a companion diagnostic test-the Vysis ALK Break Apart FISH Probe Kit. This kit was used in 1 of the 2 pivotal trials leading to the FDA approval of crizotinib and has become the gold standard for detecting ALK rearrangement in NSCLC. Although ALK FISH is clinically validated, the assay can be technically challenging and costly. Therefore, other diagnostic modalities are being explored, including immunohistochemistry (IHC) and reverse transcriptase-polymerase chain reaction. This article provides an overview of the diagnostic assays available for detecting ALK rearrangement. Each assay, including ALK FISH, has its strengths and weaknesses. Recent work with commercially available ALK antibodies suggests that IHC-based tests may represent a reliable and cost-effective screening strategy; however, large multicenter studies comparing IHC with FISH are needed to validate ALK IHC. While ALK FISH remains the current standard for diagnosing ALK positivity, large-scale screening of patients with newly diagnosed advanced NSCLC, as recommended by NCCN, may require development and validation of alternative screening strategies, such as combination IHC and FISH.

Utility of endobronchial ultrasound-guided mediastinal lymph node biopsy in patients with non-small cell lung cancer. Lee BE, Kletsman E, Rutledge JR, Korst RJ. J Thorac Cardiovasc Surg. 2011 Dec 10. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22154791>

OBJECTIVE: Invasive mediastinal biopsy is often necessary in the evaluation of non-small cell lung cancer (NSCLC), and mediastinoscopy has long been considered the reference standard. However, the emergence of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has resulted in controversy regarding it represents a suitable replacement for mediastinoscopy. We chose to

determine the utility of EBUS-TBNA in evaluating the mediastinum in patients with NSCLC.

METHODS: The present study was a retrospective review of a prospective database of consecutive patients with NSCLC who underwent EBUS-TBNA for mediastinal evaluation from 2009 to 2011. The sensitivity, specificity, negative predictive value, and accuracy of EBUS-TBNA are reported. Also reported are the size of the lymph nodes biopsied and the number of instances in which EBUS-TBNA obviated the need for cervical mediastinoscopy. **RESULTS:** A total of 73 patients had a total of 140 mediastinal stations biopsied using EBUS-TBNA. Of the 73 patients, 30 had benign findings and underwent surgical resection, 1 of whom was found to have stage N2 disease. Of the remaining patients, 42 had a positive result and 1 had nondiagnostic biopsy findings for which malignancy was confirmed by mediastinoscopy. Mediastinoscopy would have changed the tumor stage and treatment planning in only 2 (2.7%) of the 73 patients. Overall, EBUS-TBNA had a sensitivity of 95%, a specificity of 100%, a negative predictive value of 94%, and an accuracy of 97%. **CONCLUSIONS:** EBUS-TBNA might be a feasible option for most patients with NSCLC for whom histologic assessment of the mediastinum is necessary. The rates of nondiagnostic and false-negative biopsy findings using EBUS-TBNA were low, small subcentimeter nodes could be routinely biopsied, and most patients with a radiographically positive mediastinum had their disease pathologically confirmed.

Improvement of cellularity on cell block preparations using the so-called tissue coagulum clot method during endobronchial ultrasound-guided transbronchial fine-needle aspiration.

Yung RC, Otell S, Illei P, et al. *Cancer Cytopathol.* 2011 Dec 5. doi: 10.1002/cncy.20199. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22144401>

BACKGROUND: Cell block (CB) preparation during the endobronchial ultrasound-guided transbronchial fine-needle aspiration (EBUS-TBNA) procedure plays an important role in the diagnosis of lung cancer and recovery of cellular material for molecular characterization of the tumor. However, the efficiency of the conventional method of CB preparation is suboptimal. **METHODS:** In the current study, the "tissue coagulum clot" cell block (TCC-CB) method was used to prepare the CBs and its efficiency was compared with that of the conventional saline rinse cell block (NR-CB) method. A total of 84 consecutive TCC-CBs (106 lymph nodes [LNs] and 14 lung lesions) and 28 consecutive cases of NR-CB (39 LNs and 3 lung lesions) obtained within the same time period were included in the current study.

RESULTS: In the TCC-CB specimens, 94 of 106 LN cases (88.7%) yielded sufficient diagnostic material, as did 11 of 14 lung lesions (78.6%). In the NR-CB group, which was used as the control, 22 of 39 LN specimens (56.4%) and none of 3 lung specimens (0%) were found to provide sufficient diagnostic material. Although the average size of the LNs in the study group were not significantly different from those in the control group (1.76 cm vs 1.82 cm; $P > .05$), the overall nondiagnostic rates in the TCC-CB and NR-CB groups were 11.2% and 43.6%, respectively ($P < .001$). The nondiagnostic rates of the lung specimens were 15.4% in the TCC-CB group and 100% in the NR-CB group ($P < .05$). In addition, immunohistochemistry studies and epidermal growth factor receptor (EGFR)/KRAS mutational analyses were performed in 26 and 14 TCC-CB cases, respectively. With the exception of 1 case, all of them had satisfactory results. **CONCLUSIONS:** The data from the current study demonstrate that the TCC-CB method significantly increases the cellular yield of CB preparations without compromising cytomorphological characterization of tumor cells.

Histologic subtypes, immunohistochemistry, FISH or molecular screening for the accurate diagnosis of ALK-rearrangement in lung cancer: A comprehensive study of Caucasian non-smokers.

Just PA, Cazes A, Audebourg A, et al. *Lung Cancer.* 2011 Dec 6. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22153831>

EML4-ALK adenocarcinomas constitute a new molecular subgroup of lung tumours that respond very well to crizotinib, an ALK inhibitor. However, the diagnosis of ALK rearrangement in lung cancer is challenging. The aim of this study was to compare the diagnostic accuracy of five different methods in a series of 20 EGFR(wt/wt) lung adenocarcinomas from non- or light- smokers. Multiplex RT-PCR was considered as gold standard and identified four ALK-rearranged tumours among the 20 tested tumours. qRT-PCR got an interpretability rate of 100% and accurately typed all 20 tumours. qRT-PCR from corresponding formalin-fixed paraffin-embedded (FFPE) specimens got an interpretability rate of 65%. Out of the four previously identified ALK-rearranged cases, three were interpretable and two were retrieved using FFPE qRT-PCR. ALK break-apart FISH got an interpretability rate of 60% and accurately typed all of the twelve remaining cases. Anti-ALK immunohistochemistry (IHC) accurately typed all twenty tumours using a cut-off value of strong staining of 100% tumour cells. The 16 non ALK-rearranged tumours got no/light staining in 13 cases, and a moderate staining of 80-100% tumour cells in 3 cases. We then analysed four solid signet-ring lung adenocarcinomas. FFPE qRT-PCR, FISH and immunohistochemistry were concordant in three cases, with positive and negative results in respectively one and two cases. The fourth case, which was positive by FISH and immunohistochemistry but negative by RT-PCR, was shown to have a non-EML4-ALK ALK-rearrangement. As various factors such as RNA quality, fixation quality and type of ALK rearrangement may impede ALK screening, we propose a combined FISH/molecular biology diagnostic algorithm in which anti-ALK immunohistochemistry is used as a pre-screening step.

EGFR and KRAS mutation analysis in cytologic samples of lung adenocarcinoma enabled by laser capture microdissection. Chowdhuri SR, Xi L, Pham TH, et al. *Mod Pathol*. 2011 Dec 9. doi:

10.1038/modpathol.2011.184. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22157931>

The discovery of activating mutations in EGFR and KRAS in a subset of lung adenocarcinomas was a major advance in our understanding of lung adenocarcinoma biology, and has led to groundbreaking studies that have demonstrated the efficacy of tyrosine kinase inhibitor therapy. Fine-needle aspirates and other cytologic procedures have become increasingly popular for obtaining diagnostic material in lung carcinomas. However, frequently the small amount of material or sparseness of tumor cells obtained from cytologic preparations limit the number of specialized studies, such as mutation analysis, that can be performed. In this study we used laser capture microdissection to isolate small numbers of tumor cells to assess for EGFR and KRAS mutations from cell block sections of 19 cytology samples from patients with known lung adenocarcinomas. We compared our results with previous molecular assays that had been performed on either surgical or cytology specimens as part of the patient's initial clinical work-up. Not only were we able to detect the identical EGFR or KRAS mutation that was present in the patient's prior molecular assay in every case, but we were also able to consistently detect the mutation from as few as 50 microdissected tumor cells. Furthermore, isolating a more pure population of tumor cells resulted in increased sensitivity of mutation detection as we were able to detect mutations from laser capture microdissection-enriched cases where the tumor load was low and traditional methods of whole slide scraping failed. Therefore, this method can not only significantly increase the number of lung adenocarcinoma patients that can be screened for EGFR and KRAS mutations, but can also facilitate the use of cytologic samples in the newly emerging field of molecular-based personalized therapies.

Pulmonary Nodules: Growth Rate Assessment in Patients by Using Serial CT and Three-dimensional Volumetry. Ko JP, Berman EJ, Kaur M, et al. *Radiology*. 2011 Dec 9. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22156993>

PURPOSE: To determine the precision of a three-dimensional (3D) method for measuring the growth rate of solid and subsolid nodules and its ability to detect abnormal growth rates. **MATERIALS AND**

METHODS: This study was approved by the Institutional Research Board and was HIPAA compliant. Informed consent was waived. The growth rates of 123 lung nodules in 59 patients who had undergone lung cancer screening computed tomography (CT) were measured by using a 3D semiautomated computer-assisted volume method. Clinical stability was established with long-term CT follow-up (mean, 6.4 years \pm 1.9 [standard deviation]; range, 2.0-8.5 years). A mean of 4.1 CT examinations per patient \pm 1.2 (range, two to seven CT examinations per patient) was analyzed during 2.4 years \pm 0.5 after baseline CT. Nodule morphology, attenuation, and location were characterized. The analysis of standard deviation of growth rate in relation to time between scans yielded a normative model for detecting abnormal growth. **RESULTS:** Growth rate precision increased with greater time between scans. Overall estimate for standard deviation of growth rate, on the basis of 939 growth rate determinations in clinically stable nodules, was 36.5% per year. Peripheral location ($P = .01$; 37.1% per year vs 25.6% per year) and adjacency to pleural surface ($P = .05$; 38.9% per year vs 34.0% per year) significantly increased standard deviation of growth rate. All eight malignant nodules had an abnormally high growth rate detected. By using 3D volumetry, growth rate-based diagnosis of malignancy was made at a mean of 183 days \pm 158, compared with radiologic or clinical diagnosis at 344 days \pm 284. **CONCLUSION:** A normative model derived from the variability of growth rates of nodules that were stable for an average of 6.4 years may enable identification of lung cancer.©

Clinical Significance of BRAF Gene Mutations in Patients with Non-small Cell Lung Cancer.

Kobayashi M, Sonobe M, Takahashi T, et al. *Anticancer Res.* 2011 Dec;31(12):4619-23.

<http://www.ncbi.nlm.nih.gov/pubmed/22199339>

BACKGROUND: V-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutations are attractive molecular targets for cancer treatment. Detection of BRAF gene mutation and analyses in non-small cell lung cancer (NSCLC) are of great scientific interest. **PATIENTS AND METHODS:** The study included 581 NSCLC patients (377 males, 204 female) undergoing pulmonary resection. BRAF gene mutations were screened using the PCR-SSCP method and were confirmed by direct DNA sequencing. Mutations of epidermal growth factor receptor (EGFR), v-erb-b2 erythroblastic leukemia viral oncogene homolog 2 (ERBB2), and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) gene were also analyzed. **RESULTS:** Five patients (0.8%) had BRAF mutations within exon 15. In 581 NSCLC patients, EGFR gene mutations within exons 18 to 21 were detected in 191 (32.8%) patients, KRAS codon 12 mutations in 56 (9.6%) patients, and ERBB2 codon 20 mutations in 11 (1.8%) patients. All mutations were mutually exclusive. The NSCLC patients with BRAF mutations were proved to be men who were heavy smokers. **CONCLUSIONS:** PCR-SSCP analysis of BRAF exon 15 in NSCLC patients without other gene mutations may be sufficient to identify candidates for treatment.

Comparison of video-assisted mediastinoscopy and video-assisted mediastinoscopic lymphadenectomy for lung cancer. Sayar A, Citak N, Metin M, et al. *Gen Thorac Cardiovasc Surg.* 2011 Dec;59(12):793-8. Epub 2011 Dec 16.

<http://www.ncbi.nlm.nih.gov/pubmed/22173676>

PURPOSE: We compared the efficacy and complications of video-assisted mediastinoscopy (VAM) and video-assisted mediastinal lymphadenectomy (VAMLA) for mediastinal staging of lung cancer. **METHODS:** Between March 2006 and July 2008, a total of 157 patients with non-small-cell lung cancer (NSCLC) underwent VAM ($n = 113$, 72%) or VAMLA ($n = 44$, 28%). We studied them retrospectively. Data for the operating time, node stations sampled/dissected, number of biopsies, and the patients who were pN0 by mediastinoscopy and underwent thoracotomy were collected. The false-negative rate was calculated. Demographics and operative complications were analyzed. **RESULTS:** The overall complication rate was 5.7% ($n = 9$). The most common complication was hoarseness ($n = 8$). Complications were seen significantly more often after VAMLA than after VAM (11.3% vs. 2.6%, $P =$

0.04). There were no deaths. The mean number of removed lymph nodes (8.43 ± 1.08) and the station numbers (4.81 ± 0.44) per patient were higher with VAMLA than with VAM (7.65 ± 1.68 , $P = 0.008$ and 4.38 ± 0.80 , $P = 0.001$, respectively). The mean operating time was 44.8 ± 6.6 min for VAM and 82.0 ± 7.8 min for VAMLA. Patients diagnosed as pN2 numbered 9 in the VAMLA group and 27 in the VAM group. The patients diagnosed as pN0 with mediastinoscopy then underwent thoracotomy (VAM 77, VAMLA 32). When they were investigated for the presence of mediastinal lymph nodes, there were three (3.8%) false-negative results in the VAM group and five (15.6%) in the VAMLA group. Sensitivity, accuracy, and negative predictive values for VAM and VAMLA were 0.90/0.97/0.96 and 0.64/0.87/0.84, respectively. **CONCLUSION:** VAMLA was found to be superior to VAM with regard to the number of stations and lymph nodes. Complications after VAMLA were common. The sensitivity and NPV of VAM for mediastinal staging are significantly higher than those of VAMLA.

Pharmacologic inhibition of mTOR antagonizes the cytotoxic activity of pemetrexed in non-small cell lung cancer. Markova B, Hähnel PS, Kasper S, Herbertz S, Schuler M, Breitenbuecher F. *J Cancer Res Clin Oncol*. 2011 Dec 28. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22203472>

PURPOSE: Pemetrexed, an inhibitor of thymidylate synthase (TS) and additional folate-dependent enzymes, is clinically active in patients suffering from "non-squamous" non-small cell lung cancer (NSCLC). High expression of TS has been implied as biomarker predictive of resistance to pemetrexed. Against this background, we studied whether inhibition of mTOR could lower expression of TS and thus sensitize NSCLC cells to pemetrexed. **METHODS AND RESULTS:** Using squamous cell carcinoma and adenocarcinoma NSCLC cell lines, we observed that constitutive TS expression levels failed to correlate with sensitivity to growth inhibition or apoptosis imposed by pemetrexed in vitro. Interestingly, pemetrexed strongly induced TS RNA and protein expression in all cell lines. The allosteric "rapalogue" mTOR inhibitor everolimus suppressed constitutive, but not pemetrexed-induced TS expression. Surprisingly, cotreatment with everolimus protected NSCLC cells against pemetrexed-induced apoptosis. This resulted in increased long-term clonogenic survival of NSCLC cells treated with pemetrexed plus everolimus as compared to pemetrexed alone. No such negative interaction was observed when everolimus was combined with recombinant TRAIL, a proliferation-independent proapoptotic agent. **CONCLUSIONS:** Rapalogues may suppress the antitumor activity of pemetrexed by slowing cell cycle progression. This should be considered when combining pemetrexed and mTOR inhibitors in NSCLC treatment.

YB-1, the E2F Pathway, and Regulation of Tumor Cell Growth. Lasham A, Samuel W, Cao H, et al. *J Natl Cancer Inst*. 2011 Dec 28. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22205655>

BACKGROUND: Y-box binding factor 1 (YB-1) has been associated with prognosis in many tumor types. Reduced YB-1 expression inhibits tumor cell growth, but the mechanism is unclear. **METHODS:** YB-1 mRNA levels were compared with tumor grade and histology using microarray data from 771 breast cancer patients and with disease-free survival and distant metastasis-free survival using data from 375 of those patients who did not receive adjuvant therapy. Microarrays were further searched for genes that had correlated expression with YB-1 mRNA. Small interfering RNA (siRNA) was used to study the effects of reduced YB-1 expression on growth of three tumor cell lines (MCF-7 breast, HCT116 colon, and A549 lung cancer cells), on tumorigenesis by A549 cells in nude mice, and on global transcription in the three cancer cell lines. Reporter gene assays were used to determine whether YB-1 siRNAs affected the expression of E2F1, and chromatin immunoprecipitation was used to determine whether YB-1 bound to various E2F promoters as well as E2F1-regulated promoters. All P values were from two-sided tests. **RESULTS:** YB-1 levels were elevated in more aggressive tumors and were strongly associated with poor

disease-free survival and distant metastasis-free survival. YB-1 expression was often associated with the expression of genes with E2F sites in their promoters. Cells expressing YB-1 siRNA grew substantially more slowly than control cells and formed tumors less readily in nude mice. Transcripts that were altered in cancer cell lines with YB-1 siRNA included 32 genes that are components of prognostic gene expression signatures. YB-1 regulated expression of an E2F1 promoter-reporter construct in A549 cells (eg, relative E2F1 promoter activity with control siRNA = 4.04; with YB-1 siRNA = 1.40, difference = -2.64, 95% confidence interval = -3.57 to -1.71, $P < .001$) and bound to the promoters of several well-defined E2F1 target genes. **CONCLUSION:** YB-1 expression is associated with the activity of E2F transcription factors and may control tumor cell growth by this mechanism.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Results of a Surgical Resection for Patients With Stage IV Non-Small-Cell Lung Cancer. Hanagiri T, Takenaka M, Oka S, et al. Clin Lung Cancer. 2011 Dec 2. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22138036>

PURPOSE: This study retrospectively investigated the clinical significance of surgical treatment for stage IV non-small-cell lung cancer (NSCLC). **SUBJECTS:** There were 36 patients who underwent surgical resection for stage IV NSCLC between 1999 and 2008. **RESULTS:** The patients included 22 males and 14 females. All patients had either synchronous distant metastasis or pleural dissemination. The mean age of the patients was 65.8 years (range, 18 to 90 years). The histological types included 29 adenocarcinomas, 5 squamous-cell carcinomas and 2 large-cell carcinomas. The organs of metastasis were bone in 5 patients, brain in 4, adrenal gland in 4, axillary lymph nodes in 3, liver in 2, and 1 patient had a contralateral pulmonary metastasis. The number of metastases was one site in 13, two sites in 3, three sites in 1, and five sites in 2 patients. The patients with bone metastasis were treated with radiation, and the patients with brain metastasis underwent stereotaxic radiosurgery. The patients with either adrenal metastasis, axillary lymph node metastasis, or contralateral lung metastasis underwent surgical resection. Among the patients with distant metastasis, the 5-year survival rate was 30.1%. There were 17 patients with pleural dissemination. The 5-year survival rate in these patients was 25.3%. The overall 5-year survival rate after surgery in the patients with stage IV disease was 26.8%. **CONCLUSION:** Selected patients who can undergo surgical resection for the primary tumor and effective local therapy for metastatic lesions still have a chance to obtain long-term survival. Surgical treatment for NSCLC with oligometastatic disease can be considered as one arm of multidisciplinary treatment.

Oncologic Efficacy of Anatomic Segmentectomy in Stage IA Lung Cancer Patients With T1a Tumors. Donahue JM, Morse CR, Wigle DA, et al. Ann Thorac Surg. 2011 Dec 29. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22209375>

BACKGROUND: Segmentectomy provides an anatomic, parenchymal-sparing strategy for patients with limited lung function. Recently, interest has been renewed in segmentectomy for the treatment of early stage lung cancer. **METHODS:** We reviewed the medical records of all patients undergoing segmentectomy from January 1999 through December 2004. Survival curves were estimated using the Kaplan-Meier method. **RESULTS:** There were 113 consecutive patients (58 men, 55 women); median age was 72.5 years (range, 30 to 94 years). Median forced expiratory volume in 1 second was 1.53 L (range, 0.5 L to 3.27 L). Median diffusion capacity of lung for carbon monoxide was 69% predicted (range, 23% to 129%). Significant comorbidities were present in 62 patients (55%). There was no

perioperative mortality. Major morbidity occurred in 28 patients (25%). Mean tumor size was 2.1 cm. Resection margins were negative in all cases. Ninety-two patients (81%) were stage I. Overall 5-year survival was 79% for stage IA patients. Current smoking, diffusion capacity of lung for carbon monoxide less than 69%, tumor size greater than 2 cm, N2 disease, and advanced histology grade were associated with decreased survival by univariate analysis. In a multivariate model, only tumor size greater than 2 cm remained significant. Tumor recurrence was observed in 39 patients (35%): local in 17 patients (15%) and distant only in 22 (20%). For stage IA patients with T1a lesions, local recurrence was 5% and distant recurrence was 13%. Five-year recurrence-free survival of these patients was 69%. **CONCLUSIONS:** Pulmonary segmentectomy can be performed safely in selected patients with preoperative reduced lung function and comorbidities. For stage IA disease, survival approximates that seen after lobectomy, with similar local recurrence rates for patients with T1a tumors.

Time Trends of Overall Survival and Survival after Recurrence in Completely Resected Stage I Non-small Cell Lung Cancer. Hung JJ, Jeng WJ, Hsu WH, Huang BS, Wu YC. *J Thorac Oncol.* 2011 Dec 14. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22173701>

INTRODUCTION: The seventh edition of the tumor, node, metastasis classification for lung cancer has been published in 2009. The aim of this study is to evaluate time trends of surgical outcomes and clinicopathologic factors in patients with pathological stage I non-small cell lung cancer according to the seventh edition of the tumor, node, metastasis classification. **METHODS:** We retrospectively reviewed the clinicopathologic characteristics of 1249 patients with pathological stage I non-small cell lung cancer from Taipei Veterans General Hospital between January 1980 and December 2006, during the three periods of 1980-1990, 1991-2000, and 2001-2006. The overall survival, disease-specific survival, and postrecurrence survival were analyzed. **RESULTS:** The 5-year overall survival rates during the three periods improved significantly: 53.7, 59.9, and 69.3%, respectively ($p < 0.001$). The 2-year postrecurrence survival rates during the three periods improved significantly: 10.6, 25.4, and 43.2%, respectively ($p < 0.001$). The percentage of female patients increased during each period: 15.4, 24.9, and 32.0%, respectively ($p < 0.001$). The percentage of adenocarcinoma also increased during each period: 51.2, 62.2, and 74.9%, respectively ($p < 0.001$). Tumor size during each period was 3.2, 3.2, and 2.8 cm, tending to be smaller when diagnosed in the last period ($p < 0.001$). The overall survival in patients with squamous cell carcinoma and those undergoing pneumonectomy or bilobectomy did not improve over time. **CONCLUSIONS:** Stage migration, improved postrecurrence survival, increased frequencies of female gender and adenocarcinoma, and decreased tumor size lead to improved overall survival over the past three decades.

Impact of tumor size on outcomes after anatomic lung resection for stage 1A non-small cell lung cancer based on the current staging system. Carr SR, Schuchert MJ, Pennathur A, et al. *J Thorac Cardiovasc Surg.* 2011 Dec 9. [Epub ahead of print]

Wilson

<http://www.ncbi.nlm.nih.gov/pubmed/22169444>

OBJECTIVE: Anatomic segmentectomy may achieve results comparable to lobectomy for early-stage non-small cell lung cancer. The 7th edition of the AJCC Cancer Staging Handbook stratified the previous T1 tumor designation into T1a and T1b subsets, which still define stage 1A node-negative non-small cell lung cancer. We are left to hypothesize whether this classification may aid in directing the extent of surgical resection. We retrospectively reviewed our anatomic segmentectomy and lobectomy management of stage 1A non-small cell lung cancer to determine differences in survival and local recurrence rates based on the new stratification. **METHODS:** We performed a retrospective review of 429 patients undergoing resection of pathologically confirmed stage 1A non-small cell lung cancer via lobectomy or

anatomic segmentectomy. Primary outcome variables included mortality, recurrence, and survival. Recurrence-free and cancer-specific survivals were estimated using the Kaplan-Meier method.

RESULTS: Patients undergoing segmentectomy were older than patients undergoing lobectomy (mean age 69.2 vs 66.8 years, $P < .006$). The mean preoperative forced expiratory volume in 1 second was significantly lower in the segmentectomy group than in the lobectomy group (71.8% vs 81.1%, $P = .02$). Mortality was similar after segmentectomy (1.1%) and lobectomy (1.2%). There was no difference in mortality, recurrence rates (14.0% vs 14.7%, $P = 1.00$), or 5-year cancer-specific survival (T1a: 90% vs 91%, $P = .984$; T1b: 82% vs 78%, $P = .892$) when comparing segmentectomy and lobectomy for pathologic stage 1A non-small cell lung cancer, when stratified by T stage. **CONCLUSIONS:** Anatomic segmentectomy may achieve equivalent recurrence and survival compared with lobectomy for patients with stage 1A non-small cell lung cancer. Prospective studies will be necessary to delineate the potential merits of anatomic segmentectomy in this setting.

A comparison of surgical intervention and stereotactic body radiation therapy for stage I lung cancer in high-risk patients: A decision analysis. Puri V, Crabtree TD, Kymes S, et al. *J Thorac Cardiovasc Surg*. 2011 Dec 9. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22169443>

OBJECTIVE: We sought to compare the relative cost-effectiveness of surgical intervention and stereotactic body radiation therapy in high risk patients with clinical stage I lung cancer (non-small cell lung cancer). **METHODS:** We compared patients chosen for surgical intervention or SBRT for clinical stage I non-small cell lung cancer. Propensity score matching was used to adjust estimated treatment hazard ratios for the confounding effects of age, comorbidity index, and clinical stage. We assumed that Medicare-allowable charges were \$15,034 for surgical intervention and \$13,964 for stereotactic body radiation therapy. The incremental cost-effectiveness ratio was estimated as the cost per life year gained over the patient's remaining lifetime by using a decision model. **RESULTS:** Fifty-seven patients in each arm were selected by means of propensity score matching. Median survival with surgical intervention was 4.1 years, and 4-year survival was 51.4%. With stereotactic body radiation therapy, median survival was 2.9 years, and 4-year survival was 30.1%. Cause-specific survival was identical between the 2 groups, and the difference in overall survival was not statistically significant. For decision modeling, stereotactic body radiation therapy was estimated to have a mean expected survival of 2.94 years at a cost of \$14,153 and mean expected survival with surgical intervention was 3.39 years at a cost of \$17,629, for an incremental cost-effectiveness ratio of \$7753. **CONCLUSIONS:** In our analysis stereotactic body radiation therapy appears to be less costly than surgical intervention in high-risk patients with early stage non-small cell lung cancer. However, surgical intervention appears to meet the standards for cost-effectiveness because of a longer expected overall survival. Should this advantage not be confirmed in other studies, the cost-effectiveness decision would be likely to change. Prospective randomized studies are necessary to strengthen confidence in these results.

NSCLC - CHEMOTHERAPY

A Randomized Phase III Trial of Combined Paclitaxel, Carboplatin, and Radiation Therapy Followed by Weekly Paclitaxel or Observation for Patients With Locally Advanced Inoperable Non-Small-Cell Lung Cancer. Carter DL, Garfield D, Hathorn J, et al. *Clin Lung Cancer*. 2011 Dec 3. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22138037>

BACKGROUND: This study was designed to determine the efficacy and safety of additional maintenance chemotherapy after standard induction chemotherapy/radiation therapy (XRT) in stage III non-small-cell lung cancer (NSCLC). The primary objective was to increase 1-year survival. **PATIENTS**

AND METHODS: Eligible patients (N = 220) had confirmed stage IIIA or IIIB NSCLC, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. Patients received induction chemotherapy (paclitaxel 200 mg/m² + carboplatin AUC = 6/3 weeks) for 2 cycles, followed by paclitaxel 45 mg/m² + carboplatin AUC = 2 weekly ×7 and concurrent daily XRT (cumulative dose = 66.6 Gy in 37 fractions) and then observation or maintenance. Before randomization, 101 patients (46%) discontinued treatment due to progressive disease (n = 34), toxicity (n = 33), patient request (n = 13), death (n = 7), or other (n = 14). The remaining 119 patients were randomly assigned to either "observation" or "maintenance" (6 cycles of paclitaxel 70 mg/m²/wk [3 weeks on/1 week off]); a median of 5 of 6 planned cycles was delivered in the maintenance arm. **RESULTS:** For the observation group vs. the maintenance group, the estimated 1- and 4-year survival rates were 77% vs. 66% and 38% vs. 17% (median, 26.9 months vs. 16.1 months, respectively [p = 0.07]); the estimated 1- and 4-year performance-free survival (PFS) were 46% vs. 24% and 25% vs. 13% (median, 10.2 months vs. 8.2 months, respectively [p = 0.04]). Common toxicities were neutropenia, thrombocytopenia, and fatigue. **CONCLUSION:** Median survival in both groups surpassed the standard, most notably the 26.9-month survival in the observation group. Maintenance chemotherapy, when added to a regimen of both induction and concurrent chemoradiotherapy, did not improve clinical outcomes, with endpoints favoring the standard arm.

Trabectedin in patients with advanced non-small-cell lung cancer (NSCLC) with XPG and/or ERCC1 overexpression and BRCA1 underexpression and pretreated with platinum. Massuti B, Cobo M, Camps C, et al. Lung Cancer. 2011 Dec 22. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22197612>

BACKGROUND: Previous studies in sarcoma found that a composite gene signature, including high expression of nucleotide excision repair (NER) genes (XPG and/or ERCC1) and low expression of homologous recombination repair (HR) genes (BRCA1), identifies a highly sensitive population of patients with significantly improved outcome to trabectedin. This exploratory phase II trial evaluated a customized trabectedin treatment according to this gene signature in patients with non-small cell lung cancer (NSCLC) after the failure of standard platinum-based treatment. **METHODS:** Patients were selected according to their mRNA expression (elevated XPG and/or ERCC1, with low BRCA1) using the following values as cutoff: XPG=0.99, ERCC1=3.47 and BRCA1=12.00. Trabectedin was administered as a 1.3mg/m² 3-hour intravenous infusion every 3 weeks (q3wk). The primary efficacy endpoint was the progression-free survival rate at 3 months. Objective response according to the Response Evaluation Criteria in Solid Tumors (RECIST) was a secondary efficacy endpoint. **RESULTS:** Two of 18 evaluable patients (11.1%; 95% CI, 1.38-34.7%) achieved progression-free survival rate at 3 months. The primary efficacy objective (at least 3 of 18 patients being progression-free at 3 months) was not met, and therefore the trial was early finalized. No objective responses per RECIST were achieved. Four patients had stable disease. Median PFS was 1.3 months, and median overall survival was 5.9 months. Trabectedin was usually well tolerated, with a safety profile similar to that described in patients with other tumor types. **CONCLUSIONS:** Customized treatment with trabectedin 1.3mg/m² 3-h q3wk according to composite gene signature (XPG and/or ERCC1 overexpression, and BRCA1 underexpression) was well tolerated, but had modest activity in NSCLC patients pretreated with platinum. Therefore, further clinical trials with trabectedin as single agent in this indication are not warranted.

A Phase II Study of Halichondrin B Analog Eribulin Mesylate (E7389) in Patients with Advanced Non-small Cell Lung Cancer Previously Treated with a Taxane: A California Cancer Consortium Trial. Gitlitz BJ, Tsao-Wei DD, Groshen S, et al. J Thorac Oncol. 2011 Dec 22. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22198425>

INTRODUCTION: Eribulin mesylate (E7389) is an analog of halichondrin B with a unique mechanism of microtubule binding. The activity and toxicity of eribulin were assessed in patients with advanced non-small cell lung cancer (NSCLC) previously treated with a taxane. **METHODS:** An open-label phase II study included patients with NSCLC previously treated with platinum and taxane-based therapy, with up to two prior cytotoxic regimens, given for metastatic disease or as adjuvant therapy. Patients were stratified by taxane-sensitivity: taxane-sensitive (TS, progression >90 days after taxane) or taxane-resistant (TR, progression ≤90 days after taxane). Patients received an intravenous infusion of eribulin at 1.4 mg/m on days 1 and 8 every 21 days. The primary end point was objective response rate and secondary end points included progression-free survival and overall survival. **RESULTS:** Sixty-six patients were accrued. The objective response rate was 5% with a median duration of response of 7.8 months. In the TS arm, 3 of 45 patients (7%) achieved a partial response and another 11 of 45 (24%) achieved stable disease for at least 3 months, whereas in the TR arm, no patients achieved a partial response and 4 of 21 (19%) achieved stable disease for at least 3 months. Median progression-free survival was 2.9 months in the TS subgroup and 1.2 months in the TR subgroup. The median overall survival was 12.6 months in the TS subgroup and 8.9 months in the TR subgroup. Toxicities were primarily hematologic; only two patients developed grade 3 neuropathy. **CONCLUSIONS:** Eribulin mesylate is well tolerated and demonstrates activity in pretreated, TS NSCLC.

Age-stratified phase I trial of a combination of bortezomib, gemcitabine, and liposomal doxorubicin in patients with advanced malignancies. Falchook GS, Duvic M, Hong DS, et al. Cancer Chemother Pharmacol. 2011 Dec 29. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22205203>

BACKGROUND: Preclinical data suggest synergistic activity of bortezomib, gemcitabine, and liposomal doxorubicin. Because tolerance to therapy may be attenuated in elderly patients, we performed an age-stratified phase I trial of this combination. **PATIENTS AND METHODS:** Two parallel age-stratified arms (<65 and ≥65 years old) were accrued (3 + 3 design). Starting doses included bortezomib 0.7 mg/m² (days 1 and 8), gemcitabine 500 mg/m² (days 1 and 8), and liposomal doxorubicin 20 mg/m² (day 1). **RESULTS:** In the <65-year-old group, 65 patients were treated; the maximum-tolerated dose was bortezomib 1.3 mg/m², gemcitabine 800 mg/m², and liposomal doxorubicin 35 mg/m². In the ≥65-year-old group, 28 patients were treated; the recommended phase II dose was bortezomib 1.0 mg/m², gemcitabine 800 mg/m², and liposomal doxorubicin 20 mg/m². Dose-limiting toxicities included thrombocytopenia and neutropenia. The most common toxicities were mild cytopenias, fatigue, and neuropathy. Ten patients achieved partial responses (6 of 7 patients with cutaneous T-cell lymphoma; 4 of 16 patients with small cell carcinomas, including lung, prostate, ovarian, and nasopharyngeal). **CONCLUSION:** Combination of bortezomib, gemcitabine, and liposomal doxorubicin is well tolerated, but with a lower recommended phase II dose in elderly patients, and demonstrated antitumor activity, especially in T-cell and small cell histology malignancies.

Gemcitabine metabolic pathway genetic polymorphisms and response in patients with non-small cell lung cancer. Li L, Schaid DJ, Fridley BL, et al. Pharmacogenet Genomics. 2011 Dec 15. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22173087>

BACKGROUND AND OBJECTIVE: Gemcitabine is widely used to treat non-small cell lung cancer (NSCLC). The aim of this study was to assess the pharmacogenomic effects of the entire gemcitabine metabolic pathway, we genotyped single nucleotide polymorphisms (SNPs) within the 17 pathway genes using DNA samples from patients with NSCLC treated with gemcitabine to determine the effect of genetic variants within gemcitabine pathway genes on overall survival (OS) of patients with NSCLC after treatment of gemcitabine. **METHODS:** Eight of the 17 pathway genes were resequenced with DNA

samples from Coriell lymphoblastoid cell lines (LCLs) using Sanger sequencing for all exons, exon-intron junctions, and 5'-, 3'-UTRs. A total of 107 tagging SNPs were selected on the basis of the resequencing data for the eight genes and on HapMap data for the remaining nine genes, followed by successful genotyping of 394 NSCLC patient DNA samples. Association of SNPs/haplotypes with OS was performed using the Cox regression model, followed by functional studies performed with LCLs and NSCLC cell lines. **RESULTS:** Five SNPs in four genes (CDA, NT5C2, RRM1, and SLC29A1) showed associations with OS of those patients with NSCLC, as well as nine haplotypes in four genes (RRM1, RRM2, SLC28A3, and SLC29A1) with a P value of less than 0.05. Genotype imputation using the LCLs was performed for a region of 200 kb surrounding those SNPs, followed by association studies with gemcitabine cytotoxicity. Functional studies demonstrated that downregulation of SLC29A1, NT5C2, and RRM1 in NSCLC cell lines altered cell susceptibility to gemcitabine. **CONCLUSION:** These studies help in identifying biomarkers to predict gemcitabine response in NSCLC, a step toward the individualized chemotherapy of lung cancer.

Updated survival and outcomes for older adults with inoperable stage III non-small-cell lung cancer treated with cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel: analysis of a phase III trial from the Hoosier Oncology Group (HOG) and US Oncology.

Jalal SI, Riggs HD, Melnyk A, et al. *Ann Oncol.* 2011 Dec 9. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22156624>

BACKGROUND: Concurrent chemoradiation with etoposide and cisplatin (EP/XRT) is standard treatment for inoperable stage III locally advanced non-small-cell lung cancer (LA-NSCLC). Consolidation docetaxel (D; Taxotere) after EP/XRT resulted in increased toxicity but no improvement in survival compared with observation (O). We report updated survival for the entire study population and include an analysis of efficacy and tolerability of EP/XRT with or without D in patients aged ≥ 70 years. **PATIENTS AND METHODS:** Hoosier Oncology Group LUN 01-24 enrolled 243 patients with LA-NSCLC and randomized 166 after EP/XRT to three cycles of D versus O. The trial was terminated after an analysis of the first 203 patients demonstrated futility of D. **RESULTS:** Median survival time (MST) for the overall study population was 21.5 months, and 3-, 4-, and 5-year survival rates were 30.7%, 18.0%, and 13.9%, respectively. No differences in MST or 3-year survival were noted between D and O arms. Older patients had similar MST (17.1 versus 22.8 months for younger patients, $P = 0.15$) but higher rates of grade 3/4 toxicity and hospitalization during induction. **CONCLUSIONS:** Consolidation docetaxel after EP/XRT does not improve survival in LA-NSCLC. Fit older adults with LA-NSCLC benefit from concurrent chemoradiation similarly as younger patients but experience higher rates of hospitalization and toxicity.

Randomized phase III trial of docetaxel plus carboplatin with or without levofloxacin prophylaxis in elderly patients with advanced non-small cell lung cancer: the APRONTA trial.

Schuette W, Nagel S, von Weikersthal LF, et al. *J Thorac Oncol.* 2011 Dec;6(12):2090-6.

<http://www.ncbi.nlm.nih.gov/pubmed/22052225>

PURPOSE: To examine the effect of levofloxacin prophylaxis on infection rates during chemotherapy with docetaxel plus carboplatin in elderly patients with advanced non-small cell lung cancer. **METHODS:** In a randomized, double-blind, phase III study, patients (≥ 65 years) with untreated, histologically/cytologically proven stage IIIB/IV non-small cell lung cancer received docetaxel (75 mg/m) plus carboplatin (area under the curve 6) on day 1 every 3 weeks, plus once-daily levofloxacin (500 mg orally) or placebo on days 5 to 11. The primary end point was the rate of grade 3/4 infections or grade 1/2 infections treated with additional antibiotics. Secondary end points included overall infection rate, toxicity, overall survival, and progression-free survival. **RESULTS:** In total, 187 patients were randomized to levofloxacin ($n = 95$) or placebo ($n = 92$). The rate of grade 3/4 infections or grade 1/2

infections treated with additional antibiotics (intent-to-treat population) was 27.5% (95% confidence interval, 19.3-39.0%) for levofloxacin versus 36.7% (95% confidence interval, 27.1-48.0%) for placebo. Median time to first infection was 67 days for levofloxacin versus 46 days for placebo. Grade 3/4 infections occurred in 8.8% of patients in the levofloxacin group versus 26.7% for placebo. There was one grade 5 infection in each group. Grade ≥ 3 toxicities (levofloxacin versus placebo) included leukopenia (63.2 versus 52.2%), neutropenia (62.1 versus 51.1%), dyspnea (12.6 versus 8.7%), and pain (10.5 versus 9.8%). There was no significant difference in overall survival or progression-free survival between groups. **CONCLUSIONS:** Levofloxacin prophylaxis reduces the rate of infection compared with placebo and is well tolerated in elderly patients receiving docetaxel plus carboplatin.

NSCLC - RADIOTHERAPY

A single-nucleotide polymorphism in the MTHFR (methylene tetrahydrofolate reductase) gene is associated with risk of radiation pneumonitis in lung cancer patients treated with thoracic radiation therapy. Mak RH, Alexander BM, Asomaning K, et al. *Cancer*. 2011 Dec 5. doi: 10.1002/cncr.26667. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22144047>

BACKGROUND: This study examined the association between functional single-nucleotide polymorphisms in candidate genes from oxidative stress pathways and risk of radiation pneumonitis (RP) in patients treated with thoracic radiation therapy for locally advanced lung cancer. **METHODS:** A review was conducted of 136 patients treated with radiation therapy for lung cancer between 2001 and 2007, and who had prior genotyping of functional single-nucleotide polymorphisms in oxidative stress genes including superoxide dismutase 2 (SOD2; rs4880) and methylene tetrahydrofolate reductase (MTHFR; rs1801131, rs1801133). RP events were retrospectively scored using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Cox proportional hazard regression was performed to identify clinical variables and genotypes associated with risk of RP of grades ≥ 2 and ≥ 3 on univariate and multivariate analysis, respectively. P values were corrected for multiple hypothesis testing. **RESULTS:** With a median follow-up of 21.4 months, the incidence of grade ≥ 2 RP was 29% and grade ≥ 3 RP was 14%. On multivariate analysis, after adjusting for clinical factors such as concurrent chemotherapy and consolidation docetaxel, and lung dosimetric parameters such as volume receiving greater than 20 Gy and mean lung dose, MTHFR genotype (rs1801131; AA versus AC/CC) was significantly associated with risk of grade ≥ 2 RP (hazard ratio: 0.37; 95% confidence interval: 0.18-0.76; P = .006, corrected P = .018) and grade ≥ 3 RP (hazard ratio: 0.21; 95% confidence interval: 0.06-0.70; P = .01; corrected P = .03). SOD2 genotype was not associated with RP. **CONCLUSIONS:** This study showed an association between MTHFR genotype and risk of clinically significant RP. Further study of MTHFR-related pathways may provide insight into the mechanisms behind RP.

Hypofractionated Image-Guided Radiation Therapy for Patients with Limited Volume Metastatic Non-small Cell Lung Cancer. Hasselle MD, Haraf DJ, Rusthoven KE, et al. *J Thorac Oncol*. 2011 Dec 22. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22198429>

INTRODUCTION: Outcomes data treating patients with oligometastatic (≤ 5 metastases) non-small cell lung carcinoma (NSCLC) with hypofractionated image-guided radiotherapy (HIGRT) are limited. **METHODS:** Consecutive oligometastatic NSCLC patients were reviewed from a prospective database. Patients were included if all active diseases were treated with HIGRT. Lesions that had received prior radiation or had radiographic/metabolic resolution after chemotherapy were not treated with HIGRT. Local control of all treated lesions, distant control, progression-free survival (PFS), overall survival (OS), and control of individual lesions (LeC) were calculated. **RESULTS:** Twenty-five patients with median of

2 treated oligometastatic lesions were included. Median follow-up was 14 months. Median age was 66 years. Nineteen patients received systemic therapy before HIGRT and 11 had progressive disease after their most recent systemic therapy before HIGRT. Median OS and PFS were 22.7 and 7.6 months. The 18 months local control, distant control, OS, and PFS were 66.1%, 31.7%, 52.9%, and 28.0%. Greater than two sites treated with HIGRT, nonadenocarcinoma histology, prior systemic therapy, and progression after systemic therapy were associated with worse PFS. Sixty-two individual lesions of median size 2.7 cm were treated. For extracranial lesions, median total and fraction dose were 50 and 5 Gy. Median standard equivalent dose in 2 Gy fractions for extracranial lesions was 64.6 Gy yielding 18 months LeC of 70.7%. Standard equivalent dose ≥ 64.6 Gy increased LeC ($p = 0.04$). Two patients experienced grade 3 toxicity. **CONCLUSIONS:** HIGRT for oligometastatic NSCLC provides durable LeC and may provide long-term PFS in some patients. Future HIGRT studies should optimize patient selection and integration with systemic therapy.

Tumor, Lymph Node, and Lymph Node-to-Tumor Displacements Over a Radiotherapy Series: Analysis of Interfraction and Intrafraction Variations Using Active Breathing Control (ABC) in Lung Cancer. Weiss E, Robertson SP, Mukhopadhyay N, Hugo GD. *Int J Radiat Oncol Biol Phys.* 2011 Dec 22. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22197237>

PURPOSE: To estimate errors in soft tissue-based image guidance due to relative changes between primary tumor (PT) and affected lymph node (LN) position and volume, and to compare the results with bony anatomy-based displacements of PTs and LNs during radiotherapy of lung cancer. **METHODS AND MATERIALS:** Weekly repeated breath-hold computed tomography scans were acquired in 17 lung cancer patients undergoing radiotherapy. PTs and affected LNs were manually contoured on all scans after rigid registration. Interfraction and intrafraction displacements in the centers of mass of PTs and LNs relative to bone, as well as LNs relative to PTs (LN-PT), were calculated. **RESULTS:** The mean volume after 5 weeks was 65% for PTs and 63% for LNs. Systematic and random interfraction displacements were 2.6 to 4.6 mm and 2.7 to 2.9 mm, respectively, for PTs; 2.4 to 3.8 mm and 1.4 to 2.7 mm, respectively, for LNs; and 2.3 to 3.9 mm and 1.9 to 2.8 mm, respectively, for LN-PT. Systematic and random intrafraction displacements were less than 1 mm except in the superoinferior direction. Interfraction LN-PT displacements greater than 3 mm were observed in 67% of fractions and require a safety margin of 12 mm in the lateral direction, 11 mm in the anteroposterior direction, and 9 mm in the superoinferior direction. LN-PT displacements displayed significant time trends ($p < 0.0001$) and depended on the presence of pathoanatomic conditions of the ipsilateral lung, such as atelectasis. **CONCLUSION:** Interfraction LN-PT displacements were mostly systematic and comparable to bony anatomy-based displacements of PTs or LNs alone. Time trends, large volume changes, and the influence of pathoanatomic conditions underline the importance of soft tissue-based image guidance and the potential of plan adaptation.

Changes in Global Function and Regional Ventilation and Perfusion on SPECT During the Course of Radiotherapy in Patients with Non-Small-Cell Lung Cancer. Yuan ST, Frey KA, Gross MD, et al. *Int J Radiat Oncol Biol Phys.* 2011 Dec 22. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22197235>

PURPOSE: This study aimed to (1) examine changes in dyspnea, global pulmonary function test (PFT) results, and functional activity on ventilation (V)/perfusion (Q) single-photon emission computerized tomography (SPECT) scans during the course of radiation (RT), and (2) factors associated with the changes in patients with non-small-cell lung cancer (NSCLC). **METHODS AND MATERIALS:** Fifty-six stage I to III NSCLC patients treated with definitive RT with or without chemotherapy were enrolled prospectively. Dyspnea was graded according to Common Terminology Criteria for Adverse

Events version 3.0 prior to and weekly during RT. V/Q SPECT-computed tomography (CT) and PFTs were performed prior to and during RT at approximately 45 Gy. Functions of V and Q activities were assessed using a semiquantitative scoring of SPECT images. **RESULTS:** Breathing improved significantly at the third week (mean dyspnea grade, 0.8 vs. 0.6; paired t-test $p = 0.011$) and worsened during the later course of RT ($p > 0.05$). Global PFT results did not change significantly, while regional lung function on V/Q SPECT improved significantly after ~45 Gy. The V defect score (DS) was 4.9 pre-RT versus 4.3 during RT ($p = 0.01$); Q DS was 4.3 pre-RT versus 4.0 during RT ($p < 0.01$). Improvements in V and Q functions were seen primarily in the ipsilateral lung (V DS, 1.9 pre-RT versus 1.4 during RT, $p < 0.01$; Q DS, 1.7 pre-RT versus 1.5 during RT, $p < 0.01$). Baseline primary tumor volume was significantly correlated with pre-RT V/Q DS ($p < 0.01$). Patients with central lung tumors had greater interval changes in V and Q than those with more peripheral tumors ($p < 0.05$ for both V and Q DS). **CONCLUSIONS:** Regional ventilation and perfusion improved during RT at 45 Gy. This suggests that adaptive planning based on V/Q SPECT during RT may allow sparing of functionally recoverable lung tissue.

Predicting Chest Wall Pain from Lung Stereotactic Body Radiotherapy for Different Fractionation Schemes. Woody NM, Videtic GM, Stephans KL, Djemil T, Kim Y, Xia P. *Int J Radiat Oncol Biol Phys.* 2011 Dec 23. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22197087>

PURPOSE: Recent studies with two fractionation schemes predicted that the volume of chest wall receiving >30 Gy (V30) correlated with chest wall pain after stereotactic body radiation therapy (SBRT) to the lung. This study developed a predictive model of chest wall pain incorporating radiobiologic effects, using clinical data from four distinct SBRT fractionation schemes. **METHODS AND MATERIALS:** 102 SBRT patients were treated with four different fractionations: 60 Gy in three fractions, 50 Gy in five fractions, 48 Gy in four fractions, and 50 Gy in 10 fractions. To account for radiobiologic effects, a modified equivalent uniform dose (mEUD) model calculated the dose to the chest wall with volume weighting. For comparison, V30 and maximum point dose were also reported. Using univariable logistic regression, the association of radiation dose and clinical variables with chest wall pain was assessed by uncertainty coefficient (U) and C statistic (C) of receiver operator curve. The significant associations from the univariable model were verified with a multivariable model. **RESULTS:** 106 lesions in 102 patients with a mean age of 72 were included, with a mean of 25.5 (range, 12-55) months of follow-up. Twenty patients reported chest wall pain at a mean time of 8.1 (95% confidence interval, 6.3-9.8) months after treatment. The mEUD models, V30, and maximum point dose were significant predictors of chest wall pain ($p < 0.0005$). mEUD improved prediction of chest wall pain compared with V30 (C = 0.79 vs. 0.77 and U = 0.16 vs. 0.11). The mEUD with moderate weighting ($a = 5$) better predicted chest wall pain than did mEUD without weighting ($a = 1$) (C = 0.79 vs. 0.77 and U = 0.16 vs. 0.14). Body mass index (BMI) was significantly associated with chest wall pain ($p = 0.008$). On multivariable analysis, mEUD and BMI remained significant predictors of chest wall pain ($p = 0.0003$ and 0.03, respectively). **CONCLUSION:** mEUD with moderate weighting better predicted chest wall pain than did V30, indicating that a small chest wall volume receiving a high radiation dose is responsible for chest wall pain. Independently of dose to the chest wall, BMI also correlated with chest wall pain.

Impact of Prophylactic Cranial Irradiation Timing on Brain Relapse Rates in Patients with Stage IIIB Non-small-cell Lung Carcinoma Treated with Two Different Chemoradiotherapy Regimens. Topkan E, Parlak C, Kotek A, et al. *Int J Radiat Oncol Biol Phys.* 2011 Dec 13. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22172902>

PURPOSE: To retrospectively assess the influence of prophylactic cranial irradiation (PCI) timing on brain relapse rates in patients treated with two different chemoradiotherapy (CRT) regimens for Stage

IIIB non-small-cell lung cancer (NSCLC). **METHODS AND MATERIALS:** A cohort of 134 patients, with Stage IIIB NSCLC in recursive partitioning analysis Group 1, was treated with PCI (30 Gy at 2 Gy/fr) following one of two CRT regimens. Regimen 1 (n = 58) consisted of three cycles of induction chemotherapy (ICT) followed by concurrent CRT (C-CRT). Regimen 2 (n = 76) consisted of immediate C-CRT during thoracic radiotherapy. **RESULTS:** At a median follow-up of 27.6 months (range, 7.2-40.4), 65 patients were alive. Median, progression-free, and brain metastasis-free survival (BMFS) times for the whole study cohort were 23.4, 15.4, and 23.0 months, respectively. Median survival time and the 3-year survival rate for regimens 1 and 2 were 19.3 vs. 26.1 months (p = 0.001) and 14.4% vs. 34.4% (p < .001), respectively. Median time from the initiation of primary treatment to PCI was 123.2 (range, 97-161) and 63.4 (range, 55-74) days for regimens 1 and 2, respectively (p < 0.001). Overall, 11 (8.2%) patients developed brain metastasis (BM) during the follow-up period: 8 (13.8%) in regimen 1 and 3 (3.9%) in regimen 2 (p = 0.03). Only 3 (2.2%) patients developed BM at the site of first failure, and for 2 of them, it was also the sole site of recurrence. Median BMFS for regimens 1 and 2 were 17.4 (13.5-21.3) vs. 26.0 (22.9-29.1 months), respectively (p < 0.001). **CONCLUSION:** These results suggest that in Stage IIIB NSCLC patients treated with PCI, lower BM incidence and longer survival rates result from immediate C-CRT rather than ITC-first regimens. This indicates the benefit of earlier PCI use without delay because of induction protocols.

Classifying geometric variability by dominant eigenmodes of deformation in regressing tumours during active breath-hold lung cancer radiotherapy. Badawi AM, Weiss E, Sleeman Iv WC, Hugo GD. *Phys Med Biol.* 2011 Dec 15;57(2):395-413. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22172998>

The purpose of this study is to develop and evaluate a lung tumour interfraction geometric variability classification scheme as a means to guide adaptive radiotherapy and improve measurement of treatment response. Principal component analysis (PCA) was used to generate statistical shape models of the gross tumour volume (GTV) for 12 patients with weekly breath hold CT scans. Each eigenmode of the PCA model was classified as 'trending' or 'non-trending' depending on whether its contribution to the overall GTV variability included a time trend over the treatment course. Trending eigenmodes were used to reconstruct the original semi-automatically delineated GTVs into a reduced model containing only time trends. Reduced models were compared to the original GTVs by analyzing the reconstruction error in the GTV and position. Both retrospective (all weekly images) and prospective (only the first four weekly images) were evaluated. The average volume difference from the original GTV was $4.3\% \pm 2.4\%$ for the trending model. The positional variability of the GTV over the treatment course, as measured by the standard deviation of the GTV centroid, was 1.9 ± 1.4 mm for the original GTVs, which was reduced to 1.2 ± 0.6 mm for the trending-only model. In 3/13 cases, the dominant eigenmode changed class between the prospective and retrospective models. The trending-only model preserved GTV and shape relative to the original GTVs, while reducing spurious positional variability. The classification scheme appears feasible for separating types of geometric variability by time trend.

Respiratory gating techniques for optimization of lung cancer radiotherapy. Giraud P, Morvan E, Claude L, et al. *J Thorac Oncol.* 2011 Dec;6(12):2058-68.

<http://www.ncbi.nlm.nih.gov/pubmed/22052228>

PURPOSE: The primary objective of the STIC 2003 project was to compare the clinical and economic aspects of respiratory-gated conformal radiotherapy (RGRT), an innovative technique proposed to limit the impact of respiratory movements during irradiation, versus conventional conformal radiotherapy, the reference radiation therapy for lung cancer. **METHODS AND MATERIALS:** A comparative, nonrandomized, multicenter, and prospective cost toxicity analysis was performed in the context of this

project between April 2004 and June 2008 in 20 French centers. Only the results of the clinical study are presented here, as the results of the economic assessment have been published previously. **RESULTS:** The final results based on 401 evaluable patients confirm the feasibility and good reproducibility of the various RGRT systems. The results of this study demonstrated a marked reduction of dosimetric parameters predictive of pulmonary, cardiac and esophageal toxicity as a result of the various respiratory gating techniques. These dosimetric benefits were mainly observed with deep inspiration breath-hold (DIBH) techniques (ABC and SDX systems), which markedly increased the total lung volume compared with the inspiration-synchronized system based on tidal volume (Real-time Position Management). These theoretical dosimetric benefits were correlated clinically with a significant reduction of pulmonary acute toxicity, and the pulmonary, cardiac, and esophageal late toxicities, especially with DIBH techniques. Pulmonary function parameters, although more heterogeneous, especially DLCO, showed a tendency to reduction of pulmonary toxicity in the RGRT group. **CONCLUSIONS:** RGRT seems to be essential to reduce toxicities, especially the pulmonary, cardiac, and esophageal late toxicities with the DIBH methods.

Local Failure in Resected N1 Lung Cancer: Implications for Adjuvant Therapy. Higgins KA, Chino JP, Berry M, et al. *Int J Radiat Oncol Biol Phys.* 2011 Dec 28. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22208965>

PURPOSE: To evaluate actuarial rates of local failure in patients with pathologic N1 non-small-cell lung cancer and to identify clinical and pathologic factors associated with an increased risk of local failure after resection. **METHODS AND MATERIALS:** All patients who underwent surgery for non-small-cell lung cancer with pathologically confirmed N1 disease at Duke University Medical Center from 1995-2008 were identified. Patients receiving any preoperative therapy or postoperative radiotherapy or with positive surgical margins were excluded. Local failure was defined as disease recurrence within the ipsilateral hilum, mediastinum, or bronchial stump/staple line. Actuarial rates of local failure were calculated with the Kaplan-Meier method. A Cox multivariate analysis was used to identify factors independently associated with a higher risk of local recurrence. **RESULTS:** Among 1,559 patients who underwent surgery during the time interval, 198 met the inclusion criteria. Of these patients, 50 (25%) received adjuvant chemotherapy. Actuarial (5-year) rates of local failure, distant failure, and overall survival were 40%, 55%, and 33%, respectively. On multivariate analysis, factors associated with an increased risk of local failure included a video-assisted thoracoscopic surgery approach (hazard ratio [HR], 2.5; $p = 0.01$), visceral pleural invasion (HR, 2.1; $p = 0.04$), and increasing number of positive N1 lymph nodes (HR, 1.3 per involved lymph node; $p = 0.02$). Chemotherapy was associated with a trend toward decreased risk of local failure that was not statistically significant (HR, 0.61; $p = 0.2$). **CONCLUSIONS:** Actuarial rates of local failure in pN1 disease are high. Further investigation of conformal postoperative radiotherapy may be warranted.

NSCLC - OTHER

Efficacy and Safety of Pemetrexed Maintenance Therapy versus Best Supportive Care in Patients from East Asia with Advanced, Nonsquamous Non-small Cell Lung Cancer: An Exploratory Subgroup Analysis of a Global, Randomized, Phase 3 Clinical Trial. Belani CP, Wu YL, Chen YM, et al. *J Thorac Oncol.* 2011 Dec 7. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22157370>

INTRODUCTION: In a recent global phase 3 trial, patients with advanced non-small cell lung cancer (NSCLC), who had not progressed after four cycles of platinum-based induction chemotherapy, were randomized to maintenance therapy with pemetrexed or placebo. The objective of this retrospective, exploratory, post hoc subgroup analysis was to compare outcomes of East Asian patients with non-East

Asian patients treated with pemetrexed or placebo. **METHODS:** Only patients with nonsquamous histology were analyzed. Patients were grouped by enrollment location (East Asian = China, Korea, or Taiwan; non-East Asian = all other countries). The Kaplan-Meier method was used to calculate median progression-free survival (PFS) and overall survival (OS) times. Hazard ratios (HRs) were calculated using unadjusted Cox proportional hazard models. **RESULTS:** Of the 663 patients enrolled in the study, 481 patients had nonsquamous NSCLC: East Asian = 27% and non-East Asian = 73%. In the East Asian subgroup, there were more women, never smokers, and patients with adenocarcinoma. PFS was similar between the subgroups and significantly prolonged in patients treated with pemetrexed than placebo (median PFS: East Asian, 4.4 versus 1.6 months, HR = 0.42, $p < 0.001$; non-East Asian, 4.5 versus 2.8 months, HR = 0.45, $p < 0.001$). OS was numerically prolonged in East Asians (median OS: pemetrexed, 19.7 months; placebo, 16.4 months) compared with non-East Asians (pemetrexed, 13.2 months; placebo, 8.5 months). Pemetrexed was reasonably well tolerated with few severe adverse events reported. **CONCLUSION:** The results of this subgroup analysis support pemetrexed as maintenance therapy for East Asian patients with advanced, nonsquamous NSCLC.

Retrospective evaluation of the clinical benefit of long-term continuous use of zoledronic acid in patients with lung cancer and bone metastases. Henk HJ, Kaura S, Teitelbaum A. *J Med Econ.* 2011 Dec 23. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22175657>

BACKGROUND: For patients with bone metastases, skeletal-related events including fracture are common, can cause considerable morbidity, and may reduce overall survival (OS). This retrospective analysis assessed the effect of Zometa (zoledronic acid, ZOL), an intravenous bisphosphonate (IV-BP), on fracture risk and OS in patients with bone metastases from lung cancer (LC). (Zometa is a registered trademark of Novartis Pharmaceuticals Corporation, USA.) **METHODS:** A claims-based analysis using commercial and Medicare Advantage data from >45 US managed-care plans was used to evaluate the association between fracture risk and treatment persistency (31-90, 91-180, 181-365, and ≥ 366 days) and follow-up duration in LC patients diagnosed with bone metastases between 01/01/2001 and 12/31/2006 and treated with ZOL or without (no IV-BP). Persistency was defined as the absence of a >45-day gap between ZOL treatments. Analysis of variance tests were used to compare follow-up duration, a proxy for OS, between ZOL persistency groups. The effect of time to treatment with ZOL was also assessed. **RESULTS:** In 9874 LC patients with bone metastases ($n = 1090$ ZOL; $n = 8784$ no IV-BP) the unadjusted relative fracture risk was reduced by 40% with ZOL vs no IV-BP; fracture risk decreased consistently with increasing duration of ZOL treatment. Even short-term (31-90 days) ZOL significantly reduced fracture risk (47%) vs no IV-BP ($p = 0.005$) with adjustment for differences in demographic and clinical characteristics. Delaying ZOL until after bone metastases were diagnosed significantly increased fracture risk ($p = 0.0017$). For a sub-set of patients included in a survival analysis ($n = 550$ ZOL; $n = 4512$ no IV-BP), mortality was significantly lower (mean, 38.6 vs 46.8 deaths/100 person-years; $p = 0.038$) in those treated with ZOL vs no IV-BP. Limitations: Interpretation of this claims-based analysis must be tempered by the inherent limitations of observational data, such as limited clinical information and the ability to control for prognostic factors. **CONCLUSIONS:** This retrospective analysis demonstrates that LC patients with bone metastases receiving ZOL had significantly reduced risk of fracture ($p = 0.005$) and death ($p < 0.038$) vs patients receiving no IV-BP. Longer ZOL persistency consistently yielded better outcomes, with ≥ 12 months' treatment producing the greatest benefit.

SCLC - CHEMOTHERAPY

A Phase I Study of Amrubicin and Fixed Dose of Irinotecan (CPT-11) in Relapsed Small Cell Lung Cancer: Japan Multinational Trial Organization LC0303. Kawahara M, Kubo A, Komuta K, et al. J Thorac Oncol. 2011 Dec 1. [Epub ahead of print]

Fujita Y, Sasaki Y, Fukushima M, Daimon T, Furuse K, Mishima M, Mio T.

<http://www.ncbi.nlm.nih.gov/pubmed/22139390>

PURPOSE: To determine the maximum tolerated dose of amrubicin (AMR) with a fixed dose of irinotecan (CPT-11). **METHODS:** Patients having pathologically proven small cell lung cancer (SCLC) relapsed after one or two chemotherapies, and Eastern Cooperative Oncology Group performance status of 0 to 2 were eligible for the study. CPT-11 was delivered as 50 mg/m² on days 1 and 8, every 21 days. AMR was delivered on day 1. Doses of AMR were level 1: 80 mg/m², level 2: 90 mg/m², and level 3: 100 mg/m². Dose elevation was determined using the modified continuous reassessment method. Tolerability was assessed after the first cycle. Another two cycles were conducted when disease progression or unacceptable toxicities were not observed. **RESULTS:** Eighteen patients (mean age: 66.3 years) were enrolled. A total of 40 courses were conducted. Grade 3/4 toxicities of the first cycle were leukocytopenia: 11 (61%, grade 3/4: 8/3); neutropenia: 15 (83%, grade 3/4: 6/9); and thrombocytopenia: three (17%, grade 3/4: 2/1). Other grade 3 toxicities observed were febrile neutropenia, one; infection, three; diarrhea, one; and dyspnea, one. Dose-limiting toxicity was observed in two of six patients at level 2 (neutropenia and febrile neutropenia) and in one of six at level 3 (thrombocytopenia and infection). The maximum tolerated dose was level 3, and so, the recommended dose for phase II trials was judged to be 90 mg/m². Objective response was obtained in four of eight patients who were able to evaluate responses. Median survival time was 13 months, with 68% at 1-year survival rate. **CONCLUSIONS:** This combination was well tolerated and showed encouraging activities in SCLC. Randomized phase II trials are being planned in chemo-naïve SCLC.

SCLC - RADIOTHERAPY

Chemoradiotherapy duration correlates with overall survival in limited disease SCLC patients with poor initial performance status who successfully completed multimodality treatment.

Manapov F, Klöcking S, Niyazi M, et al. Strahlenther Onkol. 2011 Dec 23. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22189436>

BACKGROUND AND PURPOSE: Limited data concerning treatment-related prognostic factors in limited disease (LD) small-cell lung cancer (SCLC) patients with poor initial performance status (PS) who successfully completed chemoradiotherapy (CRT) are available. **PATIENTS AND METHODS:** A total of 125 patients with initial PS WHO 2-3 who successfully completed CRT were retrospectively reviewed. Thoracic radiation therapy (TRT) was applied in the concurrent (group 1) or sequential (group 2) mode. Influence of treatment type, time from diagnosis to start of TRT, number of chemotherapy cycles, prophylactic cranial irradiation (PCI), occurrence of brain metastases (BMs), and duration of CRT on overall survival (OS) were analyzed. **RESULTS:** Median duration of CRT was 156 days in group 1 and 195 days in group 2 ($p < 0.001$). Median progression-free survival and OS were 11.6 (95% confidence interval (CI) 10-13.2) and 14.9 (95% CI 11.7-17.6) months with no difference between the groups. The 2- and 3-year survival rates were $37.9 \pm 6.9\%$ and $22.7 \pm 6.3\%$ in group 1 and $22.4 \pm 4.9\%$ and $15.2 \pm 4.3\%$ in group 2, respectively. Duration of CRT was only treatment-related factor predicting OS in the uni- ($p < 0.014$) and multivariate ($p < 0.025$) analyses. Short dose-dense CRT was associated with improved OS. **CONCLUSION:** Duration of CRT affects OS in LD SCLC patients with poor initial performance status who successfully completed multimodality treatment.

Quality of life and mental health in caregivers of outpatients with advanced cancer. Wadhwa D, Burman D, Swami N, Rodin G, Lo C, Zimmermann C. *Psychooncology*. 2011 Dec 2. doi: 10.1002/pon.2104. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22135229>

OBJECTIVE: This study evaluates the quality of life (QOL) and mental health (MH) of caregivers of patients with advanced cancer who are receiving ambulatory oncology care and associations with patient, caregiver and care-related characteristics. **METHODS:** Patients with advanced gastrointestinal, genitourinary, breast, lung or gynaecologic cancer, and their caregivers, were recruited from 24 medical oncology clinics for a cluster-randomized trial of early palliative care. Caregivers completed the Caregiver QOL-Cancer scale and the Medical Outcomes Study Short Form, version 2, and a questionnaire including care-related factors such as hours/day providing care and change in work situation. Patients completed a demographic questionnaire and measures of their QOL and symptom severity. Associations of these factors with caregiver QOL and MH were examined using linear regression analyses.

RESULTS: Of the 191 caregivers, 84% were spouses/partners, 90% cohabited with the patient, half were working and 25% had a change in work situation since the patient's diagnosis. On multiple regression analysis, better caregiver QOL was associated with better caregiver MH and patient physical well-being and with not providing care for other dependents. Worse caregiver MH was associated with female caregiver sex, worse patient emotional well-being, more hours spent caregiving and change in the caregiver's work situation. **CONCLUSIONS:** Caregivers of ambulatory patients with advanced cancer may have compromised QOL and MH associated with worse patient physical and emotional well-being and with simultaneously caring for others and working outside the home. Early palliative care interventions directed at patient symptoms and caregiver support may improve QOL in this population.

Effect of Early Palliative Care on Chemotherapy Use and End-of-Life Care in Patients With Metastatic Non-Small-Cell Lung Cancer. Greer JA, Pirl WF, Jackson VA, et al. *J Clin Oncol*. 2011 Dec 27. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22203758>

PURPOSE: Prior research shows that introducing palliative care soon after diagnosis for patients with metastatic non-small-cell lung cancer (NSCLC) is associated with improvements in quality of life, mood, and survival. We sought to investigate whether early palliative care also affects the frequency and timing of chemotherapy use and hospice care for these patients. **PATIENTS AND METHODS:** This secondary analysis is based on a randomized controlled trial of 151 patients with newly diagnosed metastatic NSCLC presenting to an outpatient clinic at a tertiary cancer center from June 2006 to July 2009. Participants received either early palliative care integrated with standard oncology care or standard oncology care alone. By 18-month follow-up, 133 participants (88.1%) had died. Outcome measures included: first, number and types of chemotherapy regimens, and second, frequency and timing of chemotherapy administration and hospice referral. **RESULTS:** The overall number of chemotherapy regimens did not differ significantly by study group. However, compared with those in the standard care group, participants receiving early palliative care had half the odds of receiving chemotherapy within 60 days of death (odds ratio, 0.47; 95% CI, 0.23 to 0.99; $P = .05$), a longer interval between the last dose of intravenous chemotherapy and death (median, 64.00 days [range, 3 to 406 days] v 40.50 days [range, 6 to 287 days]; $P = .02$), and higher enrollment in hospice care for longer than 1 week (60.0% [36 of 60 patients] v 33.3% [21 of 63 patients]; $P = .004$). **CONCLUSION:** Although patients with metastatic NSCLC received similar numbers of chemotherapy regimens in the sample, early palliative care optimized the timing of final chemotherapy administration and transition to hospice services, key measures of quality end-of-life care.

The EORTC QLQ-BN20 for assessment of quality of life in patients receiving treatment or prophylaxis for brain metastases: a literature review. Leung A, Lien K, Zeng L, Nguyen J, Caissie A, Culleton S, Holden L, Chow E. *Expert Rev Pharmacoecon Outcomes Res.* 2011 Dec;11(6):693-700. <http://www.ncbi.nlm.nih.gov/pubmed/22098285>

INTRODUCTION: Brain metastases occur in approximately 20-40% of cancer patients during the course of disease. As treatment for brain metastases is palliative over curative, quality of life (QoL) is emphasized over prolonged survival. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-BN20 is a QoL assessment specific to brain neoplasms. We aim to provide a review of the current use of the EORTC QLQ-BN20 for patients with brain metastases. **MATERIALS & METHODS:** All studies utilizing the QLQ-BN20 for QoL assessment in patients receiving treatments related to brain metastases were included. Study information including treatment type, assessment periods, patient enrolment and all information pertaining to the QLQ-BN20 were extracted. **RESULTS:** A total of 13 studies were identified, five of which were randomized trials assessing prophylactic whole brain radiation for patients with small-cell lung cancer. The QLQ-BN20 was used in conjunction with the core QLQ-C30 questionnaire in all but one of the studies and together these comprised the entire QoL assessments for 11 of the 13 studies. Neurocognitive function assessments supplemented QoL in four studies and accompanying performance status indices used with the QLQ-BN20 varied. Compliance issues were commonly cited. QoL changes during study periods varied as improvements, deteriorations and stabilizations were all observed. **CONCLUSION:** QoL assessments should be conducted using disease-specific tools. Future studies should minimize patient burden in order to maximize data collection and accrual. A common set of QoL end points for patients with brain metastases should be created.

International Practice Survey on Palliative Lung Radiotherapy: Third International Consensus Workshop on Palliative Radiotherapy and Symptom Control. Rodrigues G, Macbeth F, Burmeister B, et al. *Clin Lung Cancer.* 2011 Dec 12. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/22169482>

BACKGROUND: The purpose of this work was to disseminate international practice survey results created in conjunction with the Third International Lung Cancer Consensus Workshop. **PATIENTS AND METHODS:** In conjunction with the American Society for Radiation Oncology (ASTRO) Guideline for Palliative Lung Cancer Care and International Workshop Consensus statements, an online international practice survey was conducted during the summer of 2010. The survey included demographic, educational, and clinical questions as well as 5 cases exploring the role of external beam radiotherapy, endobronchial brachytherapy, and concurrent chemoradiation. **RESULTS:** A total of 279 individuals responded to the survey over a 3-month period. Most respondents were hospital-based, academic, or government-funded radiation oncologists. Factors that consistently related to use and choice of external beam dose fractionation included estimated treatment benefit to patient, performance status (PS), symptom severity, patient choice, estimated prognosis, and previous radiation to the same site. Factors consistently not related to use and dose fractionation included requirement for future radiation therapy, department policy, and waiting lists. A significant range of dose fractionation schedules existed for external beam (n = 35) and endobronchial brachytherapy treatment (n = 10). The integration of concurrent chemotherapy was recorded by a significant minority of respondents despite lack of level I evidence to support its use. Geographic differences in the use of external beam dose fractionation and of concurrent chemotherapy were seen. **CONCLUSIONS:** Various patient, tumor, treatment, and logistic factors are associated with the variable use and external beam dose fractionation of palliative lung treatments. The copublication of the ASTRO Guideline for Palliative Lung Cancer Care and International Workshop Consensus statements should assist clinicians by providing evidence-based care.

Perception of quality of care: comparison of the views of patients' with lung cancer and their family members. Hensch I, Lövgren M, Wilde-Larsson B, Tishelman C. *J Clin Nurs*. 2011 Dec 12. doi: 10.1111/j.1365-2702.2011.03923.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22150995>

AIMS AND OBJECTIVES: To explore potential differences within dyads of patients' with lung cancer and family members' judgment of different aspects of quality of care and relationships between quality of care and personal and health-related characteristics. **Background:** High quality of care is important for acceptable quality of life in patients in palliative care. If patients are unable to participate in quality of care assessments or decision-making, family members might often act as proxies, despite the complicated nature of their own situation. **DESIGN:** Cross-sectional survey design. **METHOD:** A patient and family member version of the abbreviated questionnaire Quality from Patients' Perspective, with additional items about perceived health and opinions about care, was mailed to members of the Swedish lung cancer Patient Organisation. Wilcoxon's signed rank test was used to identify potential differences within 51 patient-family member dyads' quality of care ratings. Relationships between Quality from Patients' Perspective dimensions and demographic and health-related variables were examined with Spearman's correlations. **Results.** Patient-family member dyads had high levels of agreement in ratings of perceived reality of quality of care. Family members generally rated the subjective importance of individual items higher than did the patient in the dyad, with significant difference in the dimension 'socio-cultural approach'. Older patients were found to rate the physical-technical conditions higher than younger patients, in relation to perceived reality but not subjective importance. Women family members were found to rate the subjective importance of medical-technical competence, identity-oriented approach and socio-cultural approach significantly higher than men did. **CONCLUSIONS:** Patients with lung cancer and their family members agree in ratings of the perceived reality, but they differ more in ratings of the subjective importance of quality of care. When patients are unable to communicate their preferences, family members' opinions could be used as proxies concerning concrete aspects of quality of care. Concerning more subjective aspects, family members' ratings should be interpreted with precaution, as it could diverge from patients' own opinion. **Relevance to clinical practice.** The perceptions of the importance of different aspects of quality of care were less related to health status than were judgments of quality of care received. This might suggest that the care patients received fulfilled neither the patients' nor family members' expectations, which is an important message to healthcare professionals and which would demand further exploration.

Maintaining integrity in the face of death: A grounded theory to explain the perspectives of people affected by lung cancer about the expression of wishes for end of life care. Horne G, Seymour J, Payne S. *Int J Nurs Stud*. 2011 Dec 29. [Epub ahead of print]

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BACKGROUND: An emphasis on patient choice in health and social care underpins a growing interest in advance care planning. Few studies have explored the views and experiences of people with advanced lung cancer about discussing their wishes or preferences for end of life care. Evidence suggests that some people may want nurses and other health professionals to initiate discussions about the future. However, there is a lack of evidence about what priority patients facing death give to their preferences and wishes, and how these shape their views about end of life. **OBJECTIVES:** To explore the views and experiences of people affected by lung cancer about discussing preferences and wishes for end of life care and treatment. **DESIGN:** A qualitative study using semi-structured interviews and constant comparative method of analysis to develop a grounded theory. **SETTINGS:** One multi-cultural city and one post-industrial town in northern England, UK. Data were collected between 2006 and 2008.

PARTICIPANTS: Interviews took place with 25 patients with lung cancer and 19 family members.

METHOD: Qualitative constructivist grounded theory study. **RESULTS:** The study found that

preferences and wishes for future care and treatment were not the main concern of people with cancer; rather, any concerns for the future were about the social aspects of death. A theory 'maintaining integrity in the face of death' is proposed. This theory purports that patients with advanced lung cancer and their families focus on acting and talking as 'normal' to help them balance living in the present whilst facing death. Participants talked about their experiences of facing death whilst striving to live in the present. Planning for one's own dying and eventual death was not something that people with lung cancer reported having discussed, except when, out of concern for their families, practical arrangements needed to be made following death. **CONCLUSION:** The study suggests that people facing the end of their life primarily focus on living in the present. The findings suggest that nurses need to develop ways of helping people prepare for the 'social' rather than just the physical or 'medicalised' aspects of death.

COMPLEMENTARY & ALTERNATIVE THERAPY

External Qi of Yan Xin Qigong induces cell death and gene expression alterations promoting apoptosis and inhibiting proliferation, migration and glucose metabolism in small-cell lung cancer cells. Yan X, Li F, Dozmorov I, Frank MB, Dao M, Centola M, Cao W, Hu D. *Mol Cell Biochem.* 2011 Dec 10. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22160803>

Small-cell lung cancer (SCLC) is a highly malignant carcinoma with poor long-term survival. Effective treatment remains highly demanded. In the present study, we demonstrated that External Qi of Yan Xin Qigong (YXQ-EQ) exerted potent cytotoxic effect towards SCLC cell line NCI-H82 via induction of apoptosis. Global gene expression profiling identified 39 genes whose expression was altered by YXQ-EQ in NCI-82 cells. Among them, semi-quantitative RT-PCR and real-time qPCR analyses confirmed that the gene expression levels of apoptotic proteins death-associated protein kinase 2 and cell death-inducing DFFA-like effector b were upregulated, whereas that of oncoproteins DEK and MYCL1, cell migration-promoting proteins CD24 and integrin-alpha 9, and glycolytic enzyme aldolase A were d

MISCELLANEOUS WORKS

Lung cancer patients' decisions about clinical trials and the theory of planned behavior. Quinn GP, Pratt CL, Bryant-George K, Caraway VD, Paternoster B, Roldan T, Shaffer A, Shimizu CO, Vaughn EJ, Williams C, Bepler G. *J Cancer Educ.* 2011 Dec;26(4):641-8.

<http://www.ncbi.nlm.nih.gov/pubmed/20949381>

The theory of planned behavior explores the relationship between behavior, beliefs, attitudes, and intentions presupposing that behavioral intention is influenced by a person's attitude about the behavior and beliefs about whether individuals, who are important to them, approve or disapprove of the behavior (subjective norm). An added dimension to the theory is the idea of perceived behavioral control, or the belief that one has control over performing the behavior. The theory of planned behavior suggests that people may make greater efforts to perform a behavior if they feel they have a high level of control over it. In this examination of data, we explored the application of the theory of planned behavior to patient's decisions about participating in a clinic trial. Twelve respondents in this study had previously participated in a clinical trial for lung cancer and nine respondents had declined a clinical trial for lung cancer. The data were analyzed with regard to the four constructs associated with the theory of planned behavior: behavioral intention, attitude, subjective norm, and perceived behavioral control. Results indicate that the theory of planned behavior may be a useful tool to examine psychosocial needs in relation to behavioral intention of clinical trial participation.

IGDB.NSCLC: integrated genomic database of non-small cell lung cancer. Kao S, Shiau CK, Gu DL, Ho CM, Su WH, Chen CF, Lin CH, Jou YS. *Nucleic Acids Res.* 2012 Jan 1;40(D1):D972-D977. Epub 2011 Dec 1.

<http://www.ncbi.nlm.nih.gov/pubmed/22139933>

Lung cancer is the most common cause of cancer-related mortality with more than 1.4 million deaths per year worldwide. To search for significant somatic alterations in lung cancer, we analyzed, integrated and manually curated various data sets and literatures to present an integrated genomic database of non-small cell lung cancer (IGDB.NSCLC, <http://igdb.nslc.ibms.sinica.edu.tw>). We collected data sets derived from hundreds of human NSCLC (lung adenocarcinomas and/or squamous cell carcinomas) to illustrate genomic alterations [chromosomal regions with copy number alterations (CNAs), gain/loss and loss of heterozygosity], aberrant expressed genes and microRNAs, somatic mutations and experimental evidence and clinical information of alterations retrieved from literatures. IGDB.NSCLC provides user friendly interfaces and searching functions to display multiple layers of evidence especially emphasizing on concordant alterations of CNAs with co-localized altered gene expression, aberrant microRNAs expression, somatic mutations or genes with associated clinicopathological features. These significant concordant alterations in NSCLC are graphically or tabularly presented to facilitate and prioritize as the putative cancer targets for pathological and mechanistic studies of lung tumorigenesis and for developing new strategies in clinical interventions.

Differences Between Squamous Cell Carcinoma and Adenocarcinoma of the Lung: Are Adenocarcinoma and Squamous Cell Carcinoma Prognostically Equal? Kawase A, Yoshida J, Ishii G, et al. *Jpn J Clin Oncol.* 2011 Dec 30. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22210923>

OBJECTIVE: We analyzed pulmonary squamous cell carcinoma and adenocarcinoma patient survival in our single institution database, to evaluate the relationship of histologic analysis to survival and tumor aggressiveness. **METHODS:** We reviewed 1856 consecutive patients with surgically resected pulmonary squamous cell carcinoma or adenocarcinoma regarding their clinicopathologic characteristics, overall survival and recurrence-free proportion. **RESULTS:** In squamous cell carcinoma patients, there were more elderly male smokers and more patients with T2-4 tumors, moderately/poorly differentiated tumors, lymph node metastasis or vascular invasion than in adenocarcinoma patients. In all patients and in pN0 patients, patients with squamous cell carcinoma showed significantly poorer overall survival than those with adenocarcinoma, but there were no statistically significant differences in the recurrence-free proportion between the two histologic types. There were statistically significantly more lung cancer-specific deaths in patients with adenocarcinoma than in patients with squamous cell carcinoma ($P=0.001$). **CONCLUSIONS:** There were no differences in the development of recurrence between squamous cell carcinoma and adenocarcinoma of the lung, but considerable differences in overall survival were observed between the two histologic types. According to the stage grouping strategy of the TNM Classification for Lung and Pleural Tumours, these two histologic types need to be staged differently. This survival difference, however, may reflect the difference in patient background rather than in biologic aggressiveness between the two histologic types.

The Impact of Computed Tomography Screening for Lung Cancer on Smoking Behaviors: A Teachable Moment? Poghosyan H, Kennedy Sheldon L, Cooley ME. *Cancer Nurs.* 2011 Dec 29. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22209869>

BACKGROUND: Helical computed tomography (CT) has emerged as a potential screening test for lung cancer. An important component of care surrounding the use of this technology is the impact of screening on decisions surrounding smoking cessation. **OBJECTIVE:** The aim of this article was to conduct an

integrative review of literature on the impact of lung cancer screening with CT on smoking behaviors of current smokers. **METHODS:** Ganong's [Res Nurs Health. 1987;10(1):1-11] guidelines were used to conduct this integrative review. Computerized databases were used to identify relevant articles. Data were extracted from the studies, and then content analysis was used to synthesize the findings. **RESULTS:** Nine studies were identified and reviewed. The quit rate among participants ranged from 6.6% to 42% after screening. Among current smokers, smoking abstinence was associated with older age, worse pulmonary function, and having multiple abnormal CT findings. Motivation to quit smoking, within the next 30 days, ranged from 14% to 35% among smokers. Factors associated with increased motivation were older age, lower nicotine addiction, fewer lung cancer symptoms, higher self-efficacy, and acknowledgment of the advantages of quitting smoking. **CONCLUSIONS:** Participants undergoing lung cancer screening had increased motivation to quit smoking. Computed tomographic screening for lung cancer appears to be a teachable moment to address smoking cessation. **IMPLICATIONS FOR PRACTICE:** Screening for lung cancer is only one step to fight lung cancer. Incorporating smoking cessation interventions along with the use of technology is necessary to fight this deadly disease.

A qualitative analysis of lung cancer screening practices by primary care physicians. Henderson S, DeGross A, Richards TB, Kish-Doto J, Soloe C, Heminger C, Rohan E. J Community Health. 2011 Dec;36(6):949-56.

<http://www.ncbi.nlm.nih.gov/pubmed/21442338>

Lung cancer is the leading cause of cancer death in the United States, but no scientific organization currently recommends screening because of limited evidence for its effectiveness. Despite this, physicians often order screening tests such as chest X-rays and computerized tomography scans for their patients. Limited information is available about how physicians decide when to order these tests. To identify factors that affect whether physicians' screen patients for lung cancer, we conducted five 75-min telephone-based focus groups with 28 US primary care physicians and used inductive qualitative research methods to analyze their responses. We identified seven factors that influenced these physicians' decisions about screening patients for lung cancer: (1) their perception of a screening test's effectiveness, (2) their attitude toward recommended screening guidelines, (3) their practice experience, (4) their perception of a patient's risk for lung cancer, (5) reimbursement and payment for screening, (6) their concern about litigation, and (7) whether a patient requested screening. Because these factors may have conflicting effects on physicians' decisions to order screening tests, physicians may struggle in determining when screening for lung cancer is appropriate. We recommend (1) more clinician education, beginning in medical school, about the existing evidence related to lung cancer screening, with emphasis on the benefit of and training in tobacco use prevention and cessation, (2) more patient education about the benefits and limitations of screening, (3) further studies about the effect of patients' requests to be screened on physicians' decisions to order screening tests, and (4) larger, quantitative studies to follow up on our formative data. ownregulated. These findings suggest that YXQ-EQ may exert anticancer effect through modulating gene expression in a way that facilitates cancer cell apoptosis while represses proliferation, metastasis, and glucose metabolism.

Characteristics of lung cancer in women: Importance of hormonal and growth factors. Rouquette I, Lauwers-Cances V, Allera C, et al. Lung Cancer. 2011 Dec 22. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22197614>

Based on epidemiological, clinical, and preclinical data, lung carcinogenesis can be distinctive in women, suggesting that women should be treated differently depending on the expression of various specific biomarkers. We aimed to describe the hormonal and genetic profile of lung cancer in both men and women to identify gender specificities. Primary lung-tumor tissues from surgically treated patients, (50 men, 50 women) were analyzed and compared for expression of estrogen receptors (ER) α and β ,

progesterone receptors (PR), epidermal growth-factor receptor (EGFR), and HER2 (for EGFR and K-Ras mutations). These data were combined with clinical and outcome data. Fewer women with lung cancer were smokers ($p=0.001$) and they smoked fewer cigarettes ($p=0.001$). We observed a higher rate of EGFR mutations ($p=0.02$) and ER α expression ($p=0.006$) in women. ER β and EGFR were also expressed more frequently in women ($p=0.29$ and $p=0.16$). HER2 was overexpressed regardless of gender in three men and two women. K-Ras was mutated in 16% of both men and women. Interestingly, there was a positive link between EGFR expression and expression of ER α ($p=0.028$) and ER β ($p=0.047$) in both men and women. Expression of ER α was associated with improved disease-free survival ($p=0.007$). Our findings provide further evidence on the specificities of lung cancer in women. The differential expression of specific biomarkers, which could be targeted by therapy, favors the development of gender-based treatment guided by biomarker expression.