



Caring Ambassadors Lung Cancer Program Literature Review February, 2011

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BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

The Haptoglobin β chain as a supportive biomarker for human lung cancers. Kang SM, Sung HJ, Ahn JM, Park JY, Lee SY, Park CS, Cho JY. Mol Biosyst. 2011 Jan 21. [Epub ahead of print]
<http://www.ncbi.nlm.nih.gov/pubmed/21253648>

Haptoglobin (Hp) is produced as an acute phase reactant during inflammation, infection, malignant diseases, and several cancers. In proteomics analysis using human blood samples, the Hp peptide levels were about 3-fold higher in lung cancer patients versus normal individuals. This study is aimed at analyzing the elevation of which chain of Hp is closely related to lung cancers and can be a serum biomarker for lung cancers. In Western blot (WB) analysis, we found that the Hp β chain can be a better diagnostic biomarker for lung cancers. In the result of the Hp β chain ELISA developed by us, the concentrations of the Hp β chain in the sera increased about 4-fold in 190 lung adenocarcinoma patients versus 190 healthy controls ($8.0 \pm 3.8 \mu\text{g ml}^{-1}$) vs. $1.9 \pm 1.2 \mu\text{g ml}^{-1}$). ELISA data showed that the serum levels of the Hp β chain in breast cancer ($1.5 \pm 0.5 \mu\text{g ml}^{-1}$) and hepatocellular carcinoma (HCC) ($1.4 \pm 1.0 \mu\text{g ml}^{-1}$) patients remained similar to those of healthy controls. Compared to lung adenocarcinoma, the Hp β chain levels in the plasma of patients with other respiratory diseases such as tuberculosis (TBC), idiopathic pulmonary fibrosis (IPF) and bronchial asthma (BA) were closer to those of healthy controls. Our data suggest that an increase of the Hp β chain can be a potential serum biomarker for lung cancers.

Primary resistance to cetuximab in a panel of patient-derived tumour xenograft models: Activation of MET as one mechanism for drug resistance. Krumbach R, Schüler J, Hofmann M, Gieseemann T, Fiebig HH, Beckers T. Eur J Cancer. 2011 Jan 25. [Epub ahead of print]
<http://www.ncbi.nlm.nih.gov/pubmed/21273060>

Cetuximab (Erbix®) targets the epidermal growth factor receptor (EGFR) and is approved for treatment of colorectal and head and neck cancer. Despite wide expression of EGFR, only a subgroup of cancer patients responds to cetuximab therapy. In the present study we assessed the cetuximab response in vivo

of 79 human patient-derived xenografts originating from five tumour histotypes. We analysed basic tumour characteristics including EGFR expression and activation, mutational status of KRAS, BRAF and NRAS, the expression of EGFR ligands and the activation of HER3 (ErbB3) and the hepatocyte growth factor receptor MET. Based on these results, a cetuximab response score including positive and negative factors affecting therapeutic response is proposed. Positive factors are high expression and activation of EGFR and its ligands epiregulin or amphiregulin, negative factors are markers for downstream pathway activation independent of EGFR. In cetuximab resistant NSCL adenocarcinoma LXFA 526 and LXFA 1647, overexpression due to gene amplification and strong activation of MET was identified. Knock-down of MET by siRNA in the corresponding cell lines showed that anchorage-independent growth and migration are dependent on MET. MET knock down sensitized LXFA 526L and LXFA 1647L to EGF. Combined treatments of a MET inhibitor and cetuximab were additive. **Therefore, combination therapy of cetuximab and a MET inhibitor in selected lung cancer patients could be of high clinical significance.**

Expression and unique functions of four nuclear factor of activated T cells isoforms in non-small cell lung cancer. Chen ZL, Zhao SH, Wang Z, Qiu B, Li BZ, Zhou F, Tan XG, He J. *Chin J Cancer*. 2011 Jan;30(1):62-8.

<http://www.ncbi.nlm.nih.gov/pubmed/21192845>

Nuclear factor of activated T cells (NFAT) is an important family of transcription factors that can be activated by calmodulin and calcineurin in human cells. To investigate the expression and clinical significance of NFAT isoforms and calcineurin in non-small cell lung cancer (NSCLC), we collected tumor and adjacent normal tissues from 159 NSCLC patients and assembled them in a tissue microarray. Protein levels of NFAT1, NFAT2, NFAT3, NFAT4, and calcineurin were determined using immunohistochemistry. Correlations between NFAT and calcineurin expression and clinicopathologic characteristics were analyzed. We found that the positive rates of NFAT1 (52.8%, 84/159), NFAT2 (11.3%, 18/159), NFAT3 (28.3%, 45/159), NFAT4 (47.2%, 75/159), and calcineurin (47.8%, 76/159) expression were significantly higher in tumor tissues than in adjacent normal lung tissues ($P < 0.001$), respectively. The positive rate of NFAT1 expression was significantly higher in patients with adenocarcinoma (63.5%, 47/74) than in those with squamous cell carcinoma (43.5%, 37/85) ($\chi^2 = 6.340$, $P = 0.012$); with lymph node metastasis (61.6%, 53/86) than without lymph node metastasis (42.5%, 31/73) ($\chi^2 = 5.818$, $P = 0.016$); and with stage-II and -III diseases (61.8%, 55/89) than with stage-I disease (41.4%, 29/70) ($\chi^2 = 6.524$, $P = 0.011$). Moreover, the overexpression of NFAT1 was associated with poor survival of NSCLC patients ($\chi^2 = 5.006$, $P = 0.025$). The positive rate of NFAT4 was significantly higher in patients with squamous carcinoma (57.6%, 49/85) than in those with adenocarcinoma (35.1%, 26/74) ($\chi^2 = 8.045$, $P = 0.005$) and with high and moderate differentiation (54.9%, 61/111) than with low differentiation (29.2%, 14/48) ($\chi^2 = 8.943$, $P = 0.003$). Calcineurin overexpression was significantly associated with histologic type (higher in squamous carcinoma than in adenocarcinoma, $\chi^2 = 8.897$, $P = 0.003$), differentiation grade (higher in high-moderation grade than in low grade, $\chi^2 = 9.566$, $P = 0.002$) and gender (higher in male than in female, $\chi^2 = 5.766$, $P = 0.016$). Furthermore, calcineurin expression was significantly correlated with NFAT4 level ($r = 0.429$, $P < 0.001$). These results suggest that NFAT1 expression is associated with lung adenocarcinoma progression, and NFAT4 expression, which was higher in squamous lung cancer, is associated with calcineurin expression and differentiation grade.

Clinical implications of hedgehog signaling pathway inhibitors. Liu H, Gu D, Xie J. Chin J Cancer. 2011 Jan;30(1):13-26.

<http://www.ncbi.nlm.nih.gov/pubmed/21192841>

Hedgehog was first described in *Drosophila melanogaster* by the Nobel laureates Eric Wieschaus and Christiane Nüsslein-Volhard. The hedgehog (Hh) pathway is a major regulator of cell differentiation, proliferation, tissue polarity, stem cell maintenance, and carcinogenesis. The first link of Hh signaling to cancer was established through studies of a rare familial disease, Gorlin syndrome, in 1996. Follow-up studies revealed activation of this pathway in basal cell carcinoma, medulloblastoma and, leukemia as well as in gastrointestinal, lung, ovarian, breast, and prostate cancer. Targeted inhibition of Hh signaling is now believed to be effective in the treatment and prevention of human cancer. The discovery and synthesis of specific inhibitors for this pathway are even more exciting. In this review, we summarize major advances in the understanding of Hh signaling pathway activation in human cancer, mouse models for studying Hh-mediated carcinogenesis, the roles of Hh signaling in tumor development and metastasis, antagonists for Hh signaling and their clinical implications.

DIAGNOSIS AND STAGING

Accuracy of Fine Needle Aspiration Cytology in the Pathological Typing of Non-small Cell Lung Cancer. Nizzoli R, Tiseo M, Gelsomino F, et al. J Thorac Oncol. 2011 Jan 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21258246>

BACKGROUND: Histological typing of non-small cell lung cancer (NSCLC) has an increasing clinical relevance due to the emerging differences in medical treatment between squamous and nonsquamous tumors. However, most NSCLCs are diagnosed in an advanced stage, and the diagnosis is often obtained exclusively by cytology either exfoliative or following fine needle aspiration. We investigated the accuracy of fine needle aspiration cytology (FNAC) in NSCLC typing as compared with histology.

METHODS: Over the period 2000-2009, 1182 transbronchial needle aspirate or transthoracic needle aspirate samples were obtained from patients with suspicious thoracic lesions. In 474 patients, a cytological diagnosis of primary NSCLC was obtained, and 186 (39%) of them (108 transbronchial needle aspirates and 78 transthoracic needle aspirates) received a parallel or subsequent histologic diagnosis on endoscopic biopsy (112) or surgery (74). **RESULTS:** At cytology, 158 (85%) NSCLC cases were typed (89 adenocarcinoma and 69 squamous cell carcinoma), while 28 (15%) were classified as NSCLC not otherwise specified. At histology, 183 (98%) cases were typed (109 adenocarcinoma, 69 squamous cell carcinoma, 3 adenosquamous carcinoma, and 2 large cell carcinoma), and only 3 (2%) were classified as NSCLC not otherwise specified. Cytological and histological typing was concordant in 137 of 156 (88%) cases ($K = 0.755$; $p < 0.001$). The positive predictive value of FNAC in typing NSCLC was 92% for adenocarcinoma and 82% for squamous cell carcinoma. **CONCLUSION:** FNAC in expert hands is fairly accurate for typing NSCLC and can be regarded as an acceptable procedure for diagnostic and medical treatment planning purposes in most NSCLC cases, especially when more invasive approaches are unfeasible. In poorly differentiated and doubtful cases, the use of ancillary techniques, such as immunocytochemistry, may be required to improve the diagnostic yield.

Suitability of Thoracic Cytology for New Therapeutic Paradigms in Non-small Cell Lung Carcinoma: High Accuracy of Tumor Subtyping and Feasibility of EGFR and KRAS Molecular Testing. Rekhtman N, Brandt SM, Sigel CS, et al. J Thorac Oncol. 2011 Jan 24. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21266922>

INTRODUCTION: The two essential requirements for pathologic specimens in the era of personalized therapies for non-small cell lung carcinoma (NSCLC) are accurate subtyping as adenocarcinoma (ADC)

versus squamous cell carcinoma (SqCC) and suitability for EGFR and KRAS molecular testing. The aim of this study was to comprehensively review the performance of cytologic specimens for the above two goals in a high-volume clinical practice. **METHODS:** Subtyping of primary lung carcinomas by preoperative cytology was correlated with subsequent resection diagnoses during a 1-year period (n = 192). The contribution of various clinicopathologic parameters to subtyping accuracy and utilization of immunohistochemistry (IHC) for NSCLC subtyping were analyzed. In addition, the performance of cytologic specimens submitted for EGFR/KRAS molecular testing during a 1-year period (n = 128) was reviewed. **RESULTS:** Of the 192 preoperative cytology diagnoses, tumor subtype was definitive versus favored versus unclassified in 169 (88%) versus 15 (8%) versus 8 (4%) cases, respectively. Overall accuracy of cytologic tumor subtyping (concordance with histology) was 93% and accuracy of definitive diagnoses 96%. For a group of patients with ADC and SqCC (n = 165), the rate of unclassified cytologic diagnoses was 3% and overall accuracy 96%. IHC was used for subtyping of 9% of those cases, yielding 100% accuracy. The strongest predictors of difficulty in subtyping of ADC and SqCC were poor differentiation (p = 0.0004), low specimen cellularity (p = 0.019), and squamous histology (p = 0.003). Of 128 cytologic specimens submitted for molecular testing, 126 (98%) were suitable for analysis, revealing EGFR and KRAS mutations in 31 (25%) and 25 (20%) cases, respectively. **CONCLUSIONS:** Cytologic subtyping of NSCLC is feasible and accurate, particularly when morphologic assessment is combined with IHC. Furthermore, routine cytologic specimens can be successfully used for EGFR/KRAS mutation analysis. Our data strongly support the suitability of cytologic specimens for the new therapeutic paradigms in NSCLC.

Revolution in lung cancer: new challenges for the surgical pathologist. Cagle PT, Allen TC, Dacic S, et al. Arch Pathol Lab Med. 2011 Jan;135(1):110-6.

<http://www.ncbi.nlm.nih.gov/pubmed/21204716>

CONTEXT: Traditionally, lung cancer has been viewed as an aggressive, relentlessly progressive disease with few treatment options and poor survival. The traditional role of the pathologist has been primarily to differentiate small cell carcinoma from non-small cell carcinoma on biopsy and cytology specimens and to stage non-small cell carcinomas that underwent resection. In recent years, our concepts of lung cancer have undergone a revolution, including (1) the advent of successful, new, molecular-targeted therapies for lung cancer, many of which are associated with specific histologic cell types and subtypes; (2) new observations on the natural history of lung cancer derived from ongoing high-resolution computed tomography screening studies and recent histologic findings; and (3) proposals to revise the classification of lung cancers, particularly adenocarcinomas, in part because of the first 2 developments. **OBJECTIVE:** To summarize the important, new developments in lung cancer, emphasizing the role of the surgical pathologist in personalized care for patients with lung cancer. **DATA SOURCES:** Information about the new developments in lung cancer was obtained from the peer-review medical literature and the authors' experiences. **CONCLUSIONS:** For decades, we have perceived lung cancer as a relentlessly aggressive and mostly incurable disease for which the surgical pathologist had a limited role. Today, surgical pathologists have an important and expanding role in the diagnosis and treatment of lung cancer, and it is essential to keep informed of new advances.

Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. Yoshizawa A, Motoi N, Riely GJ, et al. Mod Pathol. 2011 Jan 21. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21252858>

A new lung adenocarcinoma classification is being proposed by the International Association for the Study of Lung Cancer, American Thoracic Society and European Respiratory Society (IASLC/ATS/ERS). This proposal has not yet been tested in clinical datasets to determine whether it defines

prognostically significant subgroups of lung adenocarcinoma. In all, 514 patients who had pathological stage I adenocarcinoma of the lung classified according to the Union for International Cancer Control/American Joint Committee on Cancer 7th Edition, and who had undergone a lobectomy with mediastinal lymph node dissection were retrospectively reviewed. Comprehensive histological subtyping was used to estimate the percentage of each histological subtype and to identify the predominant subtype. Tumors were classified according to the proposed new IASLC/ATS/ERS adenocarcinoma classification. Statistical analyses were made including Kaplan-Meier and Cox regression analyses. There were 323 females (63%) and 191 males (37%) with a median age of 69 years (33-89 years) and 298 stage IA and 216 stage IB patients. Three overall prognostic groups were identified: low grade: adenocarcinoma in situ (n=1) and minimally invasive adenocarcinoma (n=8) had 100% 5-year disease-free survival; intermediate grade: non-mucinous lepidic predominant (n=29), papillary predominant (n=143) and acinar predominant (n=232) with 90, 83 and 84% 5-year disease-free survival, respectively; and high grade: invasive mucinous adenocarcinoma (n=13), colloid predominant (n=9), solid predominant (n=67) and micropapillary predominant (n=12), with 75, 71 and 67%, 5-year disease-free survival, respectively (P<0.001). Among the clinicopathological factors, stage 1B versus 1A (P<0.001), male sex (P<0.008), high histological grade (P<0.001), vascular invasion (P=0.002) and necrosis (P<0.001) were poorer prognostic factors on univariate analysis. Both gross tumor size (P=0.04) and invasive tumor size adjusted by the percentage of lepidic growth (P<0.001) were significantly associated with disease-free survival with a slightly stronger association for the latter. Multivariate analysis showed the prognostic groups of the IASLC/ATS/ERS histological classification (P=0.038), male gender (P=0.007), tumor invasive size (P=0.026) and necrosis (P=0.002) were significant poor prognostic factors. In summary, the proposed IASLC/ATS/ERS classification of lung adenocarcinoma identifies histological categories with prognostic differences that may be helpful in identifying candidates for adjunctive therapy. The slightly stronger association with survival for invasive size versus gross size raises the need for further studies to determine whether this adjustment in measuring tumor size could impact TNM staging for small adenocarcinomas.

Accuracy of Fine Needle Aspiration Cytology in the Pathological Typing of Non-small Cell Lung Cancer. Nizzoli R, Tiseo M, Gelsomino F, et al. *J Thorac Oncol.* 2011 Jan 20. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21258246>

BACKGROUND: Histological typing of non-small cell lung cancer (NSCLC) has an increasing clinical relevance due to the emerging differences in medical treatment between squamous and nonsquamous tumors. However, most NSCLCs are diagnosed in an advanced stage, and the diagnosis is often obtained exclusively by cytology either exfoliative or following fine needle aspiration. We investigated the accuracy of fine needle aspiration cytology (FNAC) in NSCLC typing as compared with histology. **METHODS:** Over the period 2000-2009, 1182 transbronchial needle aspirate or transthoracic needle aspirate samples were obtained from patients with suspicious thoracic lesions. In 474 patients, a cytological diagnosis of primary NSCLC was obtained, and 186 (39%) of them (108 transbronchial needle aspirates and 78 transthoracic needle aspirates) received a parallel or subsequent histologic diagnosis on endoscopic biopsy (112) or surgery (74). **RESULTS:** At cytology, 158 (85%) NSCLC cases were typed (89 adenocarcinoma and 69 squamous cell carcinoma), while 28 (15%) were classified as NSCLC not otherwise specified. At histology, 183 (98%) cases were typed (109 adenocarcinoma, 69 squamous cell carcinoma, 3 adenosquamous carcinoma, and 2 large cell carcinoma), and only 3 (2%) were classified as NSCLC not otherwise specified. Cytological and histological typing was concordant in 137 of 156 (88%) cases (K = 0.755; p < 0.001). The positive predictive value of FNAC in typing NSCLC was 92% for adenocarcinoma and 82% for squamous cell carcinoma. **CONCLUSION:** FNAC in expert hands is fairly accurate for typing NSCLC and can be regarded as an acceptable procedure for diagnostic and medical treatment planning purposes in most NSCLC cases, especially when more invasive

approaches are unfeasible. In poorly differentiated and doubtful cases, the use of ancillary techniques, such as immunocytochemistry, may be required to improve the diagnostic yield.

Subclassification of non-small cell lung carcinomas lacking morphologic differentiation on biopsy specimens: Utility of an immunohistochemical panel containing TTF-1, napsin A, p63, and CK5/6.

Mukhopadhyay S, Katzenstein AL. *Am J Surg Pathol*. 2011 Jan;35(1):15-25.

<http://www.ncbi.nlm.nih.gov/pubmed/21164283>

The availability of targeted therapies has created a need for precise subtyping of non-small cell lung carcinomas (NSCLCs). The aim of this study was to assess the utility of immunohistochemical markers in subtyping poorly differentiated NSCLC and to compare the results of immunohistochemical staining on biopsies with the corresponding resections. Thirty-nine cases of NSCLC that could not be further classified on biopsy and had subsequent resection specimens were identified. Classification of the tumor was based on the resection specimen using the World Health Organization criteria. All biopsies and resections were stained with CK7, TTF-1, napsin A (novel aspartic proteinase of the pepsin family), p63, CK5/6, and 34βE12. The specimens included 20 adenocarcinomas (ACs), 15 squamous cell carcinomas (SCCs), and 4 large-cell carcinomas (LCCs). TTF-1 was positive in biopsies from 16 of 20 ACs, 2 of 4 LCCs, and none of the SCCs. p63 was positive in all 15 SCCs, 2 of 20 ACs (both were also positive for TTF-1 and napsin A), and none of the LCCs. CK5/6 was positive in 11 of 15 SCCs (all p63 positive) but none of the ACs or LCCs. Napsin A stained 11 of 19 ACs (all TTF-1 positive) but none of the other tumors. Staining for CK7 was present in 19 of 19 ACs and 9 of 15 SCCs. 34βE12 stained both SCCs (15 of 15) and ACs (12 of 20). The combination of TTF-1, napsin A, p63, and CK5/6 allowed an accurate classification of 30 of 39 (77%) cases. Of 232 pairs of slides (biopsy and resection) stained with immunohistochemical markers, 12 (5%) showed discrepancies in immunohistochemical staining between biopsies and their corresponding resections. Immunohistochemical staining using a combination of TTF-1, napsin A, p63, and CK5/6 allows subclassification of poorly differentiated NSCLCs on small lung biopsies in most cases. Discrepancies in immunohistochemical staining between biopsies and resections are uncommon.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Lung sparing surgery by means of extended broncho-angioplastic (sleeve) lobectomies. Gómez-Caro A, García S, Jiménez MJ, Matute P, Gimferrer JM, Molins L. *Arch Bronconeumol*. 2011 Jan 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21256657>

OBJECTIVE: To determine the morbidity, mortality and survival of sleeve lobectomy procedures compared to simple broncho-angioplasty procedures. **PATIENTS AND METHODS:** A total of 535 patients diagnosed with bronchogenic cancer between September 2005 and May 2010 who fulfilled the criteria of clinical, oncological and functional operability were treated in our unit. Unresectable central tumours (n=95) using simple lobectomy were scheduled for broncho-angioplasty techniques and a pneumonectomy in those where this was impossible. **RESULTS:** A total of 58 (11%) were performed, 46 simple broncho-angioplastic lobectomies (SBAL) and 12 extended broncho-angioplastic lobectomies (EBAL). In the SBAL group there were 32 bronchial (70%) and 7 (15%) bronchovascular reconstructions and only vascular (15%). In the EBAL group, 8 (66.7%) were bronchial and 4 (33.3%) were bronchovascular reconstructions. The most common type of resection was the right upper lobe (RUL)+segment 6 in five (41%) cases, followed by RUL+middle lobe. There were 2 (3%) deaths in the SBAL group. There was 34% morbidity in the SBAL and 33% in the EBAL group (P>0.05). Fifteen

patients received neoadjuvant chemo-radiotherapy treatment, due to histologically confirmed cN2; however, the number of complications was not significantly higher. No risk factors were detected in any variable studied that would affect EBAL compared to the SBAL group ($P>0.05$). The patients in both groups with a higher morbidity were pN1, located in the left upper lobe and associated with vascular reconstruction ($P<0.05$). The overall survival at 5 years was 61.6%, SBAL (61%) and EBAL (68.9%) with no differences between groups ($P>0.05$). **CONCLUSIONS:** EBALs are technically more demanding procedures, but do not increase the morbidity or mortality compared to simple broncho-angioplasty techniques, and with a similar survival.

Existing general population models inaccurately predict lung cancer risk in patients referred for surgical evaluation. Isbell JM, Deppen S, Putnam JB Jr, et al. *Ann Thorac Surg.* 2011 Jan;91(1):227-33; <http://www.ncbi.nlm.nih.gov/pubmed/21172518>

BACKGROUND: Patients undergoing resections for suspicious pulmonary lesions have a 9% to 55% benign rate. Validated prediction models exist to estimate the probability of malignancy in a general population and current practice guidelines recommend their use. We evaluated these models in a surgical population to determine the accuracy of existing models to predict benign or malignant disease.

METHODS: We conducted a retrospective review of our thoracic surgery quality improvement database (2005 to 2008) to identify patients who underwent resection of a pulmonary lesion. Patients were stratified into subgroups based on age, smoking status, and fluorodeoxyglucose positron emission tomography (PET) results. The probability of malignancy was calculated for each patient using the Mayo and solitary pulmonary nodules prediction models. Receiver operating characteristic and calibration curves were used to measure model performance. **RESULTS:** A total of 189 patients met selection criteria; 73% were malignant. Patients with preoperative PET scans were divided into four subgroups based on age, smoking history, and nodule PET avidity. Older smokers with PET-avid lesions had a 90% malignancy rate. Patients with PET-nonavid lesions, PET-avid lesions with age less than 50 years, or never smokers of any age had a 62% malignancy rate. The area under the receiver operating characteristic curve for the Mayo and solitary pulmonary nodules models was 0.79 and 0.80, respectively; however, the models were poorly calibrated ($p<0.001$). **CONCLUSIONS:** Despite improvements in diagnostic and imaging techniques, current general population models do not accurately predict lung cancer among patients referred for surgical evaluation. Prediction models with greater accuracy are needed to identify patients with benign disease to reduce nontherapeutic resections.

Simulating video-assisted thoracoscopic lobectomy: a virtual reality cognitive task simulation.

Solomon B, Bizakis C, Dellis SL, et al. *J Thorac Cardiovasc Surg.* 2011 Jan;141(1):249-55.

<http://www.ncbi.nlm.nih.gov/pubmed/21168026>

OBJECTIVE: Current video-assisted thoracoscopic surgery training models rely on animals or mannequins to teach procedural skills. These approaches lack inherent teaching/testing capability and are limited by cost, anatomic variations, and single use. In response, we hypothesized that video-assisted thoracoscopic surgery right upper lobe resection could be simulated in a virtual reality environment with commercial software. **METHODS:** An anatomy explorer (Maya [Autodesk Inc, San Rafael, Calif] models of the chest and hilar structures) and simulation engine were adapted. Design goals included freedom of port placement, incorporation of well-known anatomic variants, teaching and testing modes, haptic feedback for the dissection, ability to perform the anatomic divisions, and a portable platform. **RESULTS:** Preexisting commercial models did not provide sufficient surgical detail, and extensive modeling modifications were required. Video-assisted thoracoscopic surgery right upper lobe resection simulation is initiated with a random vein and artery variation. The trainee proceeds in a teaching or testing mode. A knowledge database currently includes 13 anatomic identifications and 20 high-yield lung cancer learning points. The "patient" is presented in the left lateral decubitus position. After initial

camera port placement, the endoscopic view is displayed and the thoracoscope is manipulated via the haptic device. The thoracoscope port can be relocated; additional ports are placed using an external "operating room" view. Unrestricted endoscopic exploration of the thorax is allowed. An endo-dissector tool allows for hilar dissection, and a virtual stapling device divides structures. The trainee's performance is reported. **CONCLUSIONS:** A virtual reality cognitive task simulation can overcome the deficiencies of existing training models. Performance scoring is being validated as we assess this simulator for cognitive and technical surgical education.

NSCLC - CHEMOTHERAPY

Sex differences in outcome with bevacizumab therapy: analysis of patients with advanced-stage non-small cell lung cancer treated with or without bevacizumab in combination with paclitaxel and carboplatin in the Eastern Cooperative Oncology Group Trial 4599. Brahmer JR, Dahlberg SE, Gray RJ, Schiller JH, Perry MC, Sandler A, Johnson DH. *J Thorac Oncol.* 2011 Jan;6(1):103-8.

<http://www.ncbi.nlm.nih.gov/pubmed/21079521>

INTRODUCTION: E4599 compared carboplatin and paclitaxel with (PCB) or without (PC) bevacizumab in patients with advanced-stage non-small cell lung cancer. Bevacizumab improved overall survival. However, an unplanned subset analysis did not show a survival benefit for females treated with bevacizumab. **METHODS:** Known prognostic factors and toxicities were compared by sex. Proportional hazards models of survival with multiple factor combinations were used to adjust for treatment effect. **RESULTS:** The analysis includes 850 patients. The median survival was 8.7 months (PC) versus 11.7 months (PCB) for males ($p = 0.001$) and 13.1 months (PC) versus 13.3 months (PCB) for females ($p = 0.87$). Progression-free survival and response rate on the PCB arm were 6.3 months and 29% for males and 6.2 months and 41% for females ($p > 0.05$). Progression-free survival and response rate on the PC arm were 4.3 months and 16% for males and 5.3 months and 14% for females ($p > 0.05$). No significant demographic differences were seen between the two arms for males, whereas fewer females on the PCB arm had liver metastasis (PCB 11.7% versus PC 23.2%, $p = 0.003$). Adverse events with a sex difference on the PCB arm included severe hypertension (males: 4.2%, females: 9.9%, $p = 0.02$), constipation (males: 1.4%, females: 4.7%, $p = 0.05$), and abdominal pain (males: 0.9%, females: 5.2%, $p = 0.01$). In the proportional hazards model adjusting for the other factors, the test for a sex by treatment interaction was not significant ($p = 0.09$). **CONCLUSIONS:** Multiple factors may contribute to the apparent sex-specific differences in efficacy of bevacizumab noted in this study.

Genome-wide association study on overall survival of advanced non-small cell lung cancer patients treated with carboplatin and paclitaxel. Sato Y, Yamamoto N, Kunitoh H, et al. *J Thorac Oncol.* 2011 Jan;6(1):132-8.

<http://www.ncbi.nlm.nih.gov/pubmed/21079520>

PURPOSE: Our goal was to identify candidate polymorphisms that could influence overall survival (OS) in advanced non-small cell lung cancer (NSCLC) patients treated with carboplatin (CBDCA) and paclitaxel (PTX). **METHODS:** Chemotherapy-naïve stage IIIB or IV NSCLC patients treated with CBDCA (area under the curve = 6 mg/mL/min) and PTX (200 mg/m, 3-hour period) were eligible for this study. The DNA samples were extracted from peripheral blood mononuclear cells before treatment, and genotypes at approximately 110,000 gene-centric single-nucleotide polymorphisms (SNPs) were obtained by Illumina's Sentrix Human-1 Genotyping BeadChip. Statistical analyses were performed by the log-rank test and Cox proportional hazards model. **RESULTS:** From July 2002 to May 2004, 105 patients received a total of 308 cycles of treatment. The median survival time (MST) of 105 patients was 17.1 months. In the genome-wide association study, three SNPs were associated significantly with shortened OS after multiple comparison adjustment: rs1656402 in the EIF4E2 gene (MST was 18.0 and 7.7 months

for AG [n = 50] + AA [n = 40] and GG [n = 15], respectively; $p = 8.4 \times 10^{-10}$), rs1209950 in the ETS2 gene (MST = 17.7 and 7.4 months for CC [n = 94] and CT [n = 11] + TT [n = 0]; $p = 2.8 \times 10^{-10}$), and rs9981861 in the DSCAM gene (MST = 17.1 and 3.8 months for AA [n = 75] + AG [n = 26] and GG [n = 4]; $p = 3.5 \times 10^{-10}$). **CONCLUSION:** Three SNPs were identified as new prognostic biomarker candidates for advanced NSCLC treated with CBDCA and PTX. The agnostic genome-wide association study may unveil unexplored molecular pathways associated with the drug response, but our findings should be replicated by other investigators.

Randomized phase II trial of irinotecan with paclitaxel or gemcitabine for non-small cell lung cancer: association of UGT1A1*6 and UGT1A1*27 with severe neutropenia. Nakamura Y, Soda H, Oka M, et al. *J Thorac Oncol.* 2011 Jan;6(1):121-7.

<http://www.ncbi.nlm.nih.gov/pubmed/21150467>

HYPOTHESIS: Irinotecan-containing regimens are known to be active and tolerable in patients with non-small cell lung cancer (NSCLC). A randomized phase II trial was conducted to evaluate the efficacy of irinotecan plus paclitaxel or gemcitabine for previously untreated stage IIIB or stage IV NSCLC. **PATIENTS AND METHODS:** Previously untreated patients with adequate organ function who gave written informed consent were randomly assigned to receive irinotecan (50 mg/m on days 1, 8, and 15) plus paclitaxel (180 mg/m on day 1) every 4 weeks (IP group) or irinotecan (100 mg/m on days 1 and 8) plus gemcitabine (1000 mg/m on days 1 and 8) every 3 weeks (IG group). The primary endpoint was the response rate. We also evaluated the relationship of response and toxicity to polymorphisms of the uridine diphosphate glucuronosyltransferase (UGT) gene. **RESULTS:** Eighty patients were enrolled, and 78 patients were eligible (38 in the IP group and 40 in the IG group). The response rate was 31.6% (95% confidence interval: 17.5-48.7%) in the IP group and 20.0% (9.1-35.6%) in the IG group. The median progression-free survival time was 86 days and 145 days, respectively. Both regimens were well tolerated. The most common severe adverse event was grade 4 neutropenia (36.8% and 10.0%, respectively), which was associated with UGT1A1*6 and UGT1A1*27. UGT polymorphisms did not correlate with response. **CONCLUSIONS:** Irinotecan plus paclitaxel may be more active against NSCLC than irinotecan plus gemcitabine. The UGT1A1*6 and UGT1A1*27 genotypes might be useful predictors of grade 4 neutropenia in patients who receive irinotecan-based chemotherapy.

Antagonism between Gefitinib and Cisplatin in Non-small Cell Lung Cancer Cells: Why Randomized Trials Failed? Tsai CM, Chen JT, Stewart DJ, et al. *J Thorac Oncol.* 2011 Jan 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21258258>

INTRODUCTION: Four phase III randomized trials adding epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors to standard chemotherapeutics in patients with advanced non-small cell lung cancer (NSCLC) have failed to show benefits. The mechanism of these failures was examined. **METHODS:** Fifteen previously untreated NSCLC cell lines were simultaneously treated with gefitinib plus cisplatin. Three exhibited sensitizing-EGFR mutations. Three selected lines were further tested with paclitaxel/cisplatin, paclitaxel/ gefitinib, and paclitaxel/cisplatin/ gefitinib combinations. The tetrazolium colorimetric assay with application of the classic isobole method was used, and dose-versus-log-response curves (DRCs) were analyzed to evaluate possible resistance mechanisms. **RESULTS:** Of the 15 cell lines tested, combined gefitinib/cisplatin was significantly antagonistic in 10 wild-type and three sensitizing-EGFR mutant cell lines (group mean combination index = 1.184, 95% confidence interval = 1.12-1.24, $p = 0.001$). The mean combination index values of paclitaxel/cisplatin/ gefitinib were higher than or comparable with those of paclitaxel/cisplatin and paclitaxel/ gefitinib. DRC analysis consistently showed nonsaturable passive resistance, suggesting that gefitinib at 0.001 to 0.3 μM can interfere with cisplatin cell entry (at concentrations $>1\text{-}3 \mu\text{M}$) in a dose-dependent manner and lead to antagonism. This

antagonism may or may not be schedule dependent in different cell lines. **CONCLUSIONS:** In most EGFR wild-type or sensitizing-mutant NSCLC cells, the concomitant gefitinib/cisplatin combination showed antagonism, likely because gefitinib interfered with cisplatin entry into the cell. The findings that three-drug combination was not better than the two-drug combinations are in accordance with the results of the randomized trials. The EGFR-tyrosine kinase inhibitor/platinum antagonism is a possible reason for the failure of those randomized trials.

Sorafenib in combination with erlotinib or with gemcitabine in elderly patients with advanced non-small-cell lung cancer: a randomized phase II study. Gridelli C, Morgillo F, Favaretto A, et al. *Ann Oncol.* 2011 Jan 6. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21212155>

BACKGROUND: Sorafenib is a small-molecule multitargeted kinase inhibitor that blocks the activation of C-RAF, B-RAF, c-KIT, FLT-3, RET, vascular endothelial growth factor receptor 2 (VEGFR-2), VEGFR-3 and platelet-derived growth factor receptor β . The aim of this multicenter, randomized phase II study was to evaluate clinical activity and safety of sorafenib in combination with erlotinib or gemcitabine in unselected untreated elderly patients with non-small-cell lung cancer (NSCLC). **METHODS:** The trial was designed to select the most promising sorafenib-containing combination in previously untreated elderly (≥ 70 years) stage IIIB or IV NSCLC patients, with performance status of zero to two. Patients were randomly assigned to one of the following combinations: gemcitabine, 1200 mg/m² days 1 and 8, every 21 days, for a maximum of six cycles, plus sorafenib, 800 mg/day, until disease progression or unacceptable toxicity (arm 1); or erlotinib, 150 mg/day, plus sorafenib, 800 mg/day, until disease progression or unacceptable toxicity (arm 2). A selection design was applied with 1-year survival rate as the primary end point of the study, requiring 58 patients. **RESULTS:** Sixty patients were randomly allocated to the study (31 patients in arm 1 and 29 patients in arm 2). After a median follow-up of 15 months, 10 patients [32%, 95% confidence interval (CI) 16% to 49%] in arm 1 and 13 patients (45%, 95% CI 27% to 63%) in arm 2 were alive at 1 year. Median overall survival was 6.6 and 12.6 months in arm 1 and arm 2, respectively. Observed toxic effects were consistent with the expected drug profiles. **CONCLUSIONS:** The combination of erlotinib and sorafenib was feasible in elderly patients with advanced NSCLC and was associated with a higher 1-year survival rate than the other arm. According to the selection design, this combination warrants further investigation in phase III trials.

Long-term administration of second-line chemotherapy with S-1 and gemcitabine for platinum-resistant non-small cell lung cancer: a phase II study. Takiguchi Y, Seto T, Ichinose Y, et al. *J Thorac Oncol.* 2011 Jan;6(1):156-60.

<http://www.ncbi.nlm.nih.gov/pubmed/21107293>

BACKGROUND: Standard second-line chemotherapies for non-small cell lung cancer (NSCLC) have been established but have limited clinical relevance. S-1 is a recently developed agent with potential activity against NSCLC. **METHODS:** Patients with confirmed NSCLC recurrence after previous single- or two-regimen chemotherapy with platinum, performance status of 0 to 1, adequate organ functions, and measurable lesions were treated with S-1 (60 mg/m²/d, twice a day) on days 1 to 14 and gemcitabine (1000 mg/m²) on days 8 and 15, which were repeated every 3 weeks until tumor progression. **RESULTS:** Treatment was administered for a median of 4 courses (range, 1-13) over a median of 125-day period in 34 patients. The overall response rate was 23.5% (no complete response and eight partial response; 95% confidence interval: 9.1-38.0%). The median progression-free and overall survival times were 6.6 and 19.9 months, respectively. The 1- and 2-year survival rates were 58.8 and 30.9%, respectively. Toxicity was mild during the entire treatment period, except for three grade 3 interstitial pneumonia. **CONCLUSION:** The primary end point was met with the relatively high overall response rate. Randomized phase III studies for elucidating survival outcome of the regimen are warranted.

BRIDGE: an open-label phase II trial evaluating the safety of bevacizumab + carboplatin/paclitaxel as first-line treatment for patients with advanced, previously untreated, squamous non-small cell lung cancer. Hainsworth JD, Fang L, Huang JE, Karlin D, Russell K, Faoro L, Azzoli C. *J Thorac Oncol.* 2011 Jan;6(1):109-14.

<http://www.ncbi.nlm.nih.gov/pubmed/21107290>

BACKGROUND: Patients with predominantly squamous non-small cell lung cancer (NSCLC) have been generally excluded from studies of bevacizumab treatment, because squamous histology was identified as a possible risk factor for severe (grade ≥ 3) pulmonary hemorrhage (PH) in a phase II study. BRIDGE was designed to determine whether delaying initiation of bevacizumab treatment and selecting patients without baseline risk factors for PH would lower the incidence of severe PH among patients with squamous NSCLC. **METHODS:** Patients in this open-label, single-arm study were treated with carboplatin/paclitaxel for two cycles, followed by carboplatin/paclitaxel and bevacizumab in cycles 3 to 6, followed by bevacizumab until progression or unacceptable toxicity. Eligible patients had stage IIIb, stage IV, or recurrent squamous NSCLC. The primary end point was incidence of grade ≥ 3 PH.

RESULTS: Grade ≥ 3 PH occurred in 1 of 31 patients who received ≥ 1 dose of bevacizumab: estimated incidence was 3.2% (90% confidence interval 0.3-13.5%). The patient experienced grade 3 PH, discontinued from the study, then experienced grade 4 PH 10 days later, and died of progressive disease. No other serious bleeding events occurred. Nine patients (29.0%) experienced grade 3 adverse events, including five with hypertension; five patients experienced grade 4 adverse events (dyspnea, PH, basal ganglia infarction, cerebral ischemia, and pain). Median progression-free survival was 6.2 months (95% confidence interval 5.32-7.62 months). **CONCLUSIONS:** The incidence of grade ≥ 3 PH was 3.2% (one patient). No new safety signals were identified. Although the rate of PH was low, the number of patients in this study was also low. Treatment of squamous NSCLC with bevacizumab should be considered experimental.

Comparison of platinum-based chemotherapy in patients older and younger than 70 years: an analysis of Southwest Oncology Group Trials 9308 and 9509.

Blanchard EM, Moon J, Hesketh PJ, Kelly K, Wozniak AJ, Crowley J, Gandara D. *J Thorac Oncol.* 2011 Jan;6(1):115-20.

<http://www.ncbi.nlm.nih.gov/pubmed/21107287>

PURPOSE: This retrospective analysis sought to investigate the safety, feasibility, and outcomes of platinum doublet therapy in patients aged 70 years or older with advanced non-small cell lung cancer compared with patients younger than 70 years who participated in two randomized phase III trials conducted by the Southwest Oncology Group. **PATIENTS AND METHODS:** Outcomes and toxicity data from fit patients with stage IIIB or stage IV non-small cell lung cancer treated with cisplatin/vinorelbine and carboplatin/paclitaxel were pooled from Southwest Oncology Group trials 9308 (S9308) and 9509 (S9509) and compared with respect to age. **RESULTS:** A total of 616 patients were available for efficacy analyses, of which 122 (20%) were aged 70 years or older. The median progression-free survival was 4 months in both age groups ($p = 0.71$), and response rates were similar. Overall survival was significantly higher in the younger patient cohort (median 9 months versus 7 months, $p = 0.04$). Individual parameters of toxicity were similar in both age groups. **CONCLUSION:** Although patients aged 70 years or older derived initial benefit from platinum-based therapy, survival was better in younger patients. Additional studies in this growing patient population are needed to develop treatment strategies that minimize toxicity and increase efficacy.

Randomized Phase II Trial of Concurrent Versus Sequential Bortezomib Plus Docetaxel in Advanced Non-Small-Cell Lung Cancer: A California Cancer Consortium Trial. Lara Jr PN, Longmate J, Reckamp K, et al. Clin Lung Cancer. 2011 Jan 1;12(1):33-37.

<http://www.ncbi.nlm.nih.gov/pubmed/21273177>

BACKGROUND: The proteasome inhibitor bortezomib sensitizes tumor cells to chemotherapy-induced apoptosis. In preclinical non-small-cell lung cancer (NSCLC) models, p53-dependent growth arrest after bortezomib treatment resulted in reduced cytotoxicity if bortezomib preceded docetaxel. The reverse sequence of docetaxel before bortezomib was associated with increased apoptosis, cleavage of caspase-3 and PARP (poly [ADP-ribose] polymerase), and reduction in Bcl-2. A prospective randomized phase II trial of concurrent versus sequential docetaxel and bortezomib was conducted to assess whether administration sequence resulted in measurable clinical differences. **PATIENTS AND METHODS:** Previously treated patients with advanced NSCLC were randomized to concurrent (CON) or sequential (SEQ) docetaxel (75 mg/m² intravenous [I.V.]) followed by bortezomib, every 3 weeks. In the CON arm, bortezomib (1.6 mg/m² I.V.) was given on days 1 and 8, and in the SEQ arm, it was given on days 2 and 8. Previous erlotinib as well as treated or controlled brain metastases were allowed. The primary endpoint was objective response rate (RR); progression-free (PFS) and overall survival (OS) were secondary endpoints. **RESULTS:** Eighty-one patients were randomized (40 CON and 41 SEQ). Grade 3+ toxicities were mostly due to myelosuppression. One patient each had grade 4 hyponatremia and syncope. Toxicities were similar between the arms. There was 1 treatment-related death in the SEQ arm. There were 8 partial responders, 4 in each arm, for an overall RR of 10%. Disease control rate was similar in both arms (50% vs. 49%). Median PFS was 12 weeks in the CON arm and 11 weeks in the SEQ arm. Median OS times in the CON and SEQ arms were 13.3 and 10.5 months, respectively. **CONCLUSION:** Docetaxel plus bortezomib given sequentially or concurrently has similar RR and PFS. Median survival in the SEQ arm exceeds published survival estimates for either agent alone or in combination. Any further studies in this population would require molecular characterization of a phenotype most likely to benefit from proteasome inhibitor therapy.

NSCLC - RADIOTHERAPY

Lovastatin Sensitizes Lung Cancer Cells to Ionizing Radiation: Modulation of Molecular Pathways of Radioresistance and Tumor Suppression. Sanli T, Liu C, Rashid A, et al. J Thorac Oncol. 2011 Jan 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21258249>

INTRODUCTION: In this study, we investigated the effect of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor lovastatin, as a sensitizer of lung cancer cells to ionizing radiation (IR). **METHODS:** A549 lung adenocarcinoma cells were treated with 0 to 50 μ M lovastatin alone or in combination with 0 to 8 Gy IR and subjected to clonogenic survival and proliferation assays. To assess the mechanism of drug action, we examined the effects of lovastatin and IR on the epidermal growth factor (EGF) receptor and AMP-activated kinase (AMPK) pathways and on apoptotic markers and the cell cycle. **RESULTS:** Lovastatin inhibited basal clonogenic survival and proliferation of A549 cells and sensitized them to IR. This was reversed by mevalonate, the product of 3-hydroxy-3-methylglutaryl-CoA reductase. Lovastatin attenuated selectively EGF-induced phosphorylation of EGF receptor and Akt, and IR-induced Akt phosphorylation, in a mevalonate-sensitive fashion, without inhibition on extracellular signal-regulated kinase 1/2 phosphorylation by either stimulus. IR phosphorylated and activated the metabolic sensor and tumor suppressor AMPK, but lovastatin enhanced basal and IR-induced AMPK phosphorylation. The drug inhibited IR-induced expression of p53 and the cyclin-dependent kinase inhibitors p21 and p27, but caused a redistribution of cells from G1-S phase (control and radiated cells) and G2-M phase (radiated cells) of cell cycle into apoptosis. The latter was also evident by induction of nuclear fragmentation and

cleavage of caspase 3 by lovastatin in both control and radiated cells. **CONCLUSIONS:** We suggest that lovastatin inhibits survival and induces radiosensitization of lung cancer cells through induction of apoptosis, which may be mediated by a simultaneous inhibition of the Akt and activation of the AMPK signaling pathways.

Semiquantification and classification of local pulmonary function by V/Q single photon emission computed tomography in patients with non-small cell lung cancer: potential indication for radiotherapy planning. Yuan ST, Frey KA, Gross MD, et al. *J Thorac Oncol.* 2011 Jan;6(1):71-8.

<http://www.ncbi.nlm.nih.gov/pubmed/21119546>

INTRODUCTION: Perfusion (Q) single photon emission computed tomography (SPECT) has been used to divert dose away from higher-functioning lung during radiation therapy (RT) planning. This study aimed to (1) study regional lung function through coregistered pulmonary ventilation/perfusion (V/Q)-SPECT-CT and (2) classify these defects for its potential value in radiation planning in patients with non-small cell lung cancer (NSCLC). **METHODS:** Patients with stages I to III NSCLC requiring radiation-based therapy were eligible for this prospective study. V/Q-SPECT performed within 2 weeks before the start of radiation was interpreted by nuclear medicine physicians and then measured by a semiquantitative score. The potential mechanism of V and Q defects was analyzed; the potential impact of V/Q-SPECT over Q-SPECT alone was completed through classified applications (high-dose RT versus RT avoidance) during planning. **RESULTS:** Images of 51 consecutive patients were analyzed. The V and Q defects were matched, reverse mismatched (V defect > Q defect), and mismatched (Q defect > V defect) in 61, 31, and 8% of patients, respectively. Tumor was the leading cause of the defects of ipsilateral lung in 73% of patients. The defect scores of the ipsilateral lung were greater in patients with central primaries than those with peripheral primaries for both V-SPECT (2.3 ± 1.1 versus 1.5 ± 0.8 , $p = 0.017$) and Q-SPECT (2.2 ± 0.8 versus 1.4 ± 0.6 , $p = 0.000$). The patients with chronic obstructive pulmonary disease had greater defect scores in contralateral lung for both V-SPECT (1.5 ± 0.7 versus 1.0 ± 0.8 , $p = 0.006$) and Q-SPECT (1.4 ± 0.6 versus 1.0 ± 0.4 , $p = 0.010$). On assessing the potential value of SPECT on RT plan, 39% of patients could have their RT plan when applying V/Q-SPECT rather than Q-SPECT alone. **CONCLUSIONS:** V/Q-SPECT provides a more comprehensive functional assessment, may provide additional value over Q-SPECT alone in assessing local pulmonary function, and guide RT plan decisions in patients with NSCLC.

Feasibility of Helical Tomotherapy in Stereotactic Body Radiation Therapy for Centrally Located Early Stage Non-small-cell Lung Cancer or Lung Metastases. Chi A, Jang SY, Welsh JS, Nguyen NP, Ong E, Gobar L, Komaki R. *Int J Radiat Oncol Biol Phys.* 2011 Jan 19. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21255942>

PURPOSE: To investigate the ability of helical tomotherapy (HT) to spare critical organs immediately adjacent to the tumor target in stereotactic body radiation therapy (SBRT) for centrally located lung lesions. **METHODS AND MATERIALS:** HT SBRT plans for 10 patients with centrally located lesions or lesions immediately adjacent to a critical structure were generated. A total of 70 Gy in 10 fractions was prescribed to the planning target volume (PTV) to satisfy a target volume coverage of $\geq 95\%$ PTV receiving 70 Gy and an established set of dose constraints for the organs at risk (OARs). Quality assurance (QA) of the HT plans was performed with both ion chamber and film measurements.

RESULTS: The PTV coverage criteria was met with 95% of the PTV receiving 70.68 ± 0.33 Gy for all cases even though the OARs immediately adjacent to the PTV ranged from 0.38 to 0.85 cm away. The mean lung dose (MLD), and V(20) were 7.15 ± 1.44 Gy, and $11.93 \pm 3.24\%$ for the total lung, respectively. The dose parameters of MLD, V(5), V(10), and V(20) for the contralateral lung were significantly lower than those for the ipsilateral lung ($p < 0.05$). An average dose fall off from the PTV periphery to the edge of the immediately adjacent OAR was 47.6% over an average distance of 4.87 mm.

Comparison of calculated and measured doses with the ion chamber showed an average of 1.85% point dose error, whereas an average mean gamma and the area with a gamma larger than 1 of 0.20 and 0.94% were observed, respectively. **CONCLUSION:** HT allows the sparing of critical structures immediately adjacent to the tumor target, thus making SBRT for these centrally located lesions feasible.

Tumor Regression and Positional Changes in Non-small Cell Lung Cancer During Radical Radiotherapy. Lim G, Bezjak A, Higgins J, et al. J Thorac Oncol. 2011 Jan 20. [Epub ahead of print] Moseley D, Hope AJ, Sun A, Cho JB, Brade AM, Ma C, Bissonnette JP.

<http://www.ncbi.nlm.nih.gov/pubmed/21258244>

INTRODUCTION: We have used respiratory-correlated cone beam computed tomography (rcCBCT) imaging to study the volumetric and positional changes that occur throughout the course of radical radiotherapy in non-small cell lung cancer (NSCLC). **METHODS:** Tumor volumes and centers of mass were recorded and analyzed on weekly serial rcCBCT images of NSCLC patients treated with radical radiotherapy to a dose ≥ 45 Gy with concurrent chemotherapy. **RESULTS:** Sixty patients with locally advanced NSCLC were included; in 31 patients, the primary tumor was peripheral and thus suitable for contouring. There was a mean percent decrease of 40.2% by fraction 15 and 51.1% by treatment completion. Among all 60 patients, 19 patients (32%) had more than 30% regression by fraction 15 and 25 patients (81%) by treatment completion. Statistically significant tumor migration in at least one direction between the first and the last 2 weeks was demonstrated in 14 of 27 patients. Clinically relevant changes (atelectasis and effusions) were noted in 11 of 29 visually assessed patients. **CONCLUSIONS:** Current rcCBCT image quality allows assessment of tumors located more peripherally. Significant tumor regression was documented in the majority of patients. In view of these observations, the suitability of adaptive radiotherapy in radical lung cancer treatment should be further investigated.

Conventional 3D staging PET/CT in CT simulation for lung cancer: impact of rigid and deformable target volume alignments for radiotherapy treatment planning. Hanna GG, Van Sörnsen De Koste JR, et al. Br J Radiol. 2011 Jan 11. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21224293>

BACKGROUND: Positron emission tomography (PET)/CT scans can improve target definition in radiotherapy for non-small cell lung cancer (NSCLC). As staging PET/CT scans are increasingly available, we evaluated different methods for co-registration of staging PET/CT data to radiotherapy simulation (RTP) scans. **METHODS:** 10 patients underwent staging PET/CT followed by RTP PET/CT. On both scans, gross tumour volumes (GTVs) were delineated using CT (GTV(CT)) and PET display settings. Four PET-based contours (manual delineation, two threshold methods and a source-to-background ratio method) were delineated. The CT component of the staging scan was co-registered using both rigid and deformable techniques to the CT component of RTP PET/CT. Subsequently rigid registration and deformation warps were used to transfer PET and CT contours from the staging scan to the RTP scan. Dice's similarity coefficient (DSC) was used to assess the registration accuracy of staging-based GTVs following both registration methods with the GTVs delineated on the RTP PET/CT scan. **RESULTS:** When the GTV(CT) delineated on the staging scan after both rigid registration and deformation was compared with the GTV(CT) on RTP scan, a significant improvement in overlap (registration) using deformation was observed (mean DSC 0.66 for rigid registration and 0.82 for deformable registration, $p=0.008$). A similar comparison for PET contours revealed no significant improvement in overlap with the use of deformable registration. **CONCLUSIONS:** No consistent improvements in similarity measures were observed when deformable registration was used for transferring PET-based contours from a staging PET/CT. This suggests that currently the use of rigid registration remains the most appropriate method for RTP in NSCLC.

Stereotactic body radiation therapy for adrenal metastases: a retrospective review of a noninvasive therapeutic strategy. Torok J, Wegner RE, Burton SA, Heron DE. *Future Oncol.* 2011 Jan;7(1):145-51. <http://www.ncbi.nlm.nih.gov/pubmed/21174545>

AIMS: The role of radiation therapy in the treatment of adrenal metastases has traditionally been a palliative one, achieving excellent pain control with very limited toxicity. Recent studies have focused on the potential role of stereotactic body radiation therapy (SBRT) with curative intent in limited metastatic disease, its potential to reduce tumor burden and to prevent symptomatic progression. This study reports the single-institution outcomes of SBRT utilizing both single fraction and hypofractionated regimens in the treatment of adrenal metastases. **METHODS:** A total of seven patients with nine adrenal metastases treated with SBRT at the University of Pittsburgh Cancer Institute were retrospectively studied. The primary malignancies consisted of non-small-cell lung cancer (n = 4), small-cell lung cancer (n = 1) and hepatocellular carcinoma (n = 2). **RESULTS:** Five lesions were treated in a single fraction to a median prescription dose of 16 Gy (range: 10-22 Gy) to the 80% isodose line. The remaining four lesions were treated over three fractions to a median prescription dose of 27 Gy (range: 24-36 Gy), with a median prescription isodose line of 94% (range: 80-94%). Median follow-up from the primary diagnosis was 38 months (range: 7-88 months) and from SBRT was 14 months (range: 1-60 months). Follow-up imaging for six patients, and eight metastatic lesions, revealed one complete response, two partial responses and five stable lesions. Five of the lesions eventually failed locally, with a median time to failure of 12 months and actuarial local control of 63% at 1 year. The median overall survival was 8 months from SBRT. **CONCLUSION:** SBRT can be safely delivered in single fraction, or hypofractionated, regimens for the treatment of adrenal metastases.

NSCLC - OTHER

Pilot study of 1650-G: a simplified cellular vaccine for lung cancer. Hirschowitz EA, Mullins A, Prajapati D, et al.

<http://www.ncbi.nlm.nih.gov/pubmed/21150468>

INTRODUCTION: Cancer immunotherapy is a conceptually attractive since it is highly specific and can deal with disseminated disease with minimal impact on normal tissues. Early phase clinical trials have well established the ability of a variety of immunotherapeutic approaches to induce antigen specific immune responses in lung cancer patients. Although no immunotherapy is likely to be a panacea, recent data from randomized phase IIB studies offer promise of therapeutic activity in both early and late stage lung cancer. **METHODS:** This report describes early clinical experience with vaccine 1650-G, an allogeneic cellular vaccine using granulocyte macrophage colony stimulating factor as an adjuvant. This nonrandomized pilot study was conducted at four sites in the Commonwealth of Kentucky with primary objective of determining biological activity in a relevant patient population; the use of similar antigen source, immunization schedule, and immunological assessment facilitated comparison to DC vaccines previously tested by our group. **RESULTS:** Data indicates 1650-G is safe and generated a robust and unequivocal immunological response in 6/11 of immunized patients. The relative frequency and kinetics of the response appears similar to that achieved with DC vaccines (1650+autologous DC). The fact that this vaccine could be transported and delivered to cancer patients in community cancer clinics also fulfills an important objective of our research. **CONCLUSIONS:** These findings provide critical foundation for further testing of this simple, and comparatively inexpensive multivalent NSCLC vaccine.

Treatment of the Elderly When Cure is the Goal: The Influence of Age on Treatment Selection and Efficacy for Stage III Non-small Cell Lung Cancer. Coate LE, Massey C, Hope A, et al. *J Thorac Oncol.* 2011 Jan 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21258243>

BACKGROUND: Treatment of elderly patients with stage III NSCLC is controversial. Limited data exist, as the elderly are underrepresented in clinical trials. **METHODS:** After ethics approval, we performed a retrospective review of 1372 stage III NSCLC patients treated at our institution during the period 1997-2007. Patients with malignant effusions and microscopic N2 discovered only postoperatively were excluded, leaving 740 who were classified by treatment plan: palliative (palliative chemotherapy or radiation [≤ 40 Gy]); nonsurgical multimodality (>40 Gy radiation \pm chemotherapy); or surgical multimodality (chemotherapy, radiation, and surgery). Demographics, treatment, toxicity, and survival were analyzed by age, 0 to 65 years, $n = 384$; 66 to 75 years, $n = 256$; 76+ years, $n = 100$, and compared using log-rank, univariate, and multivariate statistical tests. **RESULTS:** Patients older than 65 years were more likely to have poor performance status ($p < 0.0001$), multiple comorbidities ($p < 0.0001$), and to receive palliative therapy only ($p < 0.0001$). Older and younger patients treated with curative intent with nonsurgical bimodality therapy or trimodality therapy including surgery had similar rates of grade 3/4 toxicity (0-65 years, 39%; 66-75 years, 43%; 76+ years, 5%; $p = 0.18$) and toxic death (0-65 years, 4%; 66-75 years, 4%; 76+ years, 0%; $p = 0.76$). Survival was worse with increasing age ($p < 0.0001$), likely due to greater use of palliative treatment in the elderly. When survival was analyzed for patients treated with curative intent, there was no difference between age groups for nonsurgical ($p = 0.32$) or surgical ($p = 0.53$) therapy. **CONCLUSION:** In select fit elderly patients, combined modality therapy is tolerable and is associated with survival similar to that of younger patients.

Radon and Lung Cancer in the American Cancer Society Cohort. Turner MC, Krewski D, Chen Y, Pope CA 3rd, Gapstur SM, Thun MJ. *Cancer Epidemiol Biomarkers Prev.* 2011 Jan 6. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21212062>

BACKGROUND: Case-control studies conducted in North America, Europe, and Asia provided evidence of increased lung cancer risk due to radon in homes. Here, the association between residential radon and lung cancer mortality was examined in a large-scale cohort study. **METHODS:** Nearly 1.2 million Cancer Prevention Study-II participants were recruited in 1982. Mean county-level residential radon concentrations were linked to study participants according to ZIP code information at enrollment (mean (SD) = 53.5 Bq/m³ (38.0)). Cox proportional hazards regression models were used to obtain adjusted hazard ratios and 95% confidence intervals (CI) for lung cancer mortality associated with radon. Potential effect modification by cigarette smoking, ambient sulfate concentrations, and other risk factors was assessed on both the additive and multiplicative scales. **RESULTS:** Through 1988, 3,493 lung cancer deaths were observed among 811,961 participants included in the analysis. A significant positive linear trend was observed between categories of radon concentrations and lung cancer mortality ($p = 0.02$). A 15% (95% CI 1 - 31%) increase in the risk of lung cancer mortality was observed per each 100 Bq/m³ increase in radon. Participants with mean radon concentrations above the EPA guideline value (148 Bq/m³) experienced a 34% (95% CI 7 - 68%) increase in risk for lung cancer mortality relative to those below the guideline value. **CONCLUSIONS:** This large prospective study showed a positive association between an ecological indicator of residential radon and lung cancer. **IMPACT:** These results further support efforts to reduce radon concentrations in homes to the lowest possible level.

SCLC - CHEMOTHERAPY

Addition of Darbepoetin Alfa to Dose-Dense Chemotherapy: Results From a Randomized Phase II Trial in Small-Cell Lung Cancer Patients Receiving Carboplatin Plus Etoposide. Nagel S, Kellner O, Engel-Riedel W, et al. *Clin Lung Cancer.* 2011 Jan 1;12(1):62-69.

<http://www.ncbi.nlm.nih.gov/pubmed/21273182>

Darbepoetin alfa, an erythropoiesis-stimulating agent (ESA), is used in cancer patients as a supportive care for anemia. For small-cell lung cancer (SCLC), several studies have shown that the administration of ESAs does not affect survival but decreases the need for blood transfusions and improves the quality of life (QOL) of patients receiving chemotherapy. The present randomized phase II study assessed the feasibility, efficacy, and safety of the administration of darbepoetin alfa to patients with SCLC receiving dose-dense (every 2 weeks) standard chemotherapy consisting of carboplatin plus etoposide, pegfilgrastim prophylactically. Seventy-four chemotherapy-naïve patients with limited or extensive SCLC received combination chemotherapy for 6 cycles, and half of the patients additionally received darbepoetin to achieve a target hemoglobin concentration of 12-13 g/dL. The primary study outcome, progression-free survival, showed no difference between the 2 arms of the study. Among the secondary endpoints, objective response was similar in the presence and absence of darbepoetin (best response rates = 75.0% vs. 77.8%). Likewise, 1-year survival rates were not different between the 2 treatment arms (40.1% vs. 45.9%). There were no significant differences in grade 3/4 toxicities. As expected, the need for blood transfusions differed significantly: 19.4% of patients in the darbepoetin arm received transfusions versus 38.9% in the control arm. Analysis of European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) scales at different time points showed that the darbepoetin group's QOL was significantly better for certain readouts and never significantly worse than that of the control group. Thus, the combination of darbepoetin alfa with dose-dense carboplatin plus etoposide was feasible and well tolerated. Addition of darbepoetin alfa to chemotherapy lowered the need for blood transfusions and did not affect measures of survival and objective response.

A German multicenter, randomized phase III trial comparing irinotecan-carboplatin with etoposide-carboplatin as first-line therapy for extensive-disease small-cell lung cancer.

Schmittel A, Sebastian M, Fischer von Weikersthal L, et al. *Ann Oncol*. 2011 Jan 25. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21266516>

BACKGROUND: This trial was designed to prove superiority of irinotecan over etoposide combined with carboplatin in extensive-disease small-cell lung cancer. **PATIENTS AND METHODS:** Patients were randomly assigned to receive carboplatin area under the curve 5 mg •min/ml either in combination with irinotecan 50 mg/m² on days 1, 8, and 15 (IP) or etoposide 140 mg/m² on days 1-3 (EP). Primary end point was progression-free survival (PFS) at 6 months. Secondary end points were overall survival (OS), response rate, and toxicity. **RESULTS:** Of 226 patients, 216 were eligible. Median PFS was 6.0 months [95% confidence interval (CI) 5.0-7.0] in the IP arm and 6.0 months (95% CI 5.2-6.8) in EP arm (P = 0.07). Median survival was 10.0 months (95% CI 8.4-11.6) and 9.0 months (95% CI 7.6-10.4) in the IP and EP arm (P = 0.06), respectively. Hazard ratios for disease progression and OS were 1.29 (95% CI 0.96-1.73, P = 0.095) and 1.34 (95% CI 0.97-1.85, P = 0.072), respectively. No difference in response rates was observed. Grade 3 and 4 hematologic toxicity favored the IP arm, whereas diarrhea was significantly more frequent in the IP arm. **CONCLUSION:** This trial failed to show superiority of irinotecan over etoposide in combination with carboplatin.

A Role for IGF-1R-Targeted Therapies in Small-Cell Lung Cancer? Gately K, Collins I, Forde L, et al. *Clin Lung Cancer*. 2011 Jan 1;12(1):38-42.

<http://www.ncbi.nlm.nih.gov/pubmed/21273178>

BACKGROUND: Small-cell lung cancer (SCLC) is an aggressive disease with a poor prognosis. The insulin-like growth factor-1 receptor (IGF-1R) is an autocrine growth factor and an attractive therapeutic target in many solid tumors, but particularly in lung cancer. **PATIENTS AND METHODS:** This study examined tumor samples from 23 patients diagnosed with SCLC, 11 resected specimens and 12 nodal biopsies obtained by mediastinoscopy, for expression of IGF-1R using the monoclonal rabbit anti-IGF-1R

(clone G11, Ventana Medical Systems, Tucson, AZ) and standard immunohistochemistry (IHC).

RESULTS: All 23 tumor samples expressed IGF-1R with a range of stain intensity from weak (1+) to strong (3+). Ten tumors had a score of 3+, 7 tumors 2+, and 6 tumors 1+. Patient survival data were available for all 23 patients. Two patients died < 30 days post biopsy, therefore, the intensity of anti-IGF-1R immunostaining for 21 patients was correlated to survival. Patients with 3+ immunostaining had a poorer prognosis ($P = .003$). The overall survival of patients who underwent surgical resection was significantly better (median survival not reached) than patients who were not resected (median survival, 7.4 months) ($P = .006$). **CONCLUSION:** IGF-1R targeted therapies may have a role in the treatment of SCLC in combination with chemotherapy or as maintenance therapy. Further studies on the clinical benefit of targeting IGF-1R in SCLC are needed.

SCLC - OTHER

Clinical Outcome of Small Cell Lung Cancer with Pericardial Effusion but without Distant Metastasis. Niho S, Kubota K, Yoh K, et al. *J Thorac Oncol.* 2011 Jan 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21258253>

BACKGROUND: Pericardial effusion is defined as M1a in the Union Internationale Contre le Cancer seventh tumor, node, metastasis edition for lung cancer. The clinical course of small cell lung cancer (SCLC) with pericardial effusion but without distant metastasis (M1a) has not been adequately investigated. **METHODS:** The medical records of patients with SCLC treated at the National Cancer Center Hospital East between July 1992 and December 2007 were reviewed. During this period, 766 patients were newly diagnosed as having SCLC. Thirty-three of the 416 patients with limited disease (LD) SCLC (8%) had pericardial effusion. Seventy-nine patients with LD-SCLC (19%) had ipsilateral pleural effusion or dissemination. Of these, 16 patients had both pericardial and ipsilateral pleural effusion. We divided the 96 M1a patients into two subgroups: group A ($n = 33$) included patients with pericardial effusion, and group B ($n = 63$) included patients with ipsilateral pleural effusion or disseminated pleural nodules but without pericardial effusion. **RESULTS:** The median survival time among the patients with LD-M1a was 13.4 months (95% confidence interval: 10.7-16.6 months), and the 1-, 2-, 3-, and 5-year survival rates were 56%, 18%, 9%, and 8%, respectively. The survival of the patients with LD-M1a was intermediate between those of the patients with LD-M0 and patients with extensive disease M1b ($p < 0.0001$). The overall survival period was not statistically different between groups A and B ($p = 0.5182$). Nineteen patients in group A received chemoradiotherapy, but only two patients survived for more than 2 years (2- and 5-year survival rate: 11% both). Twenty-six patients in group B received chemoradiotherapy, and four patients survived for more than 5 years (5-year survival rate: 18%). **CONCLUSIONS:** Long-term survival was achieved among patients with SCLC with pericardial effusion but without distant metastasis who successfully underwent chemoradiotherapy, although 5-year survival rate in these patients was relatively lower than in patients with SCLC with ipsilateral pleural effusion but without pericardial effusion or distant metastasis.

Polymorphisms in the apoptotic pathway gene BCL-2 and survival in small cell lung cancer.

Knoefel LF, Werle-Schneider G, Dally H, et al. *J Thorac Oncol.* 2011 Jan;6(1):183-9.

<http://www.ncbi.nlm.nih.gov/pubmed/21107291>

INTRODUCTION: We investigated the single-nucleotide polymorphism C-938A in the apoptotic gene BCL-2 to assess the potential impact as a genetic marker for response to chemotherapy and outcome prediction in small cell lung cancer (SCLC) patients. Such a marker might help optimize lung cancer treatment in a tailored approach. **METHODS:** DNA derived from peripheral blood lymphocytes of 188 Caucasian SCLC patients treated at the Thoraxklinik Heidelberg was genotyped. Chemotherapy response, time to progression (TTP), and overall survival (OS) were evaluated using multivariable regression

(unconditional logistic for response and Cox proportional hazard for TTP and OS) with odds ratios and hazard ratios (HRs) and their 95% confidence intervals (CIs) as quantitative outcome measures, respectively. **RESULTS:** Small cell lung cancer patients carrying the BCL-2 -938CC genotype showed significantly worse TTP than patients carrying the BCL-2 -938AA genotype (HR = 1.86; 95% CI = 1.10-3.13, p = 0.021). The same adverse effect was shown for OS (HR = 2.38; 95% CI = 1.38-4.12, p = 0.002). Also, patients with limited disease (HR = 2.57; 95% CI = 1.18-5.60, p = 0.017) showed worse OS with the BCL-2 -938CC genotype. **CONCLUSION:** BCL-2 -938CC genotype shows significantly worse outcome in small cell lung cancer patients. This genetic marker might particularly impact on treatment strategies using BCL-2 antisense approaches.

PALLIATIVE AND SUPPORTIVE CARE

Quality of life, geriatric assessment and survival in elderly patients with non-small-cell lung cancer treated with carboplatin-gemcitabine or carboplatin-paclitaxel: NVALT-3 a phase III study.

Biesma B, Wymenga AN, Vincent A, et al. Ann Oncol. 2011 Jan 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21252061>

BACKGROUND: Elderly patients with advanced non-small-cell lung cancer (NSCLC) may derive similar benefit from platinum-based chemotherapy as younger patients. Quality of life (QoL) and comprehensive geriatric assessment (CGA) is often advocated to assess benefits and risks. **PATIENTS AND METHODS:** A total of 181 chemotherapy-naïve patients [≥ 70 years, performance score (PS) of 0-2] with stage III-IV NSCLC received carboplatin and gemcitabine (CG) (n = 90) or carboplatin and paclitaxel (CP) (n = 91) every 3 weeks for up to four cycles. Primary end point was change in global QoL from baseline compared with week 18. Pretreatment CGA and mini geriatric assessment during and after treatment were undertaken. A principal component (PC) analysis was carried out to determine the underlying dimensions of CGA and QoL and subsequently related to survival. **RESULTS:** There were no changes in QoL after treatment. The number of QoL responders (CG arm, 12%; CP arm, 5%) was not significantly different. CGA items were only associated with neuropsychiatric toxicity. Quality-adjusted survival was not different between treatment arms. The PC analysis derived from nine CGA, six QoL and one PS score indicated only one dominant dimension. This dimension was strongly prognostic, and physical and role functioning, Groningen Frailty Indicator and Geriatric Depression Scale were its largest contributors. **CONCLUSIONS:** Paclitaxel or gemcitabine added to carboplatin did not have a differential effect on global QoL. CGA was associated with toxic effects in a very limited manner. CGA and QoL items measure one underlying dimension, which is highly prognostic.

Improving chemotherapy for patients with advanced non-small cell lung cancer. von Plessen C. Clin Respir J. 2011 Jan;5(1):60-1. doi: 10.1111/j.1752-699X.2010.00199.x.

<http://www.ncbi.nlm.nih.gov/pubmed/21159143>

INTRODUCTION: Lung cancer is the third most common mortal disease in industrialised countries and the prognosis has been slow to improve. The largest subgroup has locally advanced or metastatic non-small cell lung cancer (NSCLC). Unfortunately, these patients can usually not be cured and the main treatment option is palliative chemotherapy. Given the palliative intention of the chemotherapy, it is clinically highly relevant to establish the optimal treatment duration. While chemotherapy prolongs survival and improves quality of life (QoL), it also has side effects and only a minority of patients achieve an objective treatment response. Clinicians need guidance on treatment duration from controlled trials to balance these aspects. Improvements of the conditions under which chemotherapy is given can increase patient and staff satisfaction and increase system performance. This is especially relevant to incurable patients who spend a lot of their limited time at oncology outpatient clinics. Staffing, infrastructure and organisation of these units are often suboptimal to serve patients with palliative needs and reports of

improvement projects can inspire and guide clinicians in improving their microsystems of care. Clinicians, health care administrators and the public need knowledge about the outcomes of palliative chemotherapy in unselected patient populations. The efficacy of palliative chemotherapy for advanced NSCLC has been amply documented in controlled clinical trials. Meanwhile, the elderly and patients with higher performance status have usually been under-represented in these trials and population studies of the effectiveness of chemotherapy are needed. **OBJECTIVES:** (i) To establish the optimal duration of platinum-based first line chemotherapy for advanced NSCLC; (ii) To improve the care processes at an oncology outpatient clinical microsystem; (iii) To describe the use of chemotherapy in a national population and investigate associations between chemotherapy use and survival; and (iv) To explore approaches to improve the system of chemotherapy from the macro perspective of a whole country. **MATERIALS AND METHODS:** The thesis combines methods from different knowledge domains. In a randomised trial, we compared three with six courses of platinum-based chemotherapy for advanced NSCLC. In a quality improvement study, we used logistic improvement tools, qualitative and quantitative patient and staff satisfaction measurements. Finally using data from the Norwegian cancer and chemotherapy registries, we investigated temporary and geographical variations of chemotherapy use and correlations with the survival of patients with advanced NSCLC. Methods and findings from the three studies were explored to inform a national improvement strategy for the chemotherapy of advanced NSCLC. **RESULTS:** Survival and QoL were equal with three or six courses of chemotherapy for advanced NSCLC. Systematic process changes at the outpatient clinic led to increased patient and staff satisfaction. Furthermore, the study illustrates the application of established process improvement and evaluation tools in a clinical microsystem. In the registry study, we found delays of the introduction of palliative chemotherapy in Norway and significant associations between the use of chemotherapy and the survival of patients with advanced NSCLC. The general section of the thesis describes approaches to system-wide improvements and introduces a quality improvement matrix. **CONCLUSION:** We conclude from our randomised trial and related research that chemotherapy beyond three courses is not beneficial for patients with advanced NSCLC. The report from the oncology outpatient clinic illustrates the value of the clinical microsystem approach for quality improvement at the front line of care. Patient feedback through a focus group, simple methods of assessing and simplifying processes of care, as well as measuring results over time were effective tools in our project. The description of the experiences can serve as an example for the improvement of microsystems in settings with similar problems. Finally, in the registry study of Norwegian patients with lung cancer, we found significant geographical and temporal variations of the utilisation of chemotherapy that were related to survival. Potential areas of improvement in the system of care for lung cancer are recruitment of patients in clinical studies, standardisation of the processes of care in outpatient clinics, definition of strategic aims of quality, development of balanced quality indicators, as well as measuring and reporting of outcomes by means of a quality registry.

Determinants of quality of life in patients near the end of life: a longitudinal perspective. Hermann CP, Looney SW. *Oncol Nurs Forum*. 2011 Jan 1;38(1):23-31.

<http://www.ncbi.nlm.nih.gov/pubmed/21186157>

PURPOSE/OBJECTIVES: to describe the quality of life (QOL) of patients near the end of life and to identify determinants of their QOL. **DESIGN:** descriptive, longitudinal. **SETTING:** university-affiliated cancer center, two private oncologists' offices, and patients' homes. **SAMPLE:** 80 patients with either stage IIIb or IV lung cancer newly diagnosed in the previous month or recurrent lung cancer with distant disease. **METHODS:** patients were interviewed for responses to instruments to assess demographic, physical, psychosocial, and spiritual characteristics. Baseline data were collected at the patients' places of oncology care. Home visits were made for the two-month and four-month data collection points.

MAIN RESEARCH VARIABLES: QOL; symptom frequency, severity, and distress; functional status; anxiety; depression. **FINDINGS:** fifty percent of patients died within five months of their lung cancer diagnosis. Patients reported a relatively high QOL that did not change significantly as they approached the end of life. Symptom distress was the strongest determinant of QOL, followed by symptom severity, symptom frequency, and depression. **CONCLUSIONS:** QOL was most affected by symptoms experienced in patients with advanced lung cancer, particularly distress associated with symptoms. Interventions for symptom management must be implemented at diagnosis because patients in this population may approach the end of life quickly. **IMPLICATIONS FOR NURSING:** a routine and thorough symptom assessment is imperative for patients with advanced lung cancer. Attention to symptom distress is important because of its effect on QOL.

Exercise capacity, lung function, and quality of life after interventional bronchoscopy. Oviatt PL, Stather DR, Michaud G, Maceachern P, Tremblay A. *J Thorac Oncol.* 2011 Jan;6(1):38-42.

<http://www.ncbi.nlm.nih.gov/pubmed/21150471>

INTRODUCTION: Malignant airway obstruction accounts for significant morbidity and mortality in patients with lung and metastatic cancer. We prospectively assessed the effects of bronchoscopic interventions for the treatment of malignant airway obstruction, with specific attention to exercise capacity and quality of life (QoL). **METHODS:** This is a prospective cohort study. Patients with high-grade, symptomatic central malignant airway obstruction were assessed at baseline and then at days 30, 90, and 180 after bronchoscopic intervention with spirometry, 6-minute walk test (6MWT), and QoL and dyspnea questionnaires (European Organization for Research and Treatment of Cancer Quality of Life [C30] and Lung Cancer [LC-13] modules). **RESULTS:** Thirty-seven patients were included in the final statistical analysis. Increases in 6MWT distance by 99.7 m (95% CI 33.2-166.2 m, $p = 0.002$), FEV1 by 448 ml (95% CI 203-692 ml, $p < 0.001$), and FVC by 416 ml (95% CI 130-702 ml, $p = 0.003$) were seen at day 30 compared with baseline. Clinically and statistically significant improvements were noted in composite dyspnea scores at day 30 by both QoL C30 (decrease of 39.9, 95% CI 21.4-58.4, $p < 0.001$) and LC-13 (decrease of 28.2, 95% CI 12.9-43.5, $p < 0.001$) questionnaires. **CONCLUSIONS:** Bronchoscopic intervention for malignant airway obstruction is associated with improvement in 6MWT, spirometry, and dyspnea at 30 days.

Objective burden, resources, and other stressors among informal cancer caregivers: a hidden quality issue? van Ryn M, Sanders S, Kahn K, et al. *Psychooncology.* 2011 Jan;20(1):44-52.

<http://www.ncbi.nlm.nih.gov/pubmed/20201115>

A great deal of clinical cancer care is delivered in the home by informal caregivers (e.g. family, friends), who are often untrained. Caregivers' context varies widely, with many providing care despite low levels of resources and high levels of additional demands.

BACKGROUND: Changes in health care have shifted much cancer care to the home, with limited data to inform this transition. We studied the characteristics, care tasks, and needs of informal caregivers of cancer patients. **METHODS:** Caregivers of seven geographically and institutionally defined cohorts of newly diagnosed colorectal and lung cancer patients completed self-administered questionnaires ($n = 677$). We combined this information with patient survey and chart abstraction data and focused on caregivers who reported providing, unpaid, at least 50% of the patient's informal cancer care. **RESULTS:** Over half of caregivers (55%) cared for a patient with metastatic disease, severe comorbidity, or undergoing current treatment. Besides assisting with activities of daily living, caregivers provided cancer-specific care such as watching for treatment side effects (68%), helping manage pain, nausea or fatigue (47%), administering medicine (34%), deciding whether to call a doctor (30%), deciding whether medicine was needed (29%), and changing bandages (19%). However, half of caregivers reported not getting training perceived as necessary. In addition, 49% of caregivers worked for pay, 21% reported poor

or fair health, and 21% provided unpaid care for other individuals. One in four reported low confidence in the quality of the care they provided. **CONCLUSIONS:** Much assistance for cancer patients is delivered in the home by informal caregivers, often without desired training, with a significant minority having limited resources and high additional demands. Future research should explore the potentially high yield of addressing caregiver needs in improving quality of cancer care and both survivors' and caregivers' outcomes.

Fatigue and Functional Impairment in Early Stage Non-Small Cell Lung Cancer Survivors.

Hung R, Krebs P, Coups EJ, Feinstein MB, Park BJ, Burkhalter J, Ostroff JS. *J Pain Symptom Manage.* 2011 Jan 7. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21216563>

CONTEXT: Fatigue is the most common sequela among non-small cell lung cancer (NSCLC) survivors one to six years posttreatment and is associated with functional limitations. **OBJECTIVES:** This study examined the prevalence, severity, and correlates of fatigue among early stage NSCLC survivors.

METHODS: Three-hundred fifty individuals diagnosed and surgically treated for Stage IA or IB NSCLC completed a survey that included the Brief Fatigue Inventory (BFI) to assess the prevalence and severity of fatigue. The Karnofsky Self-Reported Performance Rating scale (SR-KPS) was used as a measure of functional status and was compared with the severity of fatigue through Chi-squared analyses.

demographic, psychological, and medical correlates of fatigue were examined using logistic regression.

RESULTS: The prevalence of fatigue was 57%. Forty-one percent (n=142) of participants had mild fatigue and 16.8% (n=59) had moderate or severe fatigue (BFI \geq 4). Among the individuals reporting moderate or severe fatigue, 23.7% (n=14) had significant functional impairment (SR-KPS \leq 70%) compared with 2.8% (n=8) with mild or no fatigue (χ^2 =58.1, P<0.001). In the multivariate analysis, NSCLC survivors with pulmonary disease (odds ratio [OR]=2.28), depressive symptoms (OR=6.99), and anxiety symptoms (OR=2.31) were more likely to report experiencing clinically significant fatigue, whereas those who met physical activity guidelines (OR=0.29) reported less fatigue. **CONCLUSION:** Fatigue is highly prevalent among NSCLC survivors and associated with more functional impairment. A comprehensive approach to the treatment of fatigue includes the screening and management of anxious and depressive symptoms, and pulmonary disorders such as chronic obstructive pulmonary disease.

Effectiveness of a Clinical Intervention to Eliminate Barriers to Pain and Fatigue Management in Oncology.

Borneman T, Koczywas M, Sun V, et al. *J Palliat Med.* 2011 Jan 27. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21271872>

ABSTRACT BACKGROUND: Pain and fatigue are recognized as critical symptoms that impact quality of life (QOL) in cancer, particularly in palliative care settings. Barriers to pain and fatigue relief have been classified into three categories: patient, professional, and system barriers. The overall objective of this study was to test the effects of a clinical intervention on reducing barriers to pain and fatigue management in oncology. **METHODS:** This longitudinal, three-group, quasi-experimental study was conducted in three phases: phase 1 (usual care), phase 2 (intervention), and phase 3 (dissemination). A sample of 280 patients with breast, lung, colon, or prostate cancers, stage III and IV disease (80%), and a pain and/or fatigue of 4 or more (moderate to severe) were recruited. The intervention group received four educational sessions on pain/fatigue assessment and management, whereas the control group received usual care. Pain and fatigue barriers and patient knowledge were measured at baseline, 1 month, and 3 months post-accrual for all phases. A 3 \times 2 repeated measures statistical design was utilized to derive a priori tests of immediate effects (baseline to 1 month) and sustained effects (baseline or 1 month to 3 months) for each major outcome variable, subscale, and/or scale score. **RESULTS:** There were significant immediate and sustained effects of the intervention on pain and fatigue barriers as well as knowledge. Measurable improvements in QOL were found in physical and psychological well-being only.

CONCLUSION: A clinical intervention was effective in reducing patient barriers to pain and fatigue management, increasing patient knowledge regarding pain and fatigue, and is feasible and acceptable to patients.

COMPLEMENTARY & ALTERNATIVE THERAPY

Dietary administration of berberine or Phellodendron amurense extract inhibits cell cycle progression and lung tumorigenesis. James MA, Fu H, Liu Y, Chen DR, You M. *Mol Carcinog.* 2011 Jan;50(1):1-7.

<http://www.ncbi.nlm.nih.gov/pubmed/21061266>

Phellodendron amurense extract is a Chinese herbal remedy that has recently been studied for its antitumor, antimicrobial and other biological activities. It is previously unknown if these agents are bioavailable and effective against tumors when delivered as a dietary component. It is also unknown if the anti-tumorigenic properties of berberine, an isoquinoline alkaloid component of *P. amurense*, is equally effective when administered alone. There are contrasting reports on the cellular processes involved in anti-tumorigenesis by *P. amurense* and berberine. Here we find that berberine, when administered orally through the diet, inhibits *in vivo* tumorigenesis of both p53 expressing and p53 null lung tumor xenografts equally whether administered in its pure form or as a part of *P. amurense* extract. We also show that berberine induces G1 cell cycle arrest, inhibits proliferative kinase signaling and arrests the growth of lung tumor cells in culture. Berberine administered in the diet was detectable by HPLC in the lungs of mice fed *P. amurense* or equivalent doses of berberine at concentrations of 455 and 518 ng/ml respectively and inhibited the growth of xenografted A549 cell tumors, which grew to 9.4 and 6.4 mm³ respectively, compared to 58.9 mm³ in control mice ($P < 0.001$). Phosphorylation of Akt, CREB and MAPK was inhibited in A549 cells by *P. amurense*. Demonstration of oral bioavailability and anti-tumorigenic efficacy of dietary berberine, as well as further demonstration of signaling pathway modulation and cell-cycle arrest, implicate this relatively safe, natural compound as a potentially important therapeutic and chemopreventive agent for lung cancer.

Effects of Fraction Obtained From Korean Corni Fructus Extracts Causing Anti-Proliferation and p53-Dependent Apoptosis in A549 Lung Cancer Cells. Choi WH, Chu JP, Jiang MH, Baek SH, Park HD. *Nutr Cancer.* 2011 Jan;63(1):121-9.

Department of Medical Zoology, Kyung Hee University School of Medicine, Seoul, Republic of Korea.

<http://www.ncbi.nlm.nih.gov/pubmed/21132604>

Corni Fructus has traditionally been used as herbal medicine for the treatment of tuberculosis, asthma, hepatitis, and chronic nephritis in Korea, Japan, and China. This research was carried out to evaluate the proliferative-inhibitory effect of CF extracts against cancer cells and to identify the new pro-substance from medicinal plants. Among these herbal extracts extracted from KCF (Korean Corni Fructus), JCF (Japanese Corni Fructus) and CCF (Chinese Corni Fructus), KCF extracts strongly induced anti-proliferation of cancer cells in a dose-dependent manner compared with other extracts. Moreover, after treatment with CM/F3 (fraction 3 obtained from KCF extracts) for 24 h, A549 cells were evaluated by several indicators such as cell viability, LDH release, DNA fragmentation, nuclear condensation, and apoptotic proteins *in vitro*. CM/F3 showed the tumor-selective growth inhibitory activity in a dose- and time-dependent manner in A549 cells. Consistently, CM/F3 effectively induced the activation of bax, cytochrome-c, caspase-3, -8, -9, p53, and p21 causing apoptosis, and caused the suppression of Cdk2, pRb, and E2F1 related to cell arrest in A549 cells. These results demonstrate that CM/F3 caused not only anti-proliferation but also cell death involving cell arrest through interaction between apoptotic proteins and the upregulation of p53 in A549 cells.

Spontaneous Smoking Cessation Before Lung Cancer Diagnosis. Campling BG, Collins BN, Algazy KM, Schnoll RA, Lam M. *J Thorac Oncol.* 2011 Jan 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21258255>

INTRODUCTION: We have observed that many patients with lung cancer stop smoking before diagnosis, usually before clinical symptoms, and often without difficulty. This led us to speculate that spontaneous smoking cessation may be a presenting symptom of lung cancer. **METHODS:** Patients from the Philadelphia Veterans Affairs Medical Center with lung cancer and for comparison, prostate cancer and myocardial infarction underwent a structured interview about their smoking habits preceding diagnosis. Severity of nicotine addiction was graded using the Fagerström Test for Nicotine Dependence. Among former smokers, dates of cessation, onset of symptoms, and diagnosis were recorded. Difficulty quitting was rated on a scale of 0 to 10. Distributions of intervals from cessation to diagnosis were compared between groups. **RESULTS:** All 115 patients with lung cancer had been smokers. Fifty-five (48%) quit before diagnosis, and only six of these (11%) were symptomatic at quitting. Patients with lung cancer who quit were as dependent on nicotine, when smoking the most, as those who continued to smoke, unlike the other groups. Despite this, 31% quit with no difficulty. The median interval from cessation to diagnosis was 2.7 years for lung cancer, 24.3 years for prostate cancer, and 10.0 years for patients with myocardial infarction. **CONCLUSIONS:** These results challenge the notion that patients with lung cancer usually quit smoking because of disease symptoms. The hypothesis that spontaneous smoking cessation may be a presenting symptom of lung cancer warrants further investigation.

Barriers to enrollment in non-small cell lung cancer therapeutic clinical trials. Bagstrom MQ, Waqar SN, Sezhiyan AK, Gilstrap E, Gao F, Morgensztern D, Govindan R. *J Thorac Oncol.* 2011 Jan;6(1):98-102.

<http://www.ncbi.nlm.nih.gov/pubmed/21150469>

INTRODUCTION: Despite recent advances in treatment, lung cancer remains the leading cause of cancer-related mortality in the United States. Therefore, there is a strong need for developing clinical trials in lung cancer therapeutics. Only a small fraction of patients with lung cancer are enrolled in clinical trials. It is critical to understand the barriers to participation in lung cancer clinical trials. **METHODS:** We reviewed the outpatient charts of consecutive patients with non-small cell lung cancer who presented for initial evaluation or consultation for further therapeutic management to the thoracic medical oncology group at the Alvin J. Siteman Cancer Center between January 1, 2006, and December 31, 2006. Available and appropriate clinical trials specific to the histologic subtype and stage were presented to the patients routinely, and reasons for nonenrollment were documented. We collected information on age, gender, ethnicity, histology, stage, performance status (PS), and insurance status. **RESULTS:** During the study period, 263 patients with non-small cell lung cancer were identified for the study. After initial screening, 183 patients had clinical trials available, which were appropriate for their diagnosis and stage of disease. One hundred one patients (55.2%) were ineligible for enrollment in a clinical trial. The most common reasons for ineligibility were poor PS (18%), need for emergent radiation (12%), lack of adequate staging information (6%), and comorbid conditions (4.9%). Despite being eligible for participation, 57 patients (31.1%) did not enroll in a clinical trial. Patient refusal accounted for 8.7%. The problems with transportation and distance from the medical center were reasons given for nonparticipation by 7.1%. Eleven patients (6%) did not participate in a clinical trial because of insurance issues. Ultimately, 25 patients (13.7%) were enrolled in a clinical trial. **CONCLUSIONS:** Poor PS, the need for emergent radiation, and patient refusal were the most common reasons for not participating in a clinical trial.

Pilot study of 1650-G: a simplified cellular vaccine for lung cancer. Hirschowitz EA, Mullins A, Prajapati D, et al. *J Thorac Oncol.* 2011 Jan;6(1):169-73.

<http://www.ncbi.nlm.nih.gov/pubmed/21150468>

INTRODUCTION: Cancer immunotherapy is a conceptually attractive since it is highly specific and can deal with disseminated disease with minimal impact on normal tissues. Early phase clinical trials have well established the ability of a variety of immunotherapeutic approaches to induce antigen specific immune responses in lung cancer patients. Although no immunotherapy is likely to be a panacea, recent data from randomized phase IIB studies offer promise of therapeutic activity in both early and late stage lung cancer. **METHODS:** This report describes early clinical experience with vaccine 1650-G, an allogeneic cellular vaccine using granulocyte macrophage colony stimulating factor as an adjuvant. This nonrandomized pilot study was conducted at four sites in the Commonwealth of Kentucky with primary objective of determining biological activity in a relevant patient population; the use of similar antigen source, immunization schedule, and immunological assessment facilitated comparison to DC vaccines previously tested by our group. **RESULTS:** Data indicates 1650-G is safe and generated a robust and unequivocal immunological response in 6/11 of immunized patients. The relative frequency and kinetics of the response appears similar to that achieved with DC vaccines (1650+autologous DC). The fact that this vaccine could be transported and delivered to cancer patients in community cancer clinics also fulfills an important objective of our research. **CONCLUSIONS:** These findings provide critical foundation for further testing of this simple, and comparatively inexpensive multivalent NSCLC vaccine.

Physical activity and lung cancer survivorship. Jones LW. *Recent Results Cancer Res.* 2011;186:255-74.

<http://www.ncbi.nlm.nih.gov/pubmed/21113768>

A lung cancer diagnosis and associated therapeutic management is associated with unique and varying degrees of adverse physical/functional impairments that dramatically reduce a patient's ability to tolerate exercise. Poor exercise tolerance predisposes to increased susceptibility to other common age-related diseases, poor quality of life (QOL), and likely premature death. Here we review the putative literature investigating the role of exercise as an adjunct therapy across the lung cancer continuum (i.e., diagnosis to palliation). The current evidence suggests that exercise training is a safe and feasible adjunct therapy for operable lung cancer patients both before and after pulmonary resection. Among patients with inoperable disease, feasibility and safety studies of carefully prescribed exercise training are warranted. Preliminary evidence in this area supports that exercise therapy may be an important consideration in multidisciplinary management of patients diagnosed with lung cancer.

Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. Oberg M, Jaakkola MS, Woodward A, Peruga A, Prüss-Ustün A. *Lancet.* 2011 Jan 8;377(9760):139-46.

<http://www.ncbi.nlm.nih.gov/pubmed/21112082>

BACKGROUND: Exposure to second-hand smoke is common in many countries but the magnitude of the problem worldwide is poorly described. We aimed to estimate the worldwide exposure to second-hand smoke and its burden of disease in children and adult non-smokers in 2004. **METHODS:** The burden of disease from second-hand smoke was estimated as deaths and disability-adjusted life-years (DALYs) for children and adult non-smokers. The calculations were based on disease-specific relative risk estimates and area-specific estimates of the proportion of people exposed to second-hand smoke, by comparative risk assessment methods, with data from 192 countries during 2004. **FINDINGS:** Worldwide, 40% of children, 33% of male non-smokers, and 35% of female non-smokers were exposed to second-hand smoke in 2004. This exposure was estimated to have caused 379,000 deaths from ischaemic heart disease, 165,000 from lower respiratory infections, 36,900 from asthma, and 21,400 from lung cancer. 603,000

deaths were attributable to second-hand smoke in 2004, which was about 1•0% of worldwide mortality. 47% of deaths from second-hand smoke occurred in women, 28% in children, and 26% in men. DALYs lost because of exposure to second-hand smoke amounted to 10•9 million, which was about 0•7% of total worldwide burden of diseases in DALYs in 2004. 61% of DALYs were in children. The largest disease burdens were from lower respiratory infections in children younger than 5 years (5,939,000), ischaemic heart disease in adults (2,836,000), and asthma in adults (1,246,000) and children (651,000). **INTER-
PRETATION:** These estimates of worldwide burden of disease attributable to second-hand smoke suggest that substantial health gains could be made by extending effective public health and clinical interventions to reduce passive smoking worldwide.

Measuring stigma in people with lung cancer: psychometric testing of the Cataldo lung cancer stigma scale. Cataldo JK, Slaughter R, Jahan TM, Pongquan VL, Hwang WJ. *Oncol Nurs Forum.* 2011 Jan 1;38(1):E46-54.

<http://www.ncbi.nlm.nih.gov/pubmed/21186151>

PURPOSE/OBJECTIVES: to develop an instrument to measure the stigma perceived by people with lung cancer based on the HIV Stigma Scale. **DESIGN:** psychometric analysis. **SETTING:** online survey. Sample: 186 patients with lung cancer. **METHODS:** an exploratory factor analysis with a common factor model using alpha factor extraction. **MAIN RESEARCH VARIABLES:** lung cancer stigma, depression, and quality of life. **FINDINGS:** four factors emerged: stigma and shame, social isolation, discrimination, and smoking. Inspection of unrotated first-factor loadings showed support for a general stigma factor. Construct validity was supported by relationships with related constructs: self-esteem, depression, social support, and social conflict. Coefficient alphas ranging from 0.75-0.97 for the subscales (0.96 for stigma and shame, 0.97 for social isolation, 0.9 for discrimination, and 0.75 for smoking) and 0.98 for the 43-item Cataldo Lung Cancer Stigma Scale (CLCSS) provided evidence of reliability. The final version of the CLCSS was 31 items. Coefficient alpha was recalculated for the total stigma scale (0.96) and the four subscales (0.97 for stigma and shame, 0.96 for social isolation, 0.92 for discrimination, and 0.75 for smoking). **CONCLUSIONS:** the CLCSS is a reliable and valid measure of health-related stigma in this sample of people with lung cancer. **IMPLICATIONS FOR NURSING:** the CLCSS can be used to identify the presence and impact of lung cancer stigma and allow for the development of effective stigma interventions for patients with lung cancer.