Fall *2008 | NO 35*

National Jewish Health™
Science Transforming Life®

Lung Cancer FRONTIERS

The Forum for Early Diagnosis and Treatment of Lung Cancer

Ali I. Musani, MD

The purpose of ***Lung Cancer Frontiers*** is to acquire and disseminate new knowledge about lung cancer and how it can be most quickly and effectively diagnosed and treated.

Access current and past issues of ***Lung Cancer Frontiers*** via the Internet at njhealth.org, search Lung Cancer Frontiers

Interventional Bronchoscopy in Lung Cancer Diagnosis and Staging

By Ali I. Musani, MD, FCCP

Part 2

In Issue 34 of *Lung Cancer Frontiers*, Ali I. Musani, MD, Director of the Interventional Pulmonology program at National Jewish Health, described the role of ultrasound-guided transbronchial needle aspiration in lung cancer diagnosis and staging. In this issue, he explains how other new, minimally invasive techniques are used, or may one day be used, to diagnose lung cancer. — **Esther Langmack, MD**

Electromagnetic navigation bronchoscopy

Diagnosing peripheral parenchymal lesions less than 2 cm in diameter is a common challenge for bronchoscopists. Such lesions can be difficult to visualize with fluoroscopy, which also does not delineate the airways leading to the lesion. The diagnostic yield of flexible bronchoscopy for lesions less than 2 cm has been reported to be 14 percent for lesions in the outer third of the chest and 31 percent for lesions in the proximal two-thirds[1].

Electromagnetic navigation bronchoscopy (ENB) is a novel technology that provides real-time positional guidance for sampling peripheral pulmonary lesions. The superDimension system (superDimension; Hertzliya, Israel) combines electromagnetic guidance with virtual bronchoscopy. A steerable catheter, inserted through the working channel of the bronchoscope, also facilitates precise navigation to the target. The catheter can be extended beyond the tip of the bronchoscope, providing an extended working channel for biopsy forceps, brushes, or needles. This technique has shown great promise, especially in sampling small, distal lesions. However, the equipment is costly and the learning curve is steep.

The procedure can be performed in the bronchoscopy suite under conscious sedation or deep sedation with propofol. Several landmarks are selected on a virtual airway map, which is generated from the patient's high-resolution chest CT scan. The same landmarks are registered during actual bronchoscopy to synchronize the real and virtual landmarks. The bronchoscope is then navigated through the airways under CT guidance, in the coronal, axial, and sagittal planes, as displayed on a monitor (*Fig. 1*). One

In this issue

Interventional Bronchoscopy in Lung Cancer Diagnosis and Staging (continued)

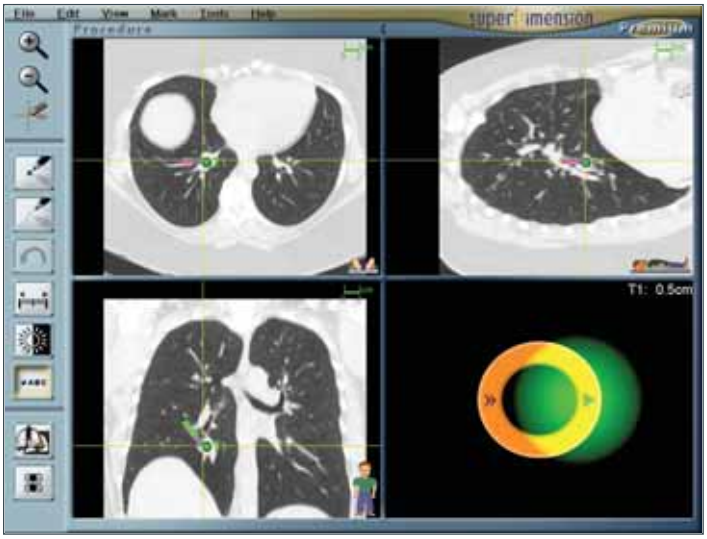


Figure 1: SuperDimension bronchoscopy navigation screen during transbronchial biopsy. Real-time CT images in the (clockwise from upper left) axial, sagittal, and coronal planes guide the operator to the lesion (green target). The lower right panel shows the "bull's eye" used to position the steerable probe for final, precise anchoring of the locatable guide.

panel of the monitor display shows the distance between the bronchoscope and the target. The bronchoscopist uses this information to steer the tip of the catheter into the lesion after the bronchoscope is in a wedge position (*Fig. 1*).

In 2006, an early prospective study[2] described 13 adult patients who underwent ENB for sampling of peripheral lung lesions ranging in size from 1.5 to 5 cm. The diagnostic sensitivity of the procedure was 69 percent. There were no device-related adverse events. The average duration of the entire procedure was 46 minutes, which the authors estimated was about 15 minutes longer than conventional fiberoptic bronchoscopy.

In a larger study from 2006, Gildea and colleagues[3] reported the results of 58 adults who underwent ENB for peripheral lesions ranging in size from 19.7 to 24.6 mm and/or mediastinal lymph adenopathy (average lymph nodes size 28.1 mm). Seventy-four percent of peripheral lesions and 100 percent of lymph nodes were successfully sampled, providing either a definitive diagnosis or evidence of benign lymphoid tissue. Malignancy was diagnosed in 74.4 percent of cases. Pneumothorax occurred in two (3.5 percent) patients. Eleven patients with non-diagnostic ENB required other procedures, including thoracotomy, CT-guided transthoracic needle aspiration, and mediastinoscopy.

Although ENB can be used for transbronchial needle aspiration (TBNA) of mediastinal lymph nodes, it has not been as popular as endobronchial ultrasound-guided TBNA, which is less expensive and more readily available. However, ENB has opened other diagnostic and therapeutic doors in the field of minimally invasive procedures. For example, fibered confocal fluorescence microscopy (described below) could work in concert with the ENB system to facilitate optical biopsy of peripheral lesions. The ENB system has also made it possible for therapeutic modalities, such as brachytherapy, to be tested for treatment of peripheral pulmonary malignancies. This marriage of different technologies may allow for minimally invasive bronchoscopy under conscious sedation to be both diagnostic and therapeutic for malignant lesions in patients for whom surgery is not a good option.

Narrow band imaging

Narrow band imaging (NBI) is based on the knowledge that carcinogenesis, and bronchial dysplasia, are associated with angiogenesis. Built into newer generation bronchoscopes, special light filters remove all but narrow bands in the blue and green spectrum, at 415 nm and 540 nm, which coincide with the absorption spectrum of oxygenated hemoglobin. When viewed with NBI, malignant or dysplastic airway lesions have a characteristic micro-vascular pattern (*Fig.2*). These vascular changes are frequently not appreciated using a conventional, full-spectrum, white light source. This technique can be used to identify areas for endobronchial biopsy. In a study of 22 subjects with known or suspected bronchial malignancy[4], NBI detected dysplasia or malignancy that was not found by white light bronchoscopy in 23 percent of subjects.

Photos by Ali I. Musani, MD

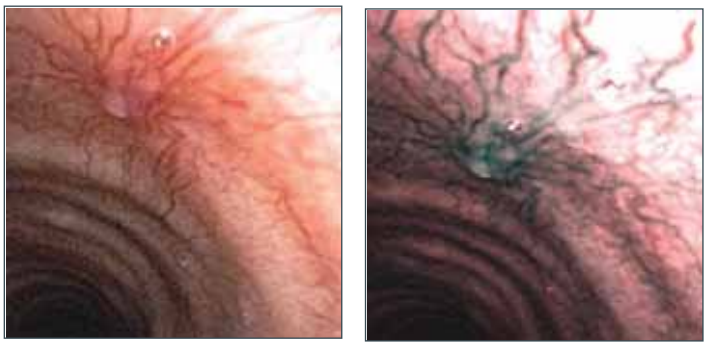


Figure 2: Conventional white light imaging (left) and narrow band imaging (right) of an endobronchial lesion with an abnormal microvascular pattern. Endobronchial biopsy showed squamous cell carcinoma.

Interventional Bronchoscopy in Lung Cancer Diagnosis and Staging (continued)

Optical coherence tomography

Like NBI, the goal of optical coherence tomography (OCT) is to identify malignant and dysplastic changes in the bronchial wall non-invasively. This rapidly evolving modality is somewhat analogous to ultrasound, except that near infrared light, instead of sound waves, is delivered to the tissue, via a probe inserted through the bronchoscope. Real-time images of nearly histologic quality can be obtained through the full thickness of the airway wall, with high spatial resolution, providing an "optical biopsy". Preliminary studies in bronchial explants[5] and smokers participating in a chemoprevention trial[6] showed that OCT is technically feasible and can be used to detect malignant and premalignant airway lesions. Validation with large, controlled clinical trials is pending.

Fibered confocal fluorescence microscopy

Last year, a new technology, fibered confocal fluorescence microscopy (FCFM) was introduced from France (Mauna Kea Technologies, Paris, France). A 1.0 mm diameter fiberoptic probe introduced through a conventional bronchoscope provides *in vivo*, real-time imaging of the bronchial mucosa and alveolar structures. The autofluorescence pattern of elastin fibers in the basement membrane provides the basis for detecting premalignant airway lesions, as well as changes associated with benign airway conditions. Thiberville and colleagues[7], using FCFM in a small group of subjects, described normal patterns of autofluorescence and found alterations in the autofluorescence microstructure in cancerous and precancerous lesions.

The role of FCFM in diagnosing premalignant lesions, or any other pathologic entity, remains to be proven. Whether this new modality will have a role in determining the structure of peripheral pulmonary lesions also remains to be seen.

Confocal bronchoscopy

One of the newest techniques for obtaining an "optical biopsy" of airway tissue is confocal bronchoscopy (CB). A confocal endomicroscopy unit is built into the tip of a flexible bronchoscope. When in contact with the airway mucosa, the confocal bronchoscope can take microscopic pictures of the airway wall at 7 micron intervals, down to 200 microns below the surface. Exquisite details, down to the cellular level, are easily appreciated. Epithelial cells, cilia, the basement membrane, muscular layer, microvasculature in the submucosa, glands and goblet cells are easily visualized (*Fig. 3*).

Photos by Ali I. Musani, MD

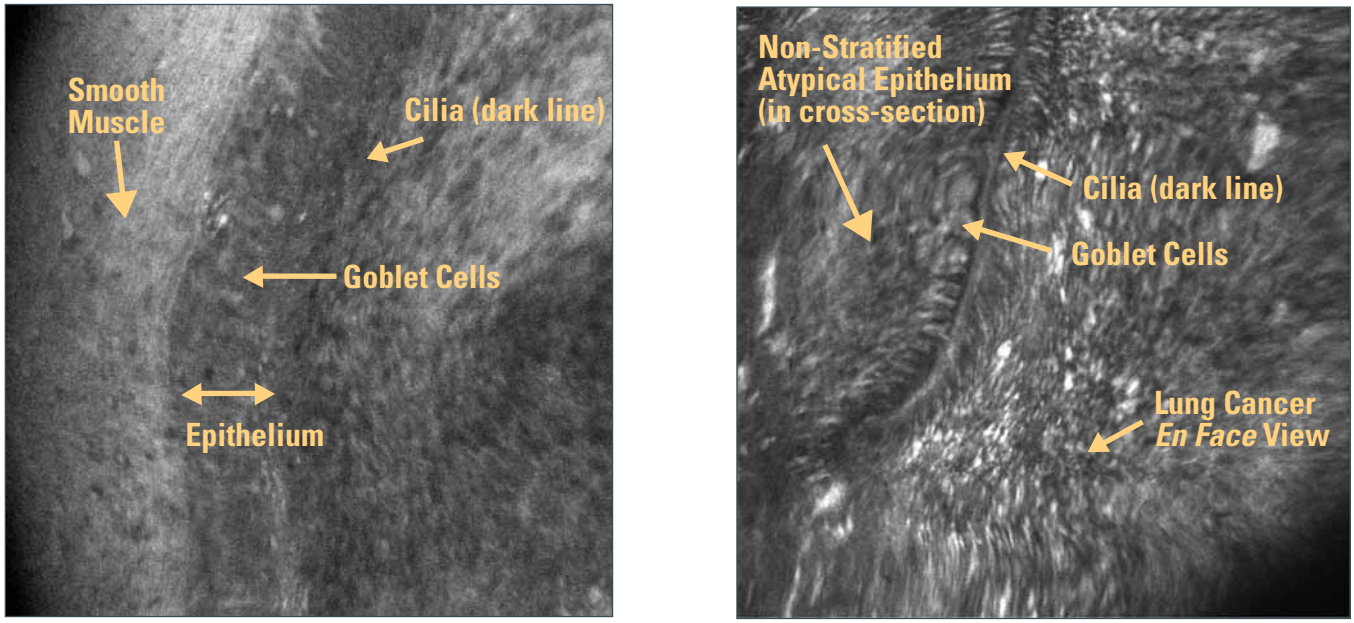


Figure 3: Confocal bronchoscopy images showing normal endobronchial tissue morphology (left) and squamous epithelium bordering a region of non-small cell carcinoma (right). In normal tissue, epithelial cells line up along the basement membrane. Mucin-containing goblet cells appear as large, dark circles. Cilia on the surface of the epithelium appear as a distinct, dark line across the top of the cells. Smooth muscle striations are seen. In comparison, lung cancer is characterized by loss of the squamous epithelium cell matrix and loss of cellular stratification. The basement membrane cannot be distinguished in regions of cancer.

Interventional Bronchoscopy in Lung Cancer Diagnosis and Staging (continued)

We recently presented our first animal and human study of this novel technology at the World Congress of Bronchology 2008 meeting in Tokyo, Japan[8]. Intravenous fluorescein was used to highlight the structures. Malignant lesions could be successfully distinguished from benign mucosa in this study. With further miniaturization, the hope is that this technique could be used to detect and characterize airway malignancies and non-malignant airway conditions.

Autofluorescence bronchoscopy

Premalignant and malignant bronchial lesions fluoresce less readily than normal healthy airway tissue. The autofluorescence (AF) bronchoscope emits light with a specific wavelength that makes premalignant or malignant tissue appear red-brown, while normal tissue appears green. Autofluorescence bronchoscopy has been used since the 1990s, primarily to detect early squamous epithelial abnormalities in the central airways[9]. Several studies comparing AF to white light bronchoscopy alone show a higher rate of detection of squamous cell metaplasia and neoplasia with AF, but no overall improvement in survival was found in the largest randomized study[10]. With the emergence of other rapidly evolving modalities in diagnostic bronchoscopy, the role of AF bronchoscopy seems to be diminishing. However, it is possible that AF could one day be used in conjunction with other modalities, such as OCT, FCFM, or CB, to improve early detection of airway malignancies.

The road ahead

Although ENB is now used in many medical centers, including National Jewish Health, the other non-invasive imaging modalities described above are not in common clinical use. For some modalities, technical issues must still be resolved. For nearly all of the modalities, bronchoscopists will need highly specialized training to become proficient in obtaining and interpreting images. Although these techniques show great promise for the early detection of lung cancer, further clinical trials and experience are also needed in the future.

1. Baaklini WA, Reinoso MA, Gorin AB, et al. *Chest* 2000; 117:1049-1054
2. Schwarz Y, Greif J, Becker HD, et al. *Chest* 2006; 129:988-994
3. Gildea TR, Mazzone PJ, Karnak D, et al. *Am J Respir Crit Care Med* 2006; 174:982-989
4. Vincent BD, Fraig M, Silvestri GA. *Chest* 2007; 131:1794-1799
5. Whiteman SC, Yang Y, Gey van Pittius D, et al. *Clin Cancer Res* 2006; 12:813-818
6. Lam S, Standish B, Baldwin C, et al. *Clin Cancer Res* 2008; 14:2006-2011
7. Thiberville L, Moreno-Swirc S, Vercauteren T, et al. *Am J Respir Crit Care Med* 2007; 175:22-31
8. Musani AI, Sims M, Sareli C, et al. A pilot study to determine the feasibility of confocal endomicroscopy to characterize human airway histology. Abstract presented at the World Congress of Bronchology, Tokyo, Japan, 2008
9. Lam S, Kennedy T, Unger M, et al. *Chest* 1998; 113:696-702
10. Haubinger K, Becker H, Stanzel F, et al. *Thorax* 2005; 60:496-503

Dr. Ali Musani (left) reviews images from an electromagnetic navigation bronchoscopy in the Minimally Invasive Diagnostic Center at National Jewish Health.

Selections from the Peer-Reviewed Literature

By Thomas L. Petty, MD, Editor Emeritus

Thomas L. Petty, M.D.

1. Association of radiographic emphysema and airflow obstruction with lung cancer

Am J Respir Crit Care Med 2008;178:738-744

Wilson DO, Weissfeld JL, Balkan A, Schragin JG, Fuhrman CR, Fisher SN, Wilson J, Leader JK, Siegfried JM, Shapiro SD, Sciurba FC

Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, University of Pittsburg, Pittsburg, PA

RATIONALE: To study the relationship between emphysema and/or airflow obstruction and lung cancer in a high-risk population.

OBJECTIVE: We studied lung cancer related to radiographic emphysema and spirometric airflow obstruction in tobacco-exposed persons who were screened for lung cancer using chest computed tomography (CT).

METHODS: Subjects completed questionnaires, spirometry, and low-dose helical chest CT. CT scans were scored for emphysema based on National Emphysema Treatment Trial criteria. Multiple logistic regressions estimated the independent associations between various factors, including radiographic emphysema and airflow obstruction, and subsequent lung cancer diagnosis.

MEASUREMENTS AND MAIN RESULTS: Among 3,638 subjects, 57.5, 18.8, 14.6, and 9.1% had no, trace, mild, and moderate-severe emphysema, and 57.3, 13.6, 22.8, and 6.4% had no, mild (Global Initiative for Chronic Obstructive Lung Disease [GOLD] I), moderate (GOLD II), and severe (GOLD III-IV) airflow obstruction. Of 3,638 subjects, 99 (2.7%) received a lung cancer diagnosis. Adjusting for sex, age, years of cigarette smoking, and number of cigarettes smoked daily, logistic regression showed the expected lung cancer association with the presence of airflow obstruction (GOLD I-IV, odds ratio [OR], 2.09; 95% confidence interval [CI], 1.33-3.27). A second logistic regression showed lung cancer related to emphysema (OR, 3.56; 95% CI, 2.21-5.73). After additional adjustments for GOLD class, emphysema remained a strong and statistically significant factor related to lung cancer (OR, 3.14; 95% CI, 1.91-5.15).

CONCLUSIONS: Emphysema on CT scan and airflow obstruction on spirometry are related to lung cancer in a high-risk population. Emphysema is independently related to lung cancer. Both radiographic emphysema and airflow obstruction should be considered when assessing lung cancer risk.

Editorial Comment: This conclusion is consistent with many other studies cited in the article and in previous editions of *Lung Cancer Frontiers*. This association deserves aggressive study, hoping to explain the basic mechanisms involved in COPD and lung cancer and to direct our attention to patients in whom screening tests are most likely to yield a diagnosis.

2. Alpha$_1$-antitrypsin deficiency carriers, tobacco smoke, chronic obstructive pulmonary disease, and lung cancer risk

Arch Intern Med 2008;168:1097-1103

Yang P, Sun Z, Krowka MJ, Aubry M-C, Bamlet WR, Wampfler JA, Thibodeau SN, Katzmann JA, Allen MS, Midthun DE, Marks RS, de Andrade M

Division of Epidemiology and Cancer Center, Mayo Clinic, Rochester, MN

BACKGROUND: Genetic susceptibility in lung cancer risk has long been recognized but remains ill defined, as does the role of tobacco smoke exposure and chronic obstructive pulmonary disease (COPD).

Selections from the Peer-Reviewed Literature (continued)

METHODS: Using a dual case-control design, we tested whether alpha$_1$-antitrypsin deficiency (α_1ATD) carriers are predisposed to a higher risk of lung cancer, adjusting for the effects of tobacco smoke exposure and COPD. A total of 1856 patients with incident lung cancer were included in the study; 1585 community residents served as controls. A second control group was composed of 902 full siblings of the patients. We first modeled 1585 case-control pairs without the α_1ATD variable using multiple logistic regression analysis and then modeled the α_1ATD allele type in the presence of other known risk factors of lung cancer.

RESULTS: We found a significantly increased lung cancer risk among α_1ATD carriers from 2 parallel case-control comparisons: when patients were compared with unrelated controls, α_1ATD carriers had a 70% higher risk of developing lung cancer than noncarriers (odds ration, 1.7; 95% confidence interval, 1.2-2.4). In a further comparison of patients with their cancer-free siblings, we found a 2-fold increased lung cancer risk in α_1ATD carriers (95% confidence interval, 1.4-2.7). Stratified analysis by tumor histologic subtypes showed a significant increase for adenocarcinoma and squamous cell carcinoma among α_1ATD carriers.

CONCLUSION: Our results suggest that α_1ATD carriers are at a 70% to 100% increased risk of lung cancer and may account for 11% to 12% of the patients with lung cancer in our study.

Editorial Comment: It is interesting that even the carrier state of alpha$_1$-antitrypsin deficiency is a risk factor for lung cancer. This raises the question of a relationship between the genes for alpha$_1$-antitrypsin deficiency and lung cancer susceptibility. This observation suggests a need for lung cancer screening in this newly defined risk group.

Lung Cancer Meetings and Symposia

10th European Congress:
Perspectives in Lung Cancer
March 6-7, 2009 Brussels, Belgium
Contact: register@imedex.com

13th World Conference on Lung Cancer
International Association for the Study of Lung Cancer
July 31-August 4, 2009 San Francisco, CA
Information: 2009worldlungcancer.org

Upcoming Continuing Medical Education Events at National Jewish Health

The 31st Annual National Jewish Health Respiratory of Allergy Update
Keystone, CO
February 4-7, 2009

The First Annual International COPD Conference: Phenotyping
Featuring: Barry Make, MD and Russell Bowler, MD, PhD
March 5-6, 2009

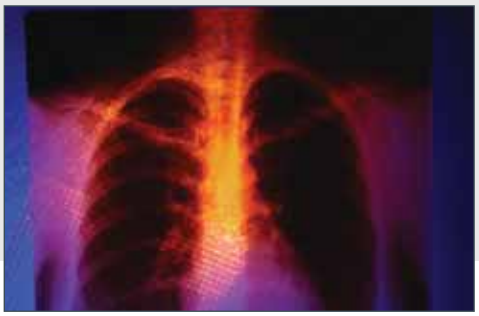
Rethinking Difficult Asthma: Changes to the Asthma Guidelines and Their Relevance to Your Practice
Online course, at rethinkingdifficultasthma.info

Phenotyping for Individualized Asthma Care Audio Book
Reserve your copy of our upcoming CME audio book CD today!

Visit njhealth.org/proed or call 800.844.2305 for more information about these opportunities.


Barry Make, MD


Russell Bowler, MD, PhD



Comments may be submitted to ***Lung Cancer Frontiers***
1400 Jackson Street J208
Denver, Colorado 80206
or by email to
langmacke@njhealth.org, or tlpdoc@aol.com