Bronchoscopy for the Diagnosis and Staging of Lung Cancer

Ezzat El-Bayoumi, M.D.[1] and Gerard A. Silvestri, M.D., M.S., F.C.C.P.[1]

ABSTRACT

Bronchoscopy is an invaluable tool utilized for the diagnosis, staging, and management of lung cancer. Advancements in computer technology and engineering have allowed for the emergence of newer modalities to evaluate endobronchial, parenchymal, and mediastinal pathology. Established techniques such as white light video bronchoscopy and its ancillary procedures (forceps biopsy, brush biopsy, bronchoalveolar lavage, bronchial washings, and transbronchial needle aspiration) are discussed here, with their accuracy described in relation to tumor location, size, and type.

Newer technologies such as autofluorescence bronchoscopy, narrow band imaging, endoscopic ultrasound, endobronchial ultrasound, electromagnetic navigation, optical coherence tomography, and confocal fluorescent laser microscopy are introduced and put into perspective. Special emphasis has been placed on their role in the early detection and staging of lung cancer. Some technology requires further study to delineate its role in the disease, whereas other modalities are emerging as the new gold standard in evaluation of lung cancer. The future holds great promise with further miniaturization of equipment and improvements in computer processing power that may allow for in vivo pathological evaluation of abnormal tissue.

KEYWORDS: Bronchoscopy, endobronchial ultrasound, electromagnetic navigation, lung cancer

Bronchoscopy is an invaluable diagnostic tool for many lung disorders. Perhaps it is most useful in the diagnosis, staging, and management of lung cancer. This technology has evolved greatly over the last 2 decades. Here we review the currently available techniques utilized for patients undergoing bronchoscopy for cancer. In addition, several new technologies have emerged that warrant description because some are likely to have important clinical application in the years to come.

The first written description of a bronchoscopy being performed was in 1897 when Gustav Killian used a laryngoscope and a rigid esophageal tube to remove a foreign body from the trachea. Later a rigid bronchoscope was developed by Chevalier Jackson and was the sole means of accessing and examining the trachea and main bronchi until the late 1960s, when Shigeto Ikeda of Japan developed the first flexible fiberoptic bronchoscope, of which variations are still in use today.

With advances in microtechnology, the flexible fiberoptic bronchoscope (FOB) has undergone its share of innovations, allowing for the development of imaging tools that have resulted in the inception of the video bronchoscope. Recently, autofluorescent bronchoscopy (AFB), narrow band imaging (NBI), and the linear endobronchial ultrasound (EBUS) bronchoscope have been introduced into clinical practice. Prior to exploring

[1]Division of Pulmonary and Critical Care Medicine, Allergy, and Clinical Immunology, Medical University of South Carolina, Charleston, South Carolina.

Address for correspondence and reprint requests: Ezzat El-Bayoumi, M.D., Division of Pulmonary and Critical Care Medicine, Allergy, and Clinical Immunology, Medical University of South Carolina, Ste. 812-CSB, 96 Jonathan Lucas St., Charleston, SC 29425 (e-mail: elbayou@musc.edu).

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some of these exciting new technologies, a review of the utility and diagnostic yield of established bronchoscopic procedures is warranted.

BRONCHOSCOPIC TECHNIQUES

ENDOBRONCHIAL DISEASE

When one is analyzing the utility of different bronchoscopic techniques in the diagnosis of malignant pathology of the lung and airways, the yield is dependent on tumor location, size, and whether there is submucosal distribution or direct erosion into the airway.[1] Central (up to the segmental bronchus) and large (greater than 2 to 3 cm) tumors, are usually visible, and endobronchial bronchoscopic biopsy, brush, and wash provide a high yield.[2]

Bronchoscopy with Forceps Biopsy

To perform this procedure small forceps are introduced via the working channel of the bronchoscope, and the lesion is biopsied under direct vision, whereas distal lesions are biopsied with the aid of fluoroscopy. The overall yield is 74% (range 50 to 92%, 20 studies)[2] for central lesions but decreases considerably for peripheral lesions to 46% (range 17 to 80%).[2]

Bronchoscopy with Brush Biopsy

This technique utilizes a shielded catheter, which is introduced through the working channel of the bronchoscope. If a lesion is visible the brush is extended from the catheter and rubbed back and forth repeatedly across the lesion to obtain a specimen for cytological examination. The technique provides better yields with visible central lesions as opposed to peripheral (distal to the segmental bronchus) or submucosal lesions. The yield of brush biopsy in centrally located visible lesions is 59% (range 23 to 92%, 18 studies).[2]

Bronchoscopy with Bronchoalveolar Lavage or Wash

Bronchoalveolar lavage (BAL) is a technique by which a predetermined amount of saline (usually 150 to 180 mL) is instilled into a distal airway after obtaining an adequate "wedge" of the bronchoscope into the smallest bronchi possible. The saline is removed, and the fluid from lung tissue distal to the bronchus is sent for analysis, which can include cell count, culture, and cytology. Bronchial washings are similar in that saline is instilled into the bronchial tree; however, a seal is not needed, and a smaller amount of saline is instilled, allowing for microbiological and cytological evaluation only. Further, the material collected is usually from the tracheobronchial tree and not from alveoli. For central endobronchial lesions the sensitivity of BAL/wash was 48% (range 28 to 78% 12 studies).[2]

Transbronchial Needle Aspiration for Endobronchial Disease

Transbronchial needle aspiration (TBNA) was introduced into practice by Wang and Terry in 1983.[3] It is a safe and relatively accurate method of diagnosing endobronchial or submucosal lesions as well as for sampling the hilum and mediastinum. The procedure entails introduction of a 21 gauge cytology needle or a larger 19 gauge histology needle for a core sample into the target area. The lesion to be biopsied is punctured under direct vision in those with central lesions. TBNA has a reported sensitivity of 67% (range 47 to 70%, five studies) for endobronchial lesions,[2] and, because the diagnostic yield of endobronchial biopsy or brush is higher for those with visible lesions, TBNA is rarely performed in this setting. For evaluation of submucosal lesions TBNA is more effective, with a yield of 71% compared with endobronchial biopsy (EBBX), which has a sensitivity of 55% in this setting.[4]

Combining Techniques

Combining different techniques produces a higher yield than any individual technique. The overall sensitivity of combining brush biopsy, forceps biopsy, wash/BAL, and needle aspiration for central lesions is 88% (range 67 to 97%, 14 studies) and decreases to 69% (range 36 to 86%, 12 studies) for peripheral lesions.[2]

PERIPHERAL LUNG LESIONS

Peripheral lung lesions are traditionally those that are located beyond the segmental bronchus and are thus rarely visible. The same bronchoscopic techniques (forceps biopsy, brush biopsy, BAL, bronchial wash, and TBNA) are applicable for the diagnosis of such lesions; however, their yield is lower than that which can be expected with centrally located lesions. In addition, the size of the lesion is an important predictor of accuracy because those with peripheral lesions less than 2 cm in diameter have the lowest diagnostic yield.

Forceps Biopsy

For this procedure a forceps is introduced via the working channel of the bronchoscope and with the aid of fluoroscopy the peripheral lesion is targeted for biopsy. Computed tomography (CT) can aid in identifying the segment in which the lesion is located. The sensitivity of this diagnostic method is reported at 46% (range 17–77%, 30 studies).[2]

Using fluoroscopy a two-dimensional view can improve localization of the tip of the forceps in relation to the peripheral lesion. The sensitivity is also dependent on the lesion size, with sensitivity for lesions less than 2 cm of 33% (range 5–76%, 8 studies)[2] and an overall sensitivity for lesions greater than 2 cm of 67% (range 31 to 82%, 8 studies).[2]

Brush Biopsy

The technique entails insertion of the brush through the bronchoscopic working channel and directing the brush catheter to the appropriate segmental bronchus. The brush is then extended and agitated back and forth to obtain a cytology sample. This can be done blindly or with fluoroscopic guidance, and the yield for peripherally located lesions was 52% (range 21 to 84%, 15 studies).[2] An important factor in predicting diagnostic yield is lesion size. Based on eight studies it is estimated that for peripheral lesions greater than 2 cm in size the yield for brush biopsy is 62% (range 31 to 82%)[2] and falls to 33% (range 11 to 76%)[2] for those less than 2 cm.[2] As a general rule, bronchoscopy is not the best diagnostic modality for lesions smaller than 3 cm located lateral to the midclavicular line.

Bronchoscopy with Bronchoalveolar Lavage or Wash for Peripheral Lesions

The technique of tissue acquisition here is the same as with proximal lesions; however, the yield as might be expected for peripherally located lesions is low at 43% (range 12 to 65%, 13 studies).[2]

Computed Tomographic Fluoroscopy

With increases in computer power and advances in CT technology it has become possible to utilize CT in real time to guide the bronchoscopist with much more precision than what can be expected using fluoroscopy alone. This technique has the advantage of visualizing the anatomy with greater resolution and in more than one plane of view. Tushima et al compared the diagnostic yield of CT fluoroscopy to traditional fluoroscopy during bronchoscopy. The yield of fluoroscopy for the diagnosis of lung cancer was 52.6% (41 of 78 patients)[5] as opposed to 62.2% (51 of 82 patients) for the CT fluoroscopy. The differences in yield were even more impressive for smaller-sized nodules. When comparing the yield of both techniques in relation to lesion size, nodules up to 10 mm were positive 7.7% of the time using traditional as opposed to 43% with CT fluoroscopy. This difference held true at every size studied in favor of CT fluoroscopy.[5] Thus CT fluoroscopy guidance is superior over traditional fluoroscopy for bronchoscopy, and the diagnostic yield is dependent on lesion size and location. It is also possible to biopsy mediastinal lymph nodes with this modality and, if necessary, readjust the positioning of the TBNA needle based on the CT image. A major drawback of this modality is that the radiation dose is double that of traditional fluoroscopy, adding risk to the bronchoscopist and staff. Further, from a practical standpoint, transporting staff, patients, and equipment to the radiology suite is a time-consuming and cumbersome undertaking.[6,7]

SAMPLING OF THE MEDIASTINUM

Surgical access to the mediastinum for purposes of diagnosis and staging has been regarded as the gold standard when compared with less invasive techniques. Recently, significant advances have been made in the area of minimally invasive mediastinal sampling in an attempt to decrease the need for surgical sampling. There are three main modalities for sampling the mediastinum in a minimally invasive manner: TBNA, endobronchial ultrasound-guided fine needle aspiration (EBUS FNA), and endoscopic ultrasound-guided fine needle aspiration (EUS FNA).

Transbronchial Needle Aspiration for Sampling the Mediastinum

When TBNA is used to sample the mediastinum, the procedure is preplanned with the aid of a computed tomographic (CT) scan of the chest to localize the lymph nodes to be biopsied. Approximate measurements are made of the relation of the target to identifiable anatomical structures. During the procedure the landmarks are identified, and the site is punctured blindly using several established techniques.[8] The sensitivity ranges from 15% to greater than 85% in the literature; however, a meta-analysis by Holty et al showed that the pooled sensitivity of TBNA was 39% and was dependent on the prevalence of lung cancer in the population.[9,10] The use of rapid on site evaluation (ROSE) increases the diagnostic yield of TBNA.[11,12] Rapid on site cytological evaluation allows for immediate identification of a malignancy and can verify the adequacy of the specimen by identification of lymphocytes. Unfortunately, TBNA is an underutilized diagnostic modality in the United States. In a survey performed by Haponic in 1997 only 10% of pulmonary fellows in training performed TBNA routinely and 40% performed it occasionally.[13] It is estimated that only 20% of practicing pulmonologists use this modality in the United States[14] (10 to 30% in Europe).[15] This may be the result of a lack of training in the technique and frustration by the poor yield in nonproficient hands. A study published in 2003 showed progress with 91% of pulmonary fellowships in the United states trained in TBNA and 69% of trainees reaching competency.[16]

Endoscopic Ultrasound with Fine Needle Aspiration

Endoscopic ultrasound has been available for nearly 10 years.[17–20] This approach entails viewing the mediastinum from the esophagus with an integrated ultrasound endoscope. In addition to allowing for detailed examination of the mucosa of the esophagus and stomach, views can be obtained of the left adrenal gland, the left lobe of the liver, and, more importantly, certain lymph node stations in the mediastinum.[19] Due to anatomical considerations EUS can sample stations 3 posteriorly, 4L, 7, 8, and 9. Stations 3 anteriorly, 2R, 2L, and 4R can sometimes be sampled, but stations 10R, 10L, 11R, and 11L are not accessible due to intervening air from the lung, and stations 5 and 6, although visible, cannot be sampled due to interposition of vascular structures[15,17] (Fig. 1). The sensitivity and specificity for EUS is 72 to 100% and 88 to 100%, respectively (Table 1).

Endobronchial ultrasound with Transbronchial Needle Aspiration

Miniaturization of ultrasonic transducers and advances in computer processing allowed for the development of endobronchial ultrasound (Fig. 2). Two types of EBUS are currently available for use in bronchoscopy, the radial EBUS and the linear (integrated) EBUS. The radial EBUS is a separate ultrasonic probe (referred to as a miniprobe) that is inserted into the working channel of the bronchoscope and allows for visualization of

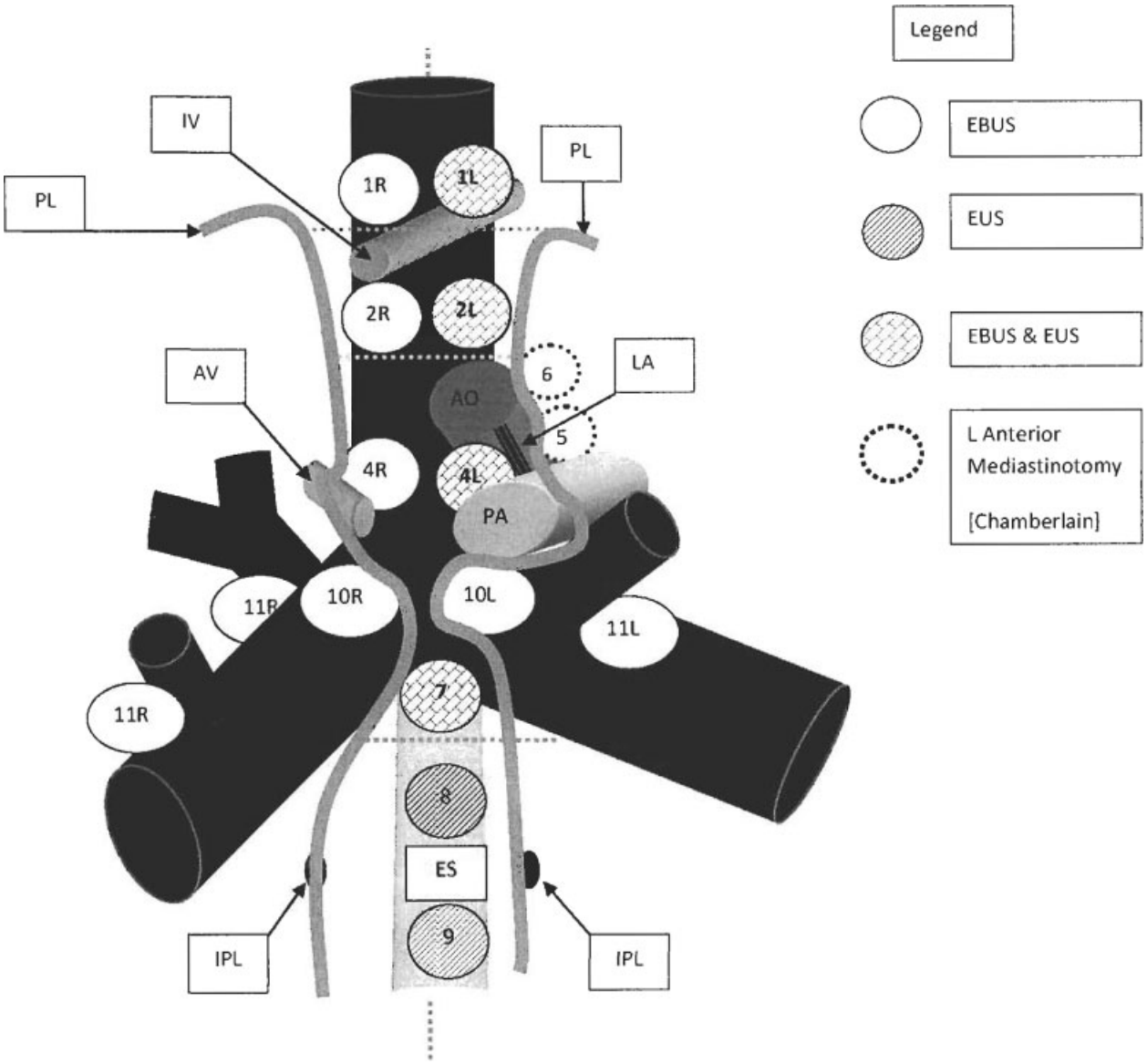

Figure 1 Schematic representation of lymph nodes accessible by EBUS, EUS, and left anterior mediastinotomy: (Chamberlain procedure). EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; IV, innominate vein; AV, azygos vein; PL, pleural; AO, aorta; PA, pulmonary artery; ES, esophagus; IPL, inferior pulmonary ligament; LA, ligamentum arteriosum. Numbers represent lymph node stations according to Mountain and Dressler.

Table 1 Comparison of Selected Techniques for Staging the Mediastinum

Procedure	Sensitivity	Specificity	Advantages	Disadvantages
Mediastinoscopy (standard with its variants)	33–81%	100%	Considered the gold standard Direct operative inspection of the mediastinum	Risks associated with surgery and anesthesia Requires operating room time Costly Cannot access entire mediastinum in one procedure (three variants available): Standard mediastinoscopy Extended Mediastinoscopy Left anterior sternotomy (Chamberlain procedure), to access stations 5 and 6 Stations 11, 8, and 9 are not accessible.
Transthoracic needle aspiration	72–100%	100%	Outpatient procedure Minimally invasive Avoids general anesthesia Computed tomographic guidance can be used for confirmation of needle tip position Can sample peripheral nodules during the same procedure Can access stations 5 and 6	Up to 34% incidence of pneumothorax, 10% may require chest tube drainage Radiation exposure Requires specialized training Not widely available
Transbronchial needle aspiration	39–76%	96–99%	Outpatient procedure Minimally invasive Avoids general anesthesia Can access the right and left paratracheal space nodes (2R, 4L, 4R), subcarinal space (level 7) as well as 11R and 11L Can perform airway inspection or interventions during the same procedure	Wide variability in trainingand techniques leads to variability in yields Cannot access (level 5 and 6) Performed ''blindly'' at most institutions Requires ''ROSE'' for higher accuracy Still underutilized in the United States and Europe
Endoscopic ultrasound (EUS)	72–100%	88–100%	Outpatient procedure Avoids risks of general anesthesia Can access stations 8 and 9 as well as mesenteric lymph nodes along with the L adrenal gland L upper and lower pretracheal lymph nodes (stations 2L,4L) as well as subcarinal (station 7) can be accessed in real time Can detect malignancy in normal sized nodes Complimentary to EBUS	Requires specialized training Not widely available Lymph nodes: R pretracheal (stations 2R,4R), Aortopulmonary window (station 5),hilar (stations 10 R and 10 L), interlobar (stations 11R and 11L) cannot be accessed
Endobronchial ultrasound (EBUS)	92–94%	100%	Outpatient procedure Avoids general anesthesia Majority of mediastinum can be accessed in a minimally invasive fashion Low complication rate Sampling is performed in real time Can detect malignancy in normal lymph nodes May become a new ''gold standard'' for mediastinal staging in lung cancer, along with EUS	- Not yet widely available - Stations 5, 6, 8, 9 cannot be accessed - Requires specialized training

Adapted, updated, and modified from Pastis NJ, Silvestri GA. Tissue procurement: bronchoscopic techniques. In: Lung Cancer Principles and Practice. 3rd edition. New York, NY: Lippincott Williams and Wilkins; 2003:358–371.

Figure 2 Olympus BF-UC140 Linear Endoscopic Ultrasound (top), Olympus BF-UC160F-OL8 linear Endobronchial Ultrasound (bottom). See Olympus USA website.

extrabronchial planes in a radial orientation. This allows for visualization of mucosal details as well as peripheral masses and mediastinal lymph nodes to a depth of 5 cm.[15,21] If sampling is necessary the device is withdrawn, and a sampling tool (forceps or needle) is inserted through the same channel and the identified area is sampled blindly. The linear integrated EBUS bronchoscope was introduced by Olympus [BF-UC160F-OL8; Olympus Medical Systems, Tokyo, Japan, (Fig. 2)] and provides real time visualization and sampling of the mediastinum in the sagittal orientation (Fig. 3). It utilizes a small curvilinear transducer with a 7.5 MHz frequency that allows for visualization of extrabronchial structures up to a depth of 5 cm. The development of this technology may be one of the most important advances in diagnosing and staging lung cancer. With the aid of the linear EBUS scope almost the entire mediastinum can be accessed in real time.[15,17,22] Mediastinal lymph node stations 8, 9, 6, and 5 are not accessible with this technique. Stations 8 and 9 can only be accessed by EUS and play an important role in esophageal rather than lung cancer. Stations 5 and 6 can be accessed by left median sternotomy (Chamberlain procedure)(Fig. 2). The procedure has a steep learning curve, however, Because the transducer is integrated into a bronchoscope the manual dexterity required should be familiar to most bronchoscopists. Serious complications with EBUS have yet to be reported.[15] After intubation with the EBUS scope, a saline-filled balloon is inflated and the extrabronchial structures are examined on the ultrasonography monitor. Once a lymph node is identified, a 22 gauge needle is introduced into the working channel, and the identified target is sampled in real time. The sagittal orientation of the viewing plane allows for the needle to be seen in its longitudinal axis and thus allows for precise assessment of depth of penetration and verification of the needle in the lymph node. Integrated EBUS is an outpatient procedure performed in most settings under conscious sedation. The sensitivity for detection of mediastinal spread of lung cancer is greater than 94%, with a specificity of 100%.[15,22,23] Herth et al conducted a prospective study of 100 patients with a radiographically normal mediastinum and proven lung cancer and found that EBUS-TBNA in this group had a sensitivity of 92%, a specificity of 100%, and an NPV of 96%.[23] This technique, along with EUS, may significantly decrease the need for a mediastinoscopy for lung cancer staging and may become the new gold standard for preoperative staging. Table 1 contains an overview of selected methods for sampling the mediastinum.

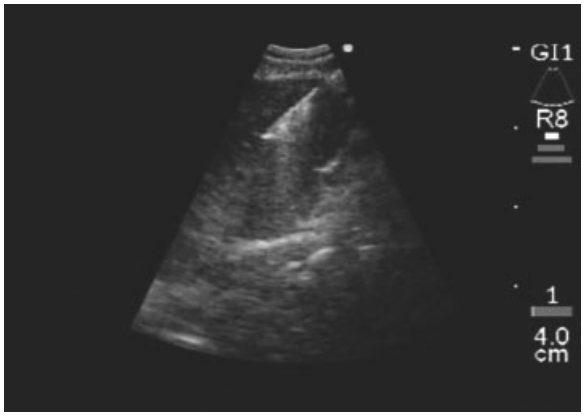

Figure 3 Picture of needle within target lymph node during linear endobronchial ultrasound guided fine needle aspiration.

EMERGING TECHNOLOGIES

A recent explosion of new technology has been developed to allow for improvement in the detection of premalignant and malignant changes in the airways. As we learn more about the natural characteristics of healthy versus diseased tissue,[24] image enhancing modalities such as autofluorescence bronchoscopy (AFB), narrow band imaging (NBI), optical coherence tomography (OCT), and confocal laser fluorescent microscopy (CLFM) may become important adjuncts for the identification and surveillance of early carcinoma in situ.

Autofluorescence Bronchoscopy

Autofluorescence is a method that takes advantage of a natural characteristic of tissue to enhance reflected light in the green spectrum range (520 nm) when illuminated with light in the blue wavelength range (380 to 460 nm). Abnormal tissue [carcinoma in situ (CIS)] or dysplastic tissue lacks this characteristic and will appear darker than the background.[25,26] The technique involves the patient undergoing "traditional" white light bronchoscopy (WLB), which is then followed by AFB, to detect lesions not apparent on WLB or to further characterize abnormalities identified by WLB. Recently, the Laser Induced Fluorescence Endoscope system (LIFE) (Xillix Technologies Corp., Richmond, BC, Canada) has been introduced, which uses a helium-cadmium blue laser beam

to excite tissue. Further enhancement included integration of AFB with WLB, obviating the need to exchange devices for visualization (D-Light AF System, Karl Storz, Tuttlingen, Germany, and the Pentax SAFE 1000 System, Pentax, Tokyo, Japan).[27]

The usefulness of AFB is still unclear. A European study by Haussinger et al evaluated 1173 patients and showed that AFB is useful in detection of premalignant lesions in a subgroup of patients with positive sputum cytology. Compared with WLB, AFB increased the detection rate of grade II to III dysplasia by a factor of 2.1 ($p = .03$) but did not detect higher rates of CIS ($p = .75$).[25] The authors concluded that AFB as a general screening tool could not be recommended because it had a low positive predictive value (PPV) of 25.1% and a low specificity of 58.4%.[25] Other studies have shown that AFB has a high false-positive result rate (34%) and a low PPV (4.3 to 33%) for malignancy.[25,26,28,29] This may be due to the fact that low-grade dysplasia, inflammation, granulation tissue, hyperplasia, and metaplasia have abnormal autofluorescence, and it is difficult to distinguish them from high-grade dysplasia (II and III) and CIS.[30] In addition, studies of the natural history of high-grade dysplasia and CIS are sparse, with small numbers of patients and a short duration of follow-up further complicating the interpretation of the results.

George et al conducted a cohort study of 22 patients with preinvasive endobronchial lesions to define the natural progression of high-grade dysplasia (HGD) and CIS. Fluorescence bronchoscopy was performed every 4 to 12 months with a chest CT scan annually. This study reported that the cumulative risk of developing lung cancer in patients with a high-grade lesion was 33% and 54% at 1 and 2 years, respectively. However, some of the lesions were not airway lesions but peripheral nodules detected by CT. In addition, during surveillance some of the airway lesions regressed. This study suggests that patients with high-grade precancerous lesions can be at high risk of developing lung cancer and that surveillance with AFB facilitated early detection but acting upon these findings may not really decrease mortality because we don't know which lesions will progress to cancer. The topic remains understudied. Larger trials are needed to further define the role of AFB in early lung cancer detection. One scenario in which AFB does have a clinical indication is in patients where sputum cytology is positive but one cannot visualize a lesion on white light bronchoscopy, though this clinical scenario is quite rare.

Narrow Band Imaging Bronchoscopy

Narrow band imaging (NBI) is a modality that can identify premalignant lesions in the bronchial tree. Malignant, premalignant, and dysplastic lesions are characterized by abnormal angiogenesis and can be detected by visualization of blood vessel entanglement and abnormal proliferation in the bronchial mucosa (angiogenic squamous dysplasia).[31] The NBI bronchoscope utilizes light filters to allow for illumination of tissue in different wavelengths. Typically light can be filtered to three wavelengths: two blue bands B1 (400 to 430 nm) and B2 (440 to 470 nm) and one green band, green G (560 to 590 nm).[32,33] Given that the absorption of light for blood vessels is maximum at 415 nm, they are best visualized using light in the blue band (B1 wavelength). This technology was first described in the gastroenterology literature for the detection of abnormal and premalignant lesions, and more recently in bronchoscopy.[33] In a pilot study by Vincent et al, 22 patients were evaluated for endobronchial dysplasia using white light bronchoscopy (WLB) immediately followed by NBI. They found that the rate of detection of dysplasia or malignancy not apparent on WLB was 23%.[33] The study also suggested that NBI did not enhance the detection rate of dysplasia in lesions readily apparent on WLB. Shibuya et al reported high magnification bronchoscopy with NBI in the blue wavelength to detect angiogenic squamous dysplasia and found that the technique enabled identification of the aforementioned premalignant lesions in 78% of biopsied abnormalities identified as abnormal on AFB.[32] At present the utility of this remains obscure as the natural history of the above premalignant lesion is not well understood and the indications for NBI have not been well established. Further studies are needed to further identify the role of this technique in early endobronchial cancer detection.

Electromagnetic Navigation

This new emerging technology allows access to peripheral pulmonary lesions not accessible to traditional bronchoscopy. It is a mergence of physics, informatics, radiology, and bronchoscopy to aid in best accessing peripheral lesions. In lay terms electromagnetic navigation (EMN) is like the GPS system of the bronchoscope rather than a car. The technology has been in use for the past few years though its effectiveness has only been evaluated in several small series.[34–39] The technique entails capturing chest CT data that are entered into a computer equipped with software that is able to process the information and merge it with electromagnetic information. The CT is reviewed by the operator, the procedure is planned, and then the patient is placed on a magnetic field generator plate. During the procedure, the operator identifies in vivo the preplanned land marks and touches them with the aid of an electro-magnetic sensor inserted through the working channel of the bronchoscope. The computer software then superimposes the preloaded and preplanned data onto the newly acquired bronchoscopic data, thus enabling the system to

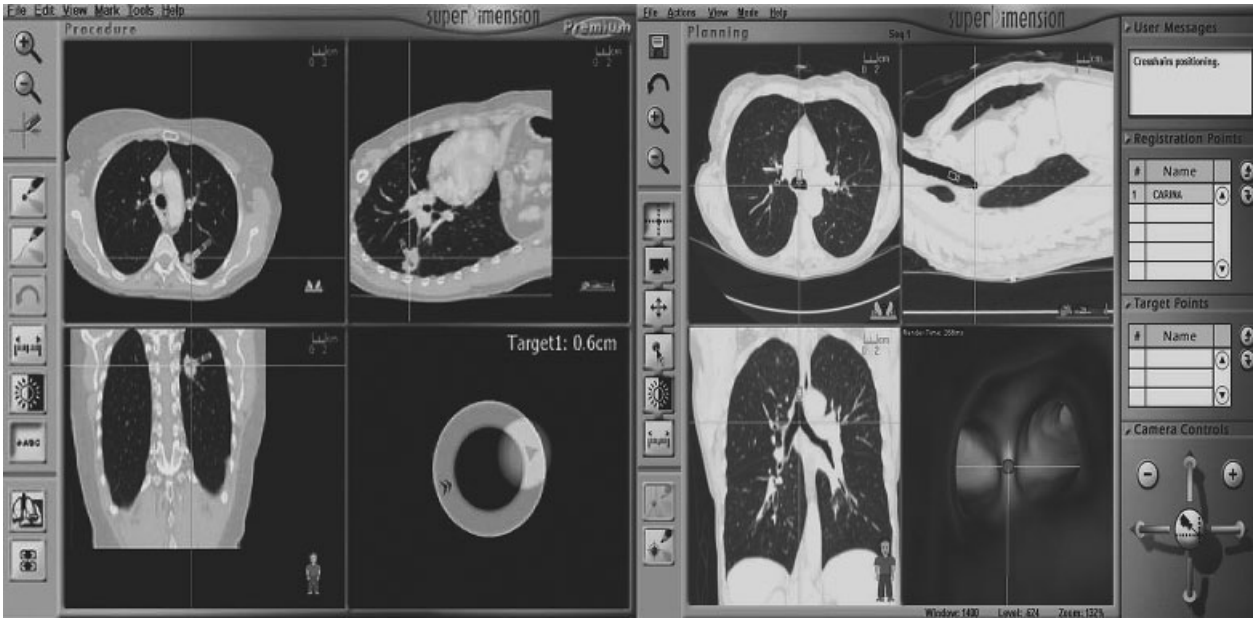

Figure 4 Electromagnetic navigation (EMN). Planning and procedure screens.

identify the exact location of the detection probe in 3 dimensions (Fig. 4). This allows the bronchoscopist to virtually navigate to a selected target (lung nodule or lymph node) with high precision. The navigation process is conducted with a steerable catheter that serves as an extended working channel for the bronchoscope (Fig. 2) Once the target is reached the catheter is left in place and the sensor is removed, allowing for insertion of a needle, brush, or biopsy forceps to obtain a sample.[36] Fluoroscopy can serve as an adjunct to verify radiographically the location of the biopsy channel in real time to avoid errors related to accidental dislodgment of the extended catheter during insertion of instruments. Radial EBUS, with extension of a probe toward the lesion can also serve this purpose and has been shown by Eberhardt et al to improve yield.[40] The technique adds ~7 minutes to the procedure, excluding the planning performed before the bronchoscopy. The diagnostic yield for EMN is 63 to 74% for peripheral lesions and 100% for lymph nodes.[34,38] With concomitant use of a radial EBUS probe to verify location of the lesion the yield is increased to ~88%,[40] whereas the yield with either EBUS probe or EMN alone for diagnosis of peripheral lesions is lower.[40] The utility of EMN is most apparent in patients who are not candidates for operative treatments or who refuse operative modalities or in whom a diagnosis was not obtained using traditional bronchoscopy or transthoracic needle aspiration.[38]

Optical Coherence Tomography and Confocal Laser Fluorescent Microscopy

This technique utilizes light reflectance to analyze tissue. OCT allows for in vivo visualization at the tissue level and allows for much better resolution than ultrasonography at those magnifications. This in turn allows for more accurate assessment of depth of invasion in in situ and locally advanced endobronchial carcinoma.[41,42] The technique has an established role in ophthalmology and has only recently been introduced to evaluate the airways.

Confocal laser fluorescence microscopy for the lungs, also called alveoloscopy, allows for microscopic views of tissue, in vivo. It utilizes a blue laser to induce fluorescence similar to autofluorescence bronchoscopy; however, the light and detector are integrated into a miniature probe that is inserted into the working channel of the bronchoscope and advanced distally as far out as into the alveolar ducts (Fig. 5). The magnification and resolution of the images is such that alveolar structures and intraalveolar cells (macrophages) can be clearly visualized.[43] This allows for evaluation at the microscopic level in vivo, a feat not possible in the past. This technology is still experimental at the present. The appearance of pathology and accuracy in detection of lung cancer have yet to be defined.

THE FUTURE

The future of bronchoscopy for lung cancer will most likely incorporate further developments in microtechnology and increases in computer processing power. This should enable the integration of these new technologies into clinically applicable devices. The approach to making an accurate diagnosis of lung cancer will likely entail combining some of the above techniques.

In conclusion, bronchoscopy is an invaluable tool in the diagnosis and staging of lung cancer. Integration

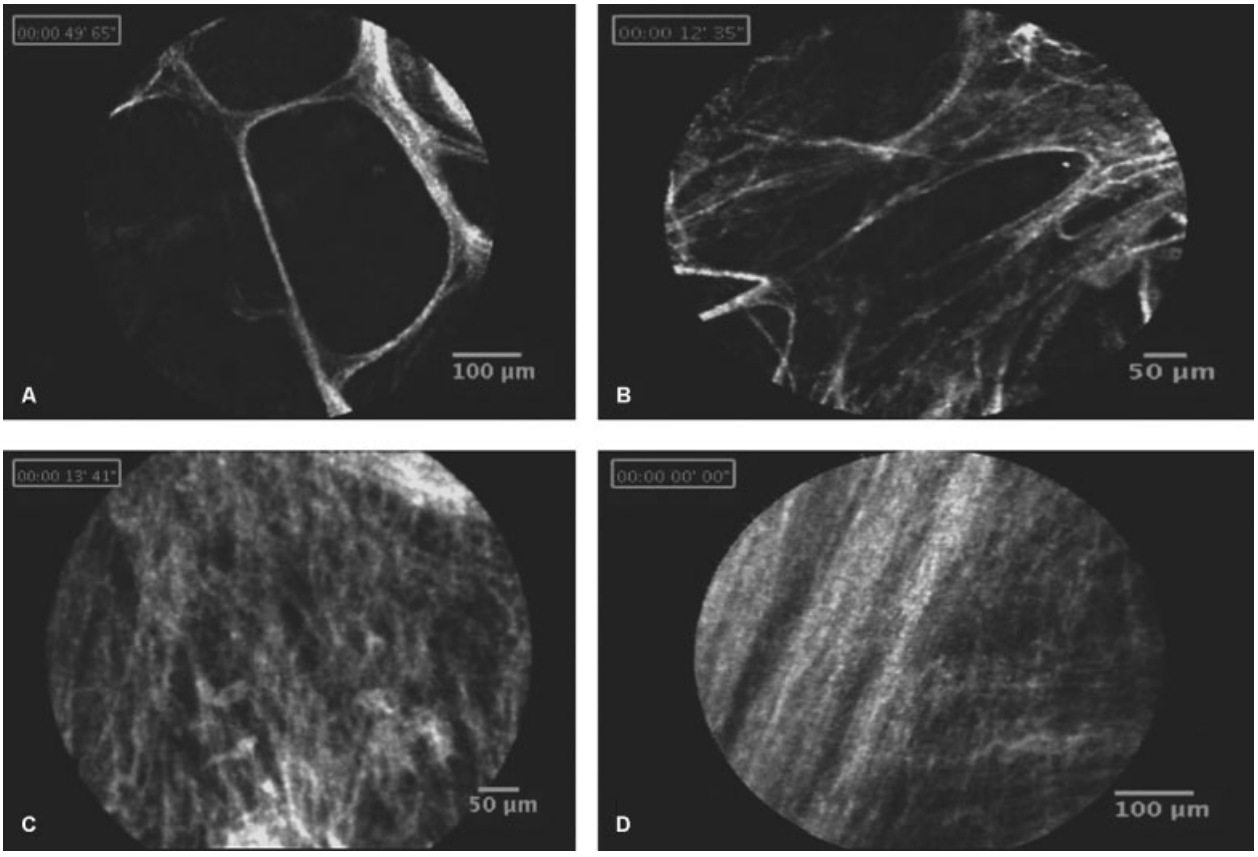

Figure 5 Confocal Fluorescent Laser Microscopy (alveoloscopy) Cellvizio (Mauna Kea Technologies, Paris). (A, B) Alveolar space. (Courtesy of Dr. Armin Ernst, Beth Israel Deaconess Hospital, Boston, MA). (C, D) Proximal bronchus. All the images are acquired by autofluorescence in the 488 nm wavelength. The main endogenous fluorophore imaged is elastin. In the alveolar space the elastin of the alveolar walls and ducts can be seen.

of radiology, electromagnetic navigation, and ultrasound technology allows for access beyond the airway and greatly facilitates adequate and accurate staging using minimally invasive approaches. Current developments will allow for investigation at the microscopic level, possibly facilitating in vivo pathological evaluation in the future. There are still many unanswered questions. How much training should be required to gain competency in these technologies? How will hospitals afford such technology? For some expensive and complicated technology, should care be regionalized? Will there be reimbursement for hospitals and physicians? Good questions for which there are few answers. Still, much progress has been made and we look forward to more advances in bronchoscopy—the procedure that defines us as pulmonologists.

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