Overview of Endobronchial Ultrasonography in Chest Medicine

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Endobronchial Ultrasonography (EBUS) can be performed using a balloon, where the probe contacts the object through a balloon filled with medium, or alternatively by a direct contact method where the probe makes direct contact with the object. We established that EBUS using 20 MHz probe shows five layers of the cartilaginous portion of the extrapulmonary bronchus and intrapulmonary bronchus, and three layers of the membranous portion. Pulmonary lesions have an echogenic texture and a sharply defined border due to a strong reflective interface between the aerated lung and the lesion. EBUS for peripheral pulmonary lesions has two main impacts in bronchoscopic diagnosis. One impact is to analyze the internal structures of peripheral pulmonary lesions, and another impact is to detect the location of peripheral pulmonary lesions during bronchoscopy. EBUS using a guide sheath (EBUS-GS) provides the pathway to peripheral pulmonary lesions. One advantage of EBUS-GS lies in the repeatability of access to the bronchial lesion for sampling. Another advantage of EBUS-GS lies in its ability to protect against bleeding into proximal bronchus from the biopsy site. The final advantage of EBUS-GS is the ability to obtain short-axis bronchial views of peripheral pulmonary lesions. For the successful EBUS with transbronchial needle aspiration EBUS-TBNA, we clarify some methods of puncturing between cartilage and obtaining adequate specimens.

KEY WORDS — depth diagnosis, EBUS-TBNA, endobronchial ultrasonography (EBUS), guide sheath, transbronchial needle aspiration (TBNA)


Introduction

Intraluminal ultrasound scanning permits scanning of intrathoracic organs and deep abdominal organs. The use of high-frequency ultrasound yields images with excellent resolution. Endobronchial ultrasonography (EBUS) is an emerging diagnostic modality that allows the bronchoscopist visual and thus diagnostic access to the majority of intrathoracic structures.

was combined with endoscopy, and endoscopic ultrasound (EUS) instruments were developed by Olympus-Aloka and the Science Research Institute. EUS was first used in clinical practice in 1982. The first reported clinical use of a narrow gauge ultrasonic probe was for intravascular ultrasonography by Pandian et al [3] in 1988. The history of EBUS began with the report by Hürter et al [4] of endobronchial ultrasonography of the lung and mediastinum in 1990. Since then, development and research has been carried out.

Balloon EBUS (EBUS Using a Balloon-tipped Ultrasound Probe)

The development of a balloon-tipped ultrasound probe designed to fit through the working channel of a bronchoscope by Drs Heinrich Becker in 1996 [5] vastly improved the efficacy and accuracy of the technique. In Japan, in many cases a balloon with the radial probe was used in the duodenum for evaluating surrounding tissue. We applied this balloon to evaluated tracheobronchial lesion via bronchoscope. Beyond the sub-sub segmental bronchus, the surface of the radial probe without the balloon attaches to the inner surface of the bronchial lumen. The currently available 20-MHz probes can scan up to about 3 cm deep into the surrounding tissues. Since the resolution and depth penetration of an ultrasonic probe is dependent on the frequency and size of the transducer, the probe needs to be selected to suit the aim of the procedure.

EBUS can be performed using either the balloon (the probe contacts the object through a balloon filled with medium) or direct contact method (the probe makes direct contact with the object) (Fig. 1). The method is usually selected according to whether the object of study is centrally or peripherally situated, and probe selection is also made according to the region being examined. When the balloon method is used, the UM-BS20-26R (Olympus Optical Co. Ltd, Tokyo, Japan) ultrasonic probe (which can be inserted in a bronchoscope instrument channel with a diameter of at least 2.8 mm) in combination with the balloon sheath (MH-676R, Olympus Optical Co. Ltd, Tokyo, Japan) is generally used. Ultrasound images are obtained by attached the endoscopic ultrasound probe to the Endoscopic Ultrasound Center (EUM-2000, EU-M30, Olympus Optical Co. Ltd, Tokyo, Japan) via the Probe Driving Unit (MH-240, Olympus Optical Co. Ltd, Tokyo, Japan).

Over last few years EBUS has been used in a variety of different ways. The initial work established the basic correlations among the histological structure, anatomic relationships, and ultrasonographic appearance of normal and abnormal airways. We were able to establish the relationship between each tissue layer of the central airways and its ultrasonographic appearance [6] (Fig. 2).
Using the balloon probe, there are some tips for getting good ultrasound images. The balloon probe was inserted into the working channel of the bronchoscope, advanced beyond the lesion, and then inflated with minimum of saline to obtain an EBUS image of the entire circumference of the bronchial wall. Orientation of the 12 o’clock position of the EBUS images did not correspond to the bronchoscopic orientation of 12 o’clock. The anatomy around the bronchus teaches us the accurate angle to rotate the EBUS image. The EBUS image therefore was rotated to the same view shown by bronchoscopic findings.

The balloon probe was withdrawn gradually for acquisition of EBUS images of the lesion and tracheobronchial wall. In order to get excellent layers of tracheobronchial wall, the bronchoscopist should control the location of the probe at the center of the balloon and assess the depth of the central tumor at the area where the top layer is the thick hyper-echoic layer. The probe needs to be located at the center of the balloon and the ultrasound wave should advance to the bronchial wall perpendicularly. The bronchial wall where the first layer is a thick hyper-echoic layer due to the reflection of ultrasound waves at the bronchial epithelium can be visualized as clear layers of the bronchial wall.

As one increases the ultrasound frequency, the resolution is higher and depth of penetration of the ultrasound decreases. The radial probe with 30 MHz shows better differentiation of the second and fourth layers than a radial probe of 20 MHz. Nakamura et al [7] compared these two types of probes using the Image Analysis Software NIH Image (National Institute of Health, USA). A normal bronchial wall image consists of five layers, and the plot profile shows a W-shape curve. A 30-MHz probe was found to be more useful than the 20-MHz probe in recognizing the laminar structures of the bronchial wall (Fig. 3).

EBUS reveals layer structures corresponding to the histopathological layers of the tracheobronchial tree. For inflammatory bronchial diseases (relapsing polychondritis, tracheobronchomalacia, Wegener’s
granulomatosis and so on), EBUS provides information about ultrasonographic luminary structures of the tracheobronchial wall. Most of these inflammatory bronchial diseases have a thickened second hypoechoic layer corresponding to submucosal tissue of both the cartilaginous and membranous portion. But relapsing polychondritis has a thickened second hypoechoic layer of the cartilaginous portion and a normal membranous portion. EBUS also shows the thickness of the bronchial cartilage. In inflammatory bronchial diseases, inflammation would occur at the thickened or destroyed bronchial cartilage.

EBUS has been employed with increasing frequency in therapeutic bronchoscopy as well. It has being used to identify major vascular structures [8] before and during debulking procedures in the airway. In patients with centrally located early stage lung cancer, and before photodynamic therapy, it can assess the depth of tumor invasion and thus potentially improve the rate of complete remissions [6,9]. EBUS appears significantly more accurate in determining the depth of tumor invasion when compared with both visual inspection and current standard, high resolution CT [10]. EBUS is also establishing its utility in other interventional procedures. A recent paper [8] evaluated the ability of EBUS to alter, guide, or change therapeutic bronchoscopic procedures in real-time. Over a 3-year period, EBUS was employed in 1,174 interventional bronchoscopies. The authors found that it alerted therapy
roughly 43% (505/1,174) of the time. We believe that the accumulated evidence suggests that the development of EBUS should be, at minimum, considered as part of any interventional bronchoscopy.

EBUS is sometimes available to evaluate whether central intrathoracic tumors invaded to bronchial tree or not. Herth et al [11] studied the utility of EBUS for differentiating between airway infiltration and compression by a tumor. Sensitivity, specificity, and an accuracy using EBUS were 89%, 100%, and 94%, respectively. Sensitivity, specificity, and an accuracy using CT were 75%, 28%, and 51%, respectively. EBUS is a highly accurate diagnostic tool and superior to chest CT in evaluating the question of airway involvement by central intrathoracic tumors.

Direct Contact Method (EBUS Without the Balloon Sheath)

Internal structures of peripheral pulmonary lesions by EBUS

Endoscopic ultrasonography (EUS) has been used to examine the internal structure of the pancreas, and the results have been correlated with histopathology in cases of cystic tumors, calcifications, and pancreatic stones [12,13]. Internal structures of peripheral pulmonary lesions as visualized by EBUS correlated these findings with the histopathology [14]. The lesions in well-differentiated adenocarcinoma had homogeneous internal echoes overall, but some hyperechoic dots (less than 1 mm in size) also were observed reflecting residual air in invaded alveoli. The distribution of the hyperechoic dots was irregular, and the margins of the lesions also were irregular. Blood vessels could be seen coursing through the lesion (Fig. 4). In most cases of moderately differentiated adenocarcinoma and squamous cell carcinoma, the EBUS images showed obstruction of blood vessels within the lesion, obstruction of bronchi, heterogeneous internal echoes, and irregular margins. In several cases of squamous cell carcinoma, numerous echo-free areas of various sizes were noted, and their distribution corresponded to areas of necrosis. In cases of poorly differentiated adenocarcinoma, EBUS revealed few patent blood vessels or bronchi, heterogeneous internal echoes, or irregular margins. In some cases of small cell carcinoma, the tumor had directly invaded the pulmonary artery adjacent to the affected bronchus, resulting in stenosis of the pulmonary artery within the lesion. Comparing EBUS images and histopathological findings, EBUS shows bronchioles, vessels, calcifications, bleeding, mucus plugs in the bronchus, necrosis, and air in peripheral pulmonary lesions (Fig. 5). Hürter et al [15] reported successful visualization of peripheral lung lesions in 19 of 26 cases, and Goldberg et al [16] reported that EBUS provided unique information that exceeded other diagnostic modalities in 18 of 25 cases (including six peripheral lesions and 19 hilar tumors).

Hosokawa and colleagues [17] reported a typical EBUS pattern of neoplastic disease was 1) a continuous marginal echo, 2) a rough internal echo, and 3) no hyperechoic spots corresponding to bronchi, or if there were any, there was no longitudinal continuity. Kuo and colleagues [18] assessed the feasibility of EBUS in differential diagnosis between malignant and benign lesions by the following three characteristic echoic features indicating malignancy: a continuous margin; absence of a linear-discrete air bronchogram; and heterogenous echogenicity. The negative predictive value for malignancy of a lesion with none of three echoic features is 93.7%. The positive predictive value for malignancy of a lesion with any two of three echoic features is 89.2%. Kurimoto and colleagues [14] reported a classification system with the aim of distinguishing between benign and malignant diseases, identifying the type of lung carcinoma and determining the degree of differentiation. The lesions were typed based on the internal echoes (whether homogenous or heterogenous), vascular patency, and the morphology of the hyperechoic areas (reflecting the presence of air and the state of the bronchi). Factors indicating malignancy were heterogenous internal echo, obstructive vessels, and obstructive bronchi. A homogenous pattern (Type I) was overwhelmingly benign (92%), whereas hyperechoic dots or a heterogenous pattern
Type II and III, respectively) portended malignancy in 98 of 99 cases (99%), (Fig. 6).

Detection of the location of the peripheral pulmonary lesion

EBUS can be used to assist transbronchial biopsy (TBB) of peripheral pulmonary lesions. Because the air content of the lung parenchyma completely reflects the ultrasound signal, and pulmonary masses can be precisely located by EBUS. EBUS-guided TBB of peripheral pulmonary lesions has been shown to yield a similar success rate as fluoroscopy guidance [19]. A large-scale, prospective, randomized study to compare EBUS-guided TBB with TBB in patients with lesions < 3 cm has been performed with good results [20]. In lesions > 3 cm, there were no significant differences in the diagnostic ability between the two procedures. However, in lesions < 3 cm and < 2 cm, a considerable decrease in TBB sensitivity (31% and 23%) was seen, whereas EBUS-guided TBB maintained its sensitivity (75% and 71%).

More recently, studies have shown the efficacy of a new procedure, EBUS using a Guide Sheath (EBUS-GS), for sampling of peripheral lesions to increase the diagnostic yield of TBB under EBUS guidance [21] (Fig. 7). A guide sheath covered the miniature radial probe and is then advanced through the working channel of a therapeutic bronchoscope with the probe tip outside the sheath until the lesion is visualized. Under fluoroscopy, the sheath

Fig. 4. A representative case of well-differentiated adenocarcinoma. The lesions in well-differentiated adenocarcinoma had homogeneous internal echoes overall, but some hyperechoic dots (less than 1 mm in size) also were observed reflecting residual air in invaded alveoli. The distribution of the hyperechoic dots was irregular, and the margins of the lesions also were irregular. Blood vessels could be seen coursing through the lesion (arrow).
is held in place while the EBUS probe is withdrawn. An instrument such as a brush, needle, or biopsy forceps is then inserted through the sheath and the lesion is sampled. EBUS-GS increases the reliability of specimen collection via bronchoscopy. Diagnostic yields of bronchoscopy for peripheral pulmonary lesions less than 2 cm in published reports have varied from 5 to 28% [22–30]. When an undetectable lesion under fluoroscopy is in contact with the probe inserted inside the bronchus, the lesion is visualized by EBUS, and EBUS-GS is particularly useful for lesions ≤20 mm that are undetectable by fluoroscopy. EBUS-GS was most successful when the probe could be placed within the lesion (Fig. 8). The yield of TBB acquired when the probe was adjacent to the lesion was very low. This suggests that the lesions visualized as adjacent to the probe may only be in contact with the outer surface of the bronchus, and therefore sampling is unlikely to be diagnostic.

At the first approach to the target lesion, the probe may not reach it in about 10% of all cases of EBUS-GS. To resolve this problem, the bronchoscopist withdraws the probe and inserts the curettage into the guide sheath. The tip of the curettage is able to be angulated and search the correct bronchus.

One advantage of EBUS-GS lies in the repeatability of access to the bronchial lesion for sampling. Without a guide sheath, it can be difficult at times to be certain that the forceps are being inserted into the same bronchial branch for the second biopsy. Further, the bronchial mucosa becomes edematous after several attempts at manipulation, and it can be difficult to insert the forceps into the bronchus. Another advantage of EBUS-GS lies in its ability to protect against bleeding into proximal bronchus from the biopsy site. Although massive hemorrhage following TBB is not frequent (<2%) [29–32] in the bronchus, excessive bleeding may require hemostasis by wedging in the tip of the bronchoscope. If bleeding occurs during EBUS-GS, blood drains through the sheath, because the outer surface of the sheath is snug against the internal surface of the bronchus. Our EBUS method using a 20 MHz probe allowed visualization of the inner structures of peripheral lesions, including vessels, bronchi, calcifications, necrosis, hemorrhage, and bronchial dilatation [30].

Many reports have been published recently. Yang [33] evaluated whether EBUS may improve the diagnostic yield of transbronchial biopsy in peripheral lung cancer. The diagnostic accuracy of transbronchial lung biopsy (TBLB) was significantly increased under EBUS guidance in small cell carcinoma (88.9%) and for non-small cell carcinoma (67.7%) than without EBUS for small cell carcinoma (22.2%) and for non-small cell carcinoma (50.0%). Under EBUS guidance, the diagnostic yield of TBLB in peripheral lung cancer was significantly improved without EBUS.

Yoshikawa [34] evaluated the feasibility and efficacy of transbronchial biopsy (TBB) and bronchial brushing by EBUS with a guide sheath (GS) as a guide for diagnosing peripheral pulmonary lesions (PPLs) without radiographic fluoroscopy. Seventy-six of 123 PPLs (61.8%) were diagnosed by EBUS-GS guidance without fluoroscopy. The diagnostic yield for PPLs >20 mm in diameter (75.6%) was significantly higher than that for those ≤20 mm in diameter. The PPLs located in the middle lobe and the lingular segment had significantly higher diagnostic yields (p < 0.05). Multivariate analysis revealed that the diameter and location of the PPL were independent predictors of
Fig. 6. Classification of peripheral pulmonary lesions by EBUS. Type I: homogeneous pattern; Type Ia: homogeneous pattern with patent vessels and patent bronchioles; Type Ib: homogeneous pattern without vessels and bronchioles; Type II: hyperechoic dots and linear arcs pattern; Type IIa: hyperechoic dots and linear arcs without vessels; Type IIb: hyperechoic dots and linear arcs with patent vessels; Type III: heterogeneous pattern; Type IIIa: heterogeneous pattern with hyperechoic dots, and short lines; Type IIIb: heterogeneous pattern without hyperechoic dots and short lines.
diagnostic sensitivity by EBUS-GS-guided bronchoscopy.

Fielding and colleagues [35] compared the diagnostic yields and pneumothorax rate of EBUS-GS and CT FNA in terms of the location of the lesion needing biopsy, in particular, whether the lesion was touching the pleura. For EBUS-GS, 140 cases were carried out with mean lesion size 29 mm. Overall diagnostic sensitivity was 66%. For lesions not touching visceral pleura it was 74% compared with 35% where it was on the pleura. For CT FNA 121 cases were carried out with mean size 37 mm. The overall diagnostic sensitivity was 64%. The rate of pneumothorax and inter costal catheter placement in EBUS-GS was 1 and 0% and in CTFNA it was 28 and 6%, with \( p < 0.001 \) for both. Lesion location, in particular, connection to the visceral pleura, can improve decision making in referral for either CT FNA or EBUS-GS to maximize diagnostic yields and minimize pneumothorax rate.

In recent years, two methods of navigation for peripheral pulmonary lesions have been developed. The electromagnetic navigation system is a localization device that assists in placing endobronchial accessories in the desired areas of the lung. This system uses low-frequency electromagnetic waves, which are emitted from an electromagnetic board placed under the bronchoscopy table mattress [36]. Harms and colleagues [37] reported the technical note introduced a new approach for the treatment
of inoperable peripheral lung tumors by combining the electromagnetic navigation system and EBUS with 3D-planned endobronchial brachytherapy. Asano and colleagues [38–40] developed a bronchoscope insertion guidance system that produces virtual images by extracting the bronchi by automatic threshold adjustment, and searching for the bronchial route to the determined target. They used this system in combination with a thin bronchoscope and EBUS-GS. The system automatically produced virtual bronchoscopy to median of fifth-order bronchi. EBUS visualized 93.8% of cases successfully, and 84.4% could be pathologically diagnosed. Using the bronchoscope insertion guidance system, virtual images can be readily produced, and the bronchoscope can be successfully guided to the target. This method is promising as a routine examination method in the biopsy of peripheral pulmonary lesions.

**EBUS Guided TBNA**

EBUS enables the bronchoscopist to visualize the mediastinal lymph nodes and surrounding mediastinal structures. Recently several studies in both EBUS-TBNA scope guided TBNA and EBUS probe guided TBNA have shown significant increases in yield and decreases in the number of punctures required to make a diagnosis.

A convex bronchoscope (BF-UC260F, 7.5 MHz, convex type, Olympus Optical Co, Ltd, Tokyo, Japan) with an outer diameter of 6.9 mm is available in many countries. The bronchoscope with the convex probe is connected to an Endoscopic Ultrasound System (EU-C6000, Olympus Optical Co, Ltd). The needle is 22G (NA-201SX, Olympus Optical Co, Ltd) and is also widely available.

For a successful TBNA procedure to be accomplished one must overcome some challenges. One challenge is not to puncture the bronchial cartilage with the needle. The angle of the needle outside of the bronchoscope is oblique toward the tracheobronchial tree, and then the space between bronchial cartilages is very narrow. After the needle is inserted into the working channel of the bronchoscope, one must watch the edge of the outer sheath just jut out of the bronchoscope. The outer sheath is pushed toward the bronchial wall, and is located at the membranous part between bronchial cartilage. Then the needle is pushed against the tracheobronchial wall and the needle, containing the partially withdrawn stylet, is then advanced into the target lesion under constant ultrasound guidance.

In order to get adequate specimens, the stylet is an important part of the needle. While the needle is inserted into the lesion, the stylet is pushed and repositioned before it is withdrawn, in order to push out the primary tissue plug containing superficial layers and bronchial cartilage from the needle. After the needle is removed from the bronchoscope, the stylet is inserted into the needle once again to push out the specimens onto the filter paper.

The suction is then equilibrated while the tip of the needle is still in the lesion. If the needle is withdrawn whilst suction is in effect, bronchial epithelium and submucosal tissue may be pulled into the needle and cause contamination.

The power Doppler mode of this bronchoscope visualizes major vessels, bronchial arteries outside the bronchial wall, and vessels in the lymph nodes. The power Doppler mode would reduce complications due to puncturing vessels. Because the internal echo of the lymph node on the B mode is hypoechoic, the differentiation between major vessels and lymph nodes is sometimes difficult. The bronchoscopists should avoid puncturing major vessels and bronchial arteries outside lymph nodes. Vessels in metastatic lymph nodes wind irregularly and vessels in sarcoidosis run straight inside lymph nodes. On ultrasonographic images in the B mode, necrotic tissue in the lymph node is difficult to differentiate from a viable area of the lymph node. Vessels are rare in the necrotic tissue and so the bronchoscopist should puncture the hypervascular area in the target lymph node.

Mediastinoscopy is the gold standard of assessing metastatic mediastinal lymph nodes. Although EBUS-TBNA is a less invasive procedure than
mediastinoscopy, more large studies should be necessary for assessing the superiority of either of these two procedures.

**Future Direction**

*Evaluation of the depth of invasion of tracheobronchial tumors*

Endobronchial therapies are indicated for tracheobronchial tumors that have not invaded as far as the tracheobronchial cartilage, in other words, are confined to the mucosa or submucosal tissue. Endobronchial ultrasonography (EBUS) is presently the most useful method of determining the depth of tumor invasion. Tissue resolution improves as the frequency of the ultrasonic transducer increases, providing clear and detailed ultrasonic images. Ultrasonic probes are presently available at two frequencies, 20 and 30 MHz, but in the future we anticipate the development of even higher frequency probes. Radial probes now in use are mechanical radial probes, meaning that images are obtained by physically rotating the probe through 360°. The development of electronic scanning will provide even better images, giving a 360° profile without having to move the probe.

Radial scanning provides a two-dimensional image, but we can now obtain three-dimensional images by withdrawing the probe at a constant speed while scanning. Large balloons required to make this method more practical do not exist at present, but we anticipate that they will become available in the future.

*EBUS for peripheral pulmonary lesions*

At present, we use a 4 mm diameter endoscope with a 2 mm working channel, through which we pass a guide sheath and ultrasonic probe, 2 mm in outer diameter, into the bronchial tree. In the future, we hope to pass even narrower bronchoscopes into ever more peripheral bronchi, detecting early lesions using narrower gauge guide sheaths and ultrasonic probes. Cytology and tissue biopsies are presently taken under fluoroscopic control, but we would like to be able to watch the real-time EBUS image as we take specimens.

*EBUS guided transbronchial needle aspiration (EBUS-TBNA)*

B mode images obtained using a convex probe remain poor in quality, so we await improvements in ultrasonographic equipment that will provide better quality ultrasonic images. The main advantage of using convex probes is the ability to utilize Doppler modes, at present only power Doppler, although in the near future the introduction of a pulse Doppler is expected to allow Fast Fourier Transform (FFT) analysis of blood flow.

It is difficult to retrieve large tissue samples using EBUS-TBNA, but this problem may come close to resolution with the development of larger needles. There are limitations to the size of the endoscope working channel however that are difficult to reconcile with the need for larger diameter needles.

**References**

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