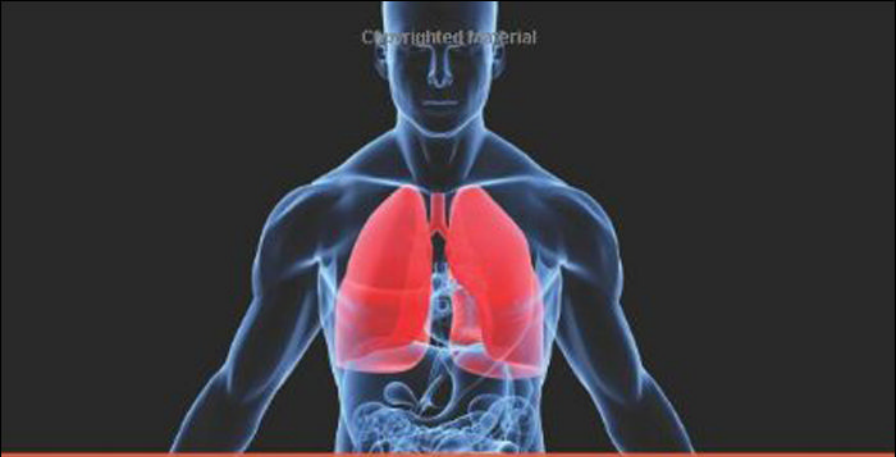

# ENDOBRONCHIAL ULTRASONOGRAPHY

NORIAKI KURIMOTO | DAVID I.K. FIELDING | ALI I. MUSANI


WILEY-BLACKWELL

# Endobronchial Ultrasonography

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- A searchable database of 36 video clips showing procedures described in the text
- All clips are referenced in the text where you see this icon:

# Endobronchial Ultrasonography


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# Contents



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Noriaki Kurimoto MD
To my wife and children:
Mayumi, Satoshi, Wataru, Misturu, and Manabu

David Fielding MD
To my wife and children:
Siobhan, Josie, Alison, Eveline, and Michael

Ali I. Musani MD
To my wife and children:
Lubna, Sara, and Sef

# Foreword

How nice it is for us to be able to learn from this textbook the up-to-date knowledge and techniques of echobronchoscopy.

The main part has been written by Professor N. Kurimoto. The few years during which I worked with Dr. Kurimoto in the Department of Chest Surgery St. Marianna Univerisity School of Medicine was very fruitful, especially because we could feel that we were contributing to our specialty by developing the theory and technique of echobronchoscopy. As soon as Dr. Kurimoto joined us, it became routine for a lobe just removed in the theater to reach the pathology section by being carried in Dr. Kurimoto's own hands for a redo echobronchoscopy.

This book shows what those lobes have taught us regarding how exact the preoperative diagnosis had been, or why the original lesion had been undiagnosed. The essence of this book is the product brought about by a tireless and enthusiastic surgeon, Dr. Kurimoto, whom I thank for his friendship and encouragement, which I will always appreciate.

The two coauthors, Drs. D. Fielding and A. Musani, are both leading bronchoscopists, and good friends of mine. Many times we shared knowledge and desire in the bronchoscopy, especially in echobronchoscopy, with each other at St. Marianna University. I am in the position to congratulate an epoch making publication in this attracting field.

Hiroaki Osada, M.D.
Professor Emeritus
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Chair of the World Association for Bronchology
and Interventional Pulmonalogy
August, 2010

# Preface

Gastrointestinal and genitourinary ultrasound technologies have gone through dramatic improvements and growth over the last three decades. However, the pulmonary applications of ultrasound, endobronchial ultrasound (EBUS), started much later, in the early 1990's.

In the first half of this book we present a comprehensive review of the principals of ultrasound and its application in thoracic medicine. We summarize mediastinal anatomy, the basic technique of needle aspiration of lymph nodes, and how to perform successful endobronchial ultrasound guided transbronchial aspiration. We also discuss the use of peripheral ultrasound for the localization of pulmonary nodules, and the role of endobronchial ultrasound in interventional pulmonology. This book is an evidence- based reflection of our collective experience of hundreds of thousands of cases.

The second half of this book focuses on the correlation of EBUS images with the histology and pathology of mediastinal lymph nodes and pulmonary nodules. In our experience, careful and methodical analysis of ultrasound images of these structures could predict the benign vs. malignant nature of these structures with significant sensitivity and specificity.

Endobronchial ultrasound has truly revolutionized the diagnosis and staging of lung cancer and many other diseases of the mediastinum and lungs. We feel honored to have been a part of its development and dissemination.

We sincerely hope that our book will help physicians learn the technique of endobronchial ultrasound and its applications to its fullest.

We would like to thank Mr K. Hirooka and Mr K. Nishina of the Ultrasound Development Group at Olympus Optical Co. Ltd, and Ms. Cathryn Gates of Wiley-Blackwell for her editing assistance. We would also like to express our gratitude to Dr F. Tanaka of the Hyougo Medical University Department of Thoracic Surgery and Dr R Amemiya of the Ibaraki Prefectural Central Hospital for the illustrations used in this book. Without their invaluable assistance, this book would not have been possible.

*August 2010*
*Noriaki Kurimoto*
*David I. K. Fielding*
*Ali I. Musani*

# 1 An Overview of Endobronchial Ultrasonography

## Introduction (A History of Endobronchial Ultrasonography)

Endobronchial ultrasonography (EBUS) is a diagnostic modality whereby a miniature ultrasonic probe is introduced into the bronchial (tracheal) lumen, providing tomographic images of the peribronchial (peritracheal) tissue. Endoscopic ultrasonography (EUS) is already an indispensable technique for examining the gastrointestinal tract, particularly the stomach and large intestine. Applications of EUS include assessment of the depth of tumor invasion, detection of lymph node metastases, tumor staging, and fine needle aspiration (FNA) under EUS guidance.

The first reported clinical use of a narrow gauge ultrasonic probe was for intravascular ultrasonography by Pandian et al. [1] in 1988. The history of EBUS began with the report by Hürter et al. [2] of endobronchial ultrasonography of the lung and mediastinum in 1990. Since then, development and research has been carried out mainly by Becker (Germany) and ourselves (Japan).

EBUS probes are typically of the 20 MHz radial type. Tissue penetration of the ultrasound waves is therefore of the order of 2–3 cm, in other words, EBUS provides a tissue cross-section image with a radius of 2–3 cm centered on the trachea or bronchus.

Some important EBUS reports include the following:

**1** Hürter 1990. Endobronchial sonography in the diagnosis of pulmonary and mediastinal tumors [in German] [2].

**2** Iizuka 1992: Evaluation of airway smooth muscle contractions in vitro by high-frequency ultrasonic imaging [3].

**3** Ono 1992: Bronchoscopic ultrasonography in the diagnosis of lung cancer [4].

**4** Goldberg 1994: US-assisted bronchoscopy with use of miniature transducer-containing catheters (delineation of central and peripheral pulmonary lesions) [5].

**5** Becker 1995: Endobronchial ultrasonography – a new perspective in bronchology? (tracheobronchial wall 7-layer structure) [6].

**6** Kurimoto 1999: Assessment of usefulness of endobronchial ultrasonography in determination of depth of tracheobronchial tumor invasion (tracheobronchial wall 5-layer structure) [7]

Based on these studies, the present applications of EBUS are:

**a** Determination of the depth of tumor invasion of the tracheal/bronchial wall (allocation of patients to localized endobronchial treatments such as photodynamic therapy (PDT).

**b** Identification of the location of a peripheral lung lesion during bronchoscopic examination (more accurate than fluoroscopy in determining contact between lesion and bronchus, thereby reducing abrasions, the time to determine biopsy sites and duration of fluoroscopy).

**c** Qualitative diagnosis of peripheral lung lesions and differentiation between benign and malignant lesions.

**d** Determination of position and shape of peribronchial structures, particularly lymph nodes (at the time of transbronchial needle aspiration).

**e** Determination of spatial relationship between bronchus and lesion in the short axial image of the bronchus (if the bronchus is situated near the center of the lesion, the lesion may have arisen from the bronchus).

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By Noriaki Kurimoto, David I. K. Fielding and Ali I. Musani.
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Problems arising from the application of EBUS until now, and the results of studies, include the following:

**1** Standardization of how the layers in the tracheobronchial wall structure are interpreted (how many layers do you see?).

**2** Changes in the layer structure of the tracheobronchial wall with the use of higher frequencies, e.g. 30 MHz.

**3** Evaluation of the accuracy of qualitative diagnosis, and differentiation between benign and malignant lesions, from EBUS images of peripheral lung lesions.

**4** Evaluation of peribronchial lymph node metastases.

**5** Comparison of the diagnostic accuracy of EBUS-guided FNA and unguided FNA cytology and histology.

**6** A worldwide standard nomenclature for this technique.

EBUS allows us to examine the state of the bronchial wall and extramural tissue that we are unable to visualize with bronchoscopy alone. This book will present an overview of EBUS with reference to actual clinical cases.

## Principles of Ultrasonography

### What is A Sound Wave?

#### Definition of Ultrasound

In general, ultrasound refers to sound wavelengths greater than 20 MHz that cannot be heard by the human ear. There are considerable variations in the range of frequencies audible to humans, however, so we often define sounds in terms of their purpose. In this case, ultrasound is "sound not intended for humans to hear".

#### Frequency and Wavelength

The frequency of a sound tells us whether it is high or low in pitch. The unit of frequency is hertz (Hz), defined as the number of oscillations per second. For example, a sound with a frequency of 20 MHz has $20 \times 10^6$ oscillations per second. Medical ultrasound equipment produces sounds with a frequency between 2 MHz and 50 MHz. The wavelength is the length of a soundwave, and varies inversely with the frequency, so the higher the frequency the shorter the wavelength (Figure 1.1).

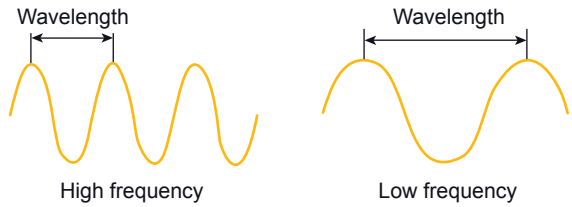


**Figure 1.1** Relationship between frequency and wavelength.

#### Speed of Sound

Sound travels through a variety of materials such as air and water (hereafter media), and the speed at which it travels through each medium is the speed of sound for that medium. The speed of sound through the human body is generally considered to be 1530 m/s, although the actual speed of passage varies for different organs and tissues.

### Production of Ultrasound Images

#### Transmitting and Receiving Ultrasound Waves (Figure 1.2)

Ultrasonic probes used in medical ultrasonography use a sensor that transforms electrical signals into ultrasound, and ultrasound into electrical signals. When an electric signal is applied to the electrode of the ultrasonic transducer (also oscillator/transformer), ultrasound waves are transmitted from the surface of the device, and when ultrasound waves are received by the device surface, an electrical signal is generated.

#### Propagation and Attenuation of Ultrasound Waves

The ultrasound waves produced by the ultrasonic transducer travel through a medium; this is called propagation. As the soundwave is propagated, the energy of its oscillations is absorbed and scattered, and becomes steadily weaker. This phenomenon is called attenuation. In general, the higher the frequency, the greater is the attenuation rate. Medical ultrasonography equipment uses high frequencies that do not propagate well through the air due to the high attenuation ratio. A medium such as water is therefore needed between the ultrasonic transducer and the object of study to allow efficient propagation of ultrasound waves.

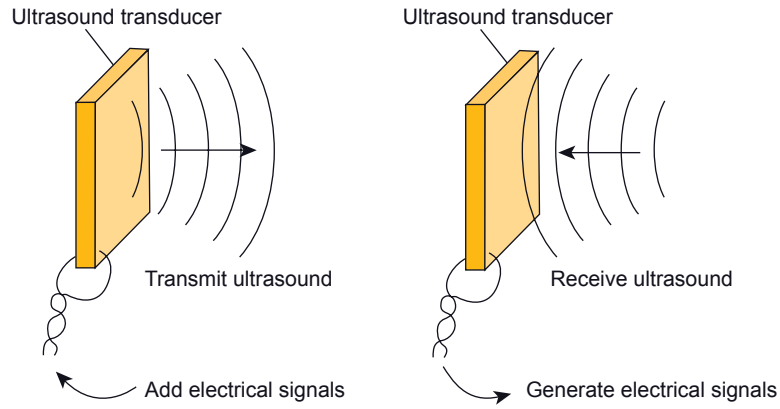


**Figure 1.2** Transmitting and receiving ultrasound waves.

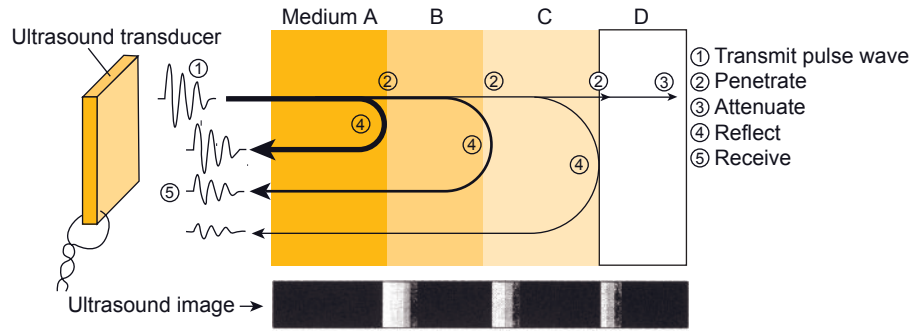


**Figure 1.3** How an ultrasound image is made.

### Reflection and Penetration

As with light, a proportion of ultrasound waves are reflected at the boundary between different media, and a proportion penetrate the boundary. The ultrasonic processor uses these reflections to construct images.

The ultrasonic transducer emits pulses of ultrasound, and receives the ultrasound pulses reflected from the boundaries between media (Figure 1.3). The ultrasonic processor calculates the positions (distance from the probe) of boundaries between media based on the time between transmitting and receiving ultrasound pulses, and converts the strength of the returning pulses into the brightness of the image.

Following the above steps alone gives information about a body along a single line, so we obtain a two-dimensional image by moving the ultrasonic transducer (mechanical scanning) or using a linear array of multiple ultrasonic transducers that sequentially emit and receive ultrasound pulses (electronic scanning). This method of ultrasound imaging is called B-mode (B is for brightness).

## Resolution

### Axial Resolution

An ultrasound pulse wave has a definite length, so a boundary between media has a definite width on an ultrasound image. If we reduce the distance between the two boundaries of a medium, the pulse waves from the two boundaries will overlap, making it difficult to distinguish the two boundaries on the ultrasound image. The ability to distinguish between objects on an ultrasound image is called the resolution, and the resolution in the direction traveled by the ultrasound pulse is the axial resolution. In general, the higher the frequency the shorter the ultrasound pulse, so distance resolution improves with higher frequencies (Figure 1.4).

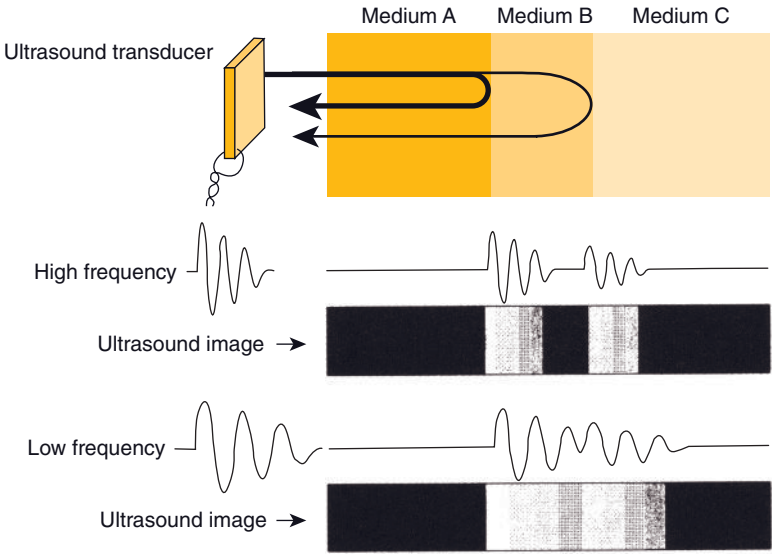


**Figure 1.4** Difference in axial resolution between different frequencies.

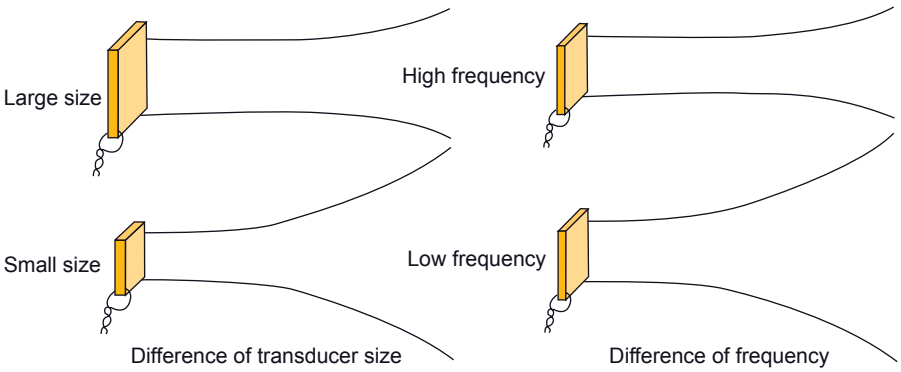


**Figure 1.5** Pulse wave spreading.

## Lateral Resolution

Resolution in the direction perpendicular to the direction traveled by the ultrasound pulse, in other words in the direction the probe moves or in the direction of the array of transducers, is called the lateral resolution. The ultrasound pulse wave emitted by the transducer gradually spreads out as it propagates through a medium. The degree of spread depends on the transducer size (aperture area) and the frequency. As the transducer size and/or frequency increases, the degree of spreading decreases (Figure 1.5). Lateral resolution improves with decreased spread (Figure 1.6).

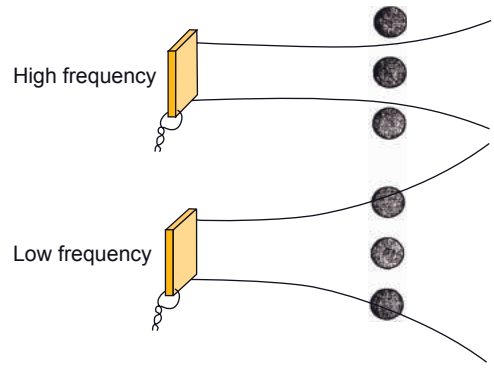


**Figure 1.6** Lateral resolution.

## Depth Penetration

Ultrasound waves are attenuated as they propagate through a medium, so they can only reach a certain distance. Ultrasound images can therefore only be attained for a certain distance from the ultrasonic probe. This distance is called the depth penetration (or penetration). The depth penetration also depends on the frequency and the transducer size (aperture area). The attenuation rate of an ultrasound wave increases as its frequency increases, so depth penetration improves as the frequency decreases (Figure 1.7). As the aperture area of the ultrasonic transducer increases, it can emit a stronger pulse, and it can also convert weaker received pulses into electrical signals. Depth penetration therefore increases as the transducer size increases.

## Image Quality Adjustment

Even when using an ultrasonic probe appropriate to the task, its abilities cannot be fully harnessed unless appropriate image quality adjustment is performed. The fundamentals of image quality adjustment are gain, contrast and sensitivity time control (STC).

## Gain

Gain, also called brightness, is the mechanism for adjusting the overall brightness of the ultrasound image. Adjustment of the gain increases or decreases the entire ultrasound signal (the signal from the ultrasonic transducer converted for display on the monitor) evenly. Changes in the gain make the entire image brighter or darker, but do not alter the differences in brightness between light and dark sections of the image (Figure 1.8).

## Contrast

Contrast is the mechanism for adjusting the difference in brightness between light and dark sections of the image. Adjustment of the contrast makes the greatest changes in the sections of the image with the strongest

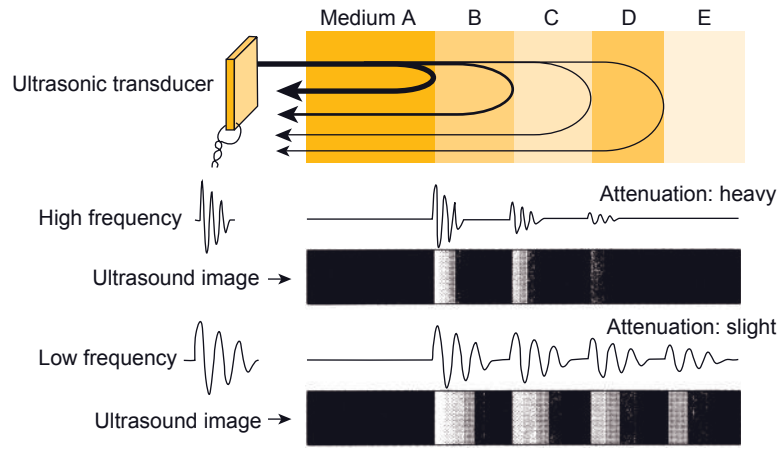


**Figure 1.7** Differences in depth penetration at different frequencies.

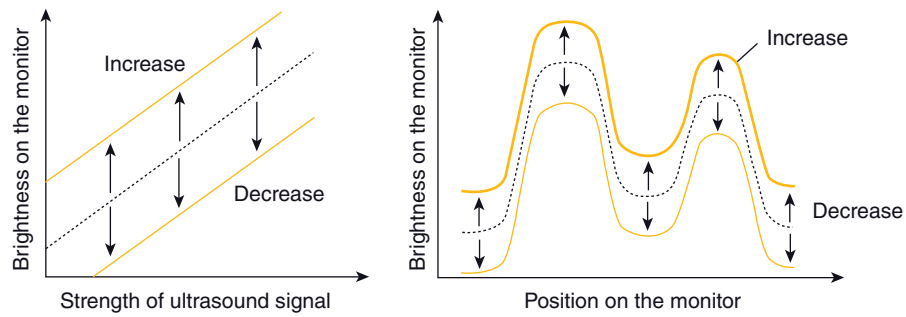


**Figure 1.8** Adjustment of gain (brightness).

ultrasound signal, in other words changing the contrast mainly alters the brightness of the lighter sections of the image, and the darker sections are changed but little. Increasing the contrast of an ultrasound image yields an image with enhanced differences between light and dark areas, whereas decreasing the contrast yields an image with minimal differences between light and dark areas (Figure 1.9).

## Sensitivity Time Control

Sensitivity time control (STC) also known as time gain compensation (TGC), is the mechanism for adjusting the gain according to the distance (depth) from the ultrasonic probe. As shown in Figure 1.7, attenuation of the ultrasound wave increases with the distance from the probe, so ultrasound signals from distant (deep) regions are weaker than those from near (shallow) regions. In order to correct this and make the overall image as even as possible, the ultrasonic processor amplifies the ultrasound signal according to the current distance from the probe (the time for the ultrasound pulse to return to the transducer) (Figure 1.10). By altering the degree of amplification, adjustment of STC can make the ultrasound image lighter or darker according to the distance from the probe (Figure 1.11).

## Procedure for Image Quality Adjustment

Image quality adjustment should be conducted in accordance with the properties of the ultrasonic processor, monitor and printer. Adjustment of gain (brightness) and contrast are performed in the following manner:

**1** Switch on the system, and bring up an image on the monitor (Figure 1.12).

**2** Adjust the brightness and contrast controls of the monitor so that the gray scale bar in the ultrasound image is displayed with smoothly varying gradations (Figure 1.13).

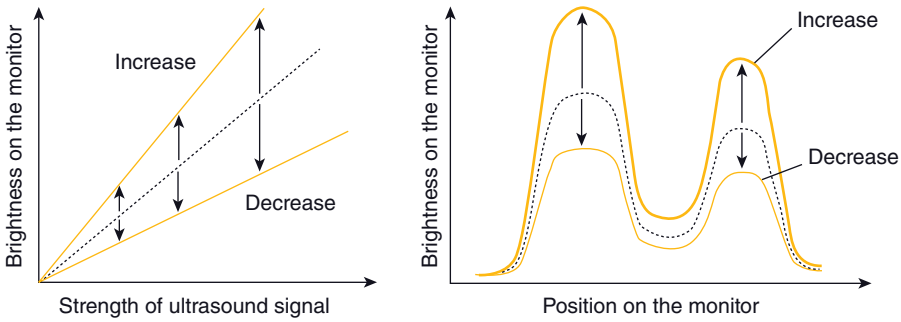


**Figure 1.9** Adjustment of contrast.

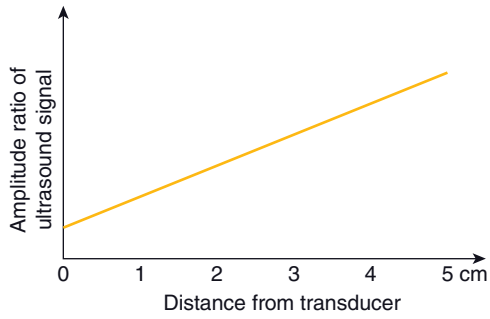


**Figure 1.10** STC default settings.

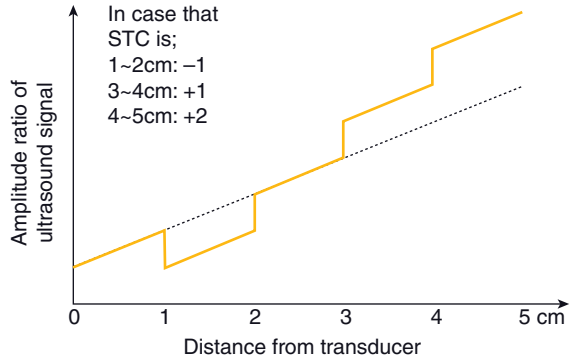


**Figure 1.11** Adjustment of STC.

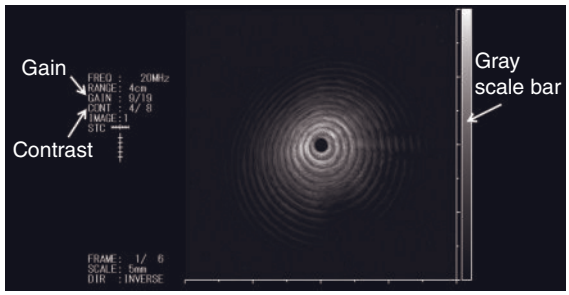


**Figure 1.12** Monitor image (EU-M2000 endoscopic ultrasound system).

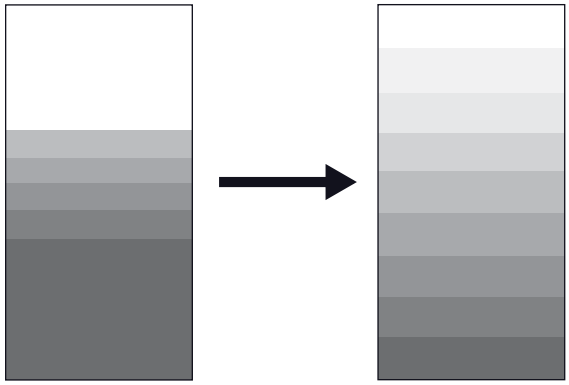

**Figure 1.13** Adjustment of gray scale bar.

**3** Adjust the brightness and contrast controls of the printer so that the gray scale bar in the printed image corresponds closely to the monitor image.
**4** Adjust the gain, contrast and STC of the ultrasonic processor according to the study subject and purpose of the study. When the EU-M30 system is used with a 20 MHz ultrasonic probe, images with appropriate gradations can be obtained by setting the gain to between 10 and 13, the contrast to between 2 and 5, and the STC to all zero (center position).

## Equipment

### Endoscopic Ultrasonic Probe

In this section, we will introduce the equipment used by the author, manufactured by Olympus Corporation.

The frequencies and outer diameters of the endoscopic ultrasonic probes we use are shown in Table 1.1. Since the resolution and depth penetration of an ultrasonic probe are dependent on the frequency and size of the transducer (as the outer diameter of the probe increases, the size of the ultrasonic transducer also increases), the probe needs to be selected to suit the aim of the procedure.

Ultrasound examinations can be performed using either the balloon (the probe contacts the object of study through a balloon filled with medium)

**Table 1.1** Ultrasonic probes

| Model name | Maximum outer diameter | Frequency | Compatible biopsy channel |
|---|---|---|---|
| UM-2R | 2.5 mm | 12 MHz | 2.8 mm or more |
| UM-3R | 2.5 mm | 20 MHz | 2.8 mm or more |
| UM-4R | 2.4 mm (2.0 mm at proximal side) | 20 MHz | 2.6 mm or more |
| UM-S20-20R | 1.7 mm (2.0 mm at proximal side)<br>2.55 mm (incl. guide sheath SG-201C) | 20 MHz | 2.2 mm or more<br>2.6 mm or more |
| UM-S30-20R | 1.7 mm (2.0 mm at proximal side)<br>2.55 mm (incl. guide sheath SG-201C) | 30 MHz | 2.2 mm or more<br>2.6 mm or more |
| UM-S30-25R | 2.5 mm | 30 MHz | 2.8 mm or more |
| UM-BS20-26R | 2.6 mm (incl. balloon sheath MAJ-643R) | 20 MHz | 2.8 mm or more |
| UM-S20-17S | 1.4 mm (1.7 mm at proximal side)<br>1.95 mm (incl. guide sheath SG-200C) | 20 MHz | 2.0 mm or more<br>2.0 mm or more |

or direct contact method (the probe makes direct contact with the object of study). 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 ultrasonic probe (which can be inserted in a bronchoscope instrument channel with a diameter of at least 2.8 mm) is generally used (Figures 1.14, 1.15). Other probes can also be used in the balloon method in combination with the balloon sheath MH-246R (Figure 1.16, outer diameter 3.6 mm). This will require a special bronchoscope such as the BF-ST49, with an instrument channel with a diameter of at least 3.7 mm, or a rigid bronchoscope with an instrument channel of 11.5 Fr or more.

The direct contact method does not require a balloon, so the probe is passed directly down the bronchoscope instrument channel.

## Bronchoscope

Having selected the ultrasonic probe in accordance with the aim of the investigation and the region being examined, it is then necessary to select a bronchoscope suitable for use with that probe. In particular when the balloon method is selected, care must be taken to prepare a bronchoscope with an instrument channel diameter of at least 2.8 mm. Table 1.2 shows the endoscopes compatible with the various probes.

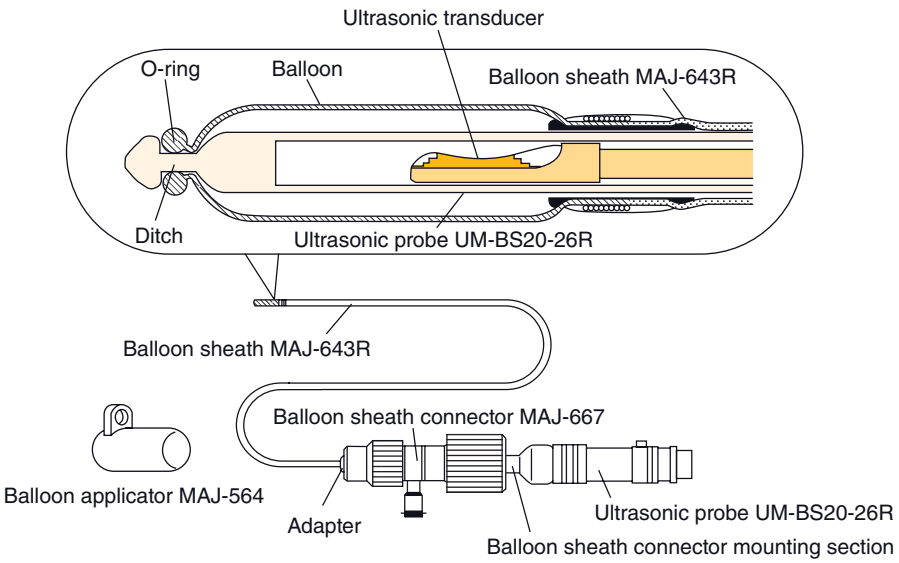


**Figure 1.14** Structure of UM-BS20-26R.

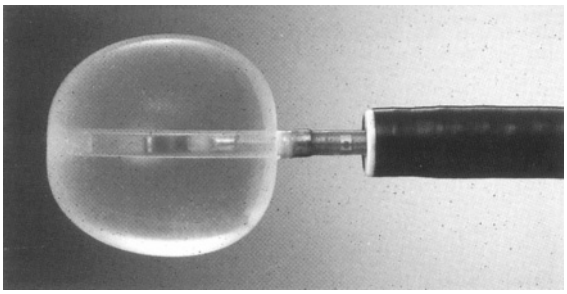

**Figure 1.15** Distal end of UM-BS20-26R with balloon sheath.

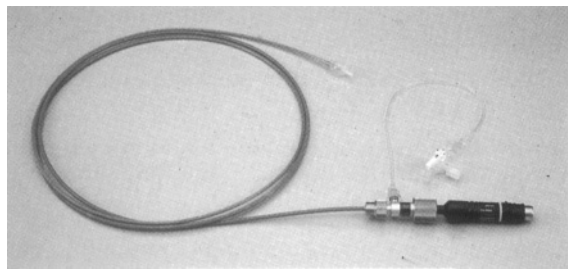

**Figure 1.16** UM-BS20-26R with balloon sheath (MH-246R).

**Table 1.2** Compatibility between bronchoscopes and ultrasound probes

| Bronchoscopes | Guide sheath method | | Direct contact method | | | | Balloon method | | |
|---|---|---|---|---|---|---|---|---|---|
| | UM-S20-17S | UM-S20-20R/ UM-S30-20R | UM-S20-17S | UM-S20-20R/ UM-S30-20R | UM-4R | UM-2R/3R UM-S30-25R | UM-BS20-26R | UM-2R/3R UM4R UM-S20-20R UM-S30-25R | +MH-246R |
| BF-200/240*1<br>BF-P200/P240*1<br>BF-6C240*1<br>BF-160/MP160F*2<br>BF-P150/P160/P180*2<br>BF-Q180*2<br>BF-Q180-AC*2<br>BF-260/6C260<br>BF-MP60<br>BF-P260F<br>(2.0 mm CH) | Yes | No | Yes | Yes | No | No | No | No | |
| BF-30*1<br>BF-40<br>BF-P30/P40*1<br>BF-P60<br>BF-20D/P20D*2<br>BF-PE/PE2*2<br>(2.2 mm CH) | Yes | No | Yes | Yes | No | No | No | No | |
| BF-1T200/1T240*1<br>(2.6 mm CH) | Yes | Yes | Yes | Yes | Yes | No | No | No | |
| BF-1T30/1T40*1<br>BF-1T240R*1<br>BF-1T150/1T160*2<br>BF-1T260<br>BF-LT30<br>BF-1T20D*2<br>BF-TE/TE2*2<br>(2.8 mm CH) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | |
| BF-1T60/1T180*2<br>(3.0 mm CH) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | |
| BF-XT20/XT30*1<br>BF-XT40<br>BF-XT160*2<br>(3.2 mm CH) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | |
| BF-ST40*1<br>(3.7 mm CH) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | |

*1: Discontinued model.
*2: Not available in Japan.

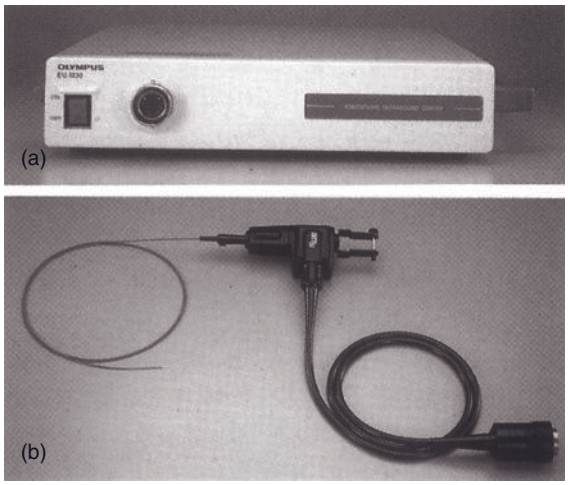


**Figure 1.17** Endoscopic Ultrasound Center (EU-M2000), Probe Driving Unit (MH-240).

Select a bronchoscope which can be used with an ultrasonic probe. When the balloon method is selected, it is necessary to use an endoscope that has an instrument channel diameter of 2.8 mm or more.

### Ultrasonic Processor and Probe Driving Unit

Ultrasound images are obtained by attaching the endoscopic ultrasound probe to the Endoscopic Ultrasound Center EU-M2000 (Figure 1.17a) via the Probe Driving Unit MH-240 (Figure 1.17b).

The EU-M30 videoconverter system is fully compatible with both videoscopes and fiberscopes, and its subscreen function allows simultaneous display of both ultrasound and endoscopic images on the one monitor, or switch between images (Figure 1.18). The EU-M30 ultrasonic processor is compatible with frequencies from 7.5 to 30 MHz, can be used for distance and area calculations, and is compatible with gastrointestinal endoscopic ultrasound (EUS) and a variety of endoscopic ultrasonic probes. It is highly compact, and fits on the standard endoscopic equipment trolley.

The EU-M30S (Figure 1.19) ultrasonic processor is designed for use with miniature probes. It is equipped with a probe drive unit as standard, and the main unit is compact and highly portable. This probe-dedicated system makes it easy to obtain high quality ultrasound images, and includes full image quality adjustment functionality.

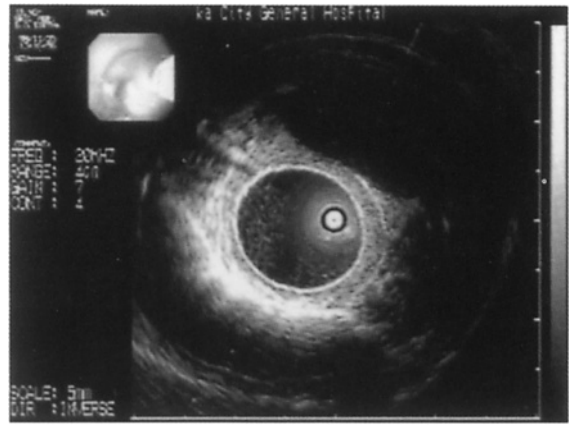

**Figure 1.18** Ultrasound image obtained with the EU-M2000.


**Figure 1.19** Ultrasound Center (EU-M30S).

## Preparations

### Required Equipment

Ultrasonic probe (sterilized).
Balloon sheath.
Balloon sheath connector (for attachment of the balloon sheath to the probe).
3-way stopcock with extension tube.
Sterile water or physiological saline, 20 mL.
20 mL syringe.

### Assembling the Balloon Probe Using the Endoscopic Ultrasound Probe UM-BS20-26R

The advantages of this probe are that it can be used with flexible bronchoscopes with a standard instrument channel with a diameter of at least 2.8 mm (BF-IT20, IT30, IT40, IT240R), and balloon deflation has become simpler.

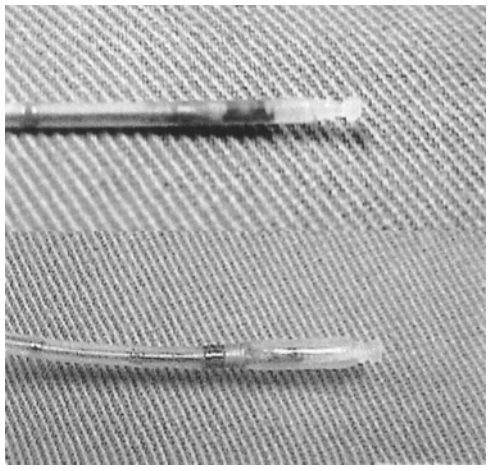

**Figure 1.20** Probe main unit (above), probe inside balloon sheath (below).

Assemble the balloon probe in accordance with the instructions in the manual provided.

**a** Pass the balloon sheath connector from the probe tip down, and fix it to the balloon sheath connector attachment on the probe.

**b** Insert the balloon sheath from the probe tip, and press the balloon sheath clasp into the balloon sheath connector.

**c** The optimum position for the ultrasonic transducer is not in the center of the balloon, but rather the transducer should just protrude from the base of the balloon (Figure 1.20). This allows the transducer to rotate within the maximally expanded portion of the balloon when it has been inflated.

**d** Draw up 15 mL of sterile water (or physiological saline) into the syringe, fill the 3-way stopcock extension tube with water, and attach the extension tube to the balloon sheath connector inlet.

**e** Pull back on the syringe to create negative pressure, drawing out as much air as possible from between the balloon sheath and probe. After performing this step three times, slowly release the negative pressure and then slowly fill inject sterile water into the balloon.

**f** Continue to push the syringe plunger with the balloon tip pointing upwards, filling the balloon with water. Although a small bubble of air will enter the balloon, the tip of the balloon is separate, with a hole in it. Pulling the balloon in the direction of the tip, express the air and water in the tip.

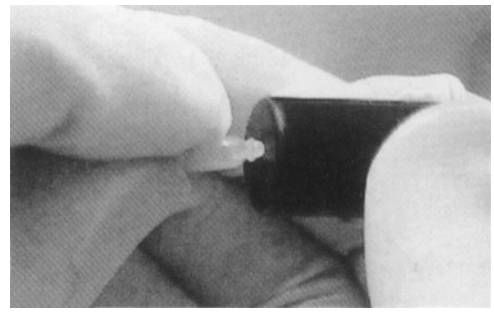

**Figure 1.21** Push the O-ring into the groove.

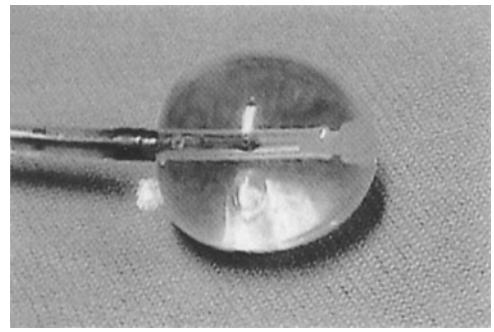

**Figure 1.22** Balloon inflated with water.

**g** After all air in the balloon has been eliminated, fix the probe by hand through the balloon, and push the O-ring on the balloon tip into the groove in the probe tip, by hand or using a balloon applicator (Figure 1.21). Once the balloon has been filled with water, and checked for leaks and air bubbles, preparation is complete (Figure 1.22).

## Connection of the Probe to the Driving Unit

Insert the connection pin of the ultrasonic probe into the connector on the driving unit, pointing the pin at the 12 o'clock position.

## Connecting the Power and Data Entry

Only turn on the power to the Ultrasound Center after the probe has been connected. The ultrasonic probe will be damaged if it is connected when the power is on. After the power has been connected, switch the monitor to the ultrasound input, and enter the patient's identity number, age and name.

### Checking the Image

Unfreeze and rotate the ultrasonic probe. If it is working properly, multiple echoes with five to seven layers will be seen centered on the probe. If multiple echoes are not seen, the probe may be disconnected or there may be air bubbles in the medium in contact with the probe.

### Inverting the Image

Next press the "Image Direction" switch to change the monitor image from normal to inverse. This inverts the ultrasound image so that left and right are the same as the endoscopic image, to an image seen from the rostral direction. In gastrointestinal EUS, the normal ultrasound image is seen from the caudal direction, for easy comparison with computer tomography (CT) scans, but in EBUS it is desirable for the directions in the ultrasound image to coincide with the image from the bronchoscope, for the purposes of FNA from the tracheobronchial lumen. The normal mode is only used in special situations, such as for comparison with CT images.

## Operation

### Anesthesia

In principle, anesthesia for EBUS is the same as for regular bronchoscopic examinations. It should be kept in mind, however, that until the operator has become more experienced, procedures will tend to be somewhat longer in duration. When EBUS is performed in conjunction with another procedure, such as laser-induced fluorescence endoscopy (LIFE), then intravenous anesthesia may be used, allowing spontaneous respiration. An important consideration for the anesthetist is to confirm, under direct observation using the laryngoscope, that local anesthetic spray is applied directly to the pharynx and larynx, in particular to the vocal chords. After bronchoscopic examination of the trachea and bronchi, local anesthetic is further applied to the bronchus (bronchi) into which the balloon probe will be introduced.

### Inserting the Probe

Apply xylocaine jelly liberally to the distal end of the balloon probe, and slowly insert it into the instrument channel of the bronchoscope. During the insertion process, hold the probe at a point 2 or 3 cm away from the instrument port with each hand in turn. It is important to be aware that there are two places with greater resistance within the instrument channel, between the instrument port and the distal end of the bronchoscope. The first site is 4–5 cm from the instrument port, where the suction and instrument channels join, and the second is 2–3 cm from the bronchoscope tip, where the instrument bends. When resistance is high at either site and the probe is difficult to pass, then the probe should be removed and jelly reapplied, and if that fails, remove the bronchoscope from the patient and reinsert the probe.

### Operating the Probe

Advance the probe to a point slightly distal to the site of interest. Inject 1–3 mL of sterile water (physiological saline may also be used with the UM-BS20-26R), inflating the balloon while scanning so that it contacts the bronchial wall circumferentially. The optimum volume of water is that which just achieves circumferential contact with the bronchial wall. Over-inflation can cause compression of bronchial wall structures or bursting of the balloon.

Then, while scanning and capturing images (always make a videorecording), retract the probe from deep (distal) to superficial (proximal). The important point to remember about scanning is to retract the probe very slowly. If necessary, ask the patient to hold their breath while scanning. Advancing the probe from superficial (proximal) to deep (distal) can cause damage to the probe, and should be avoided.

### Tips for Achieving Optimum Ultrasound Images

To obtain clear, easily understandable images:

**a** Rotate the ultrasound image so that it corresponds to the endoscopic images.

**b** To assess the depth of tumor invasion, the ultrasound pulse must penetrate the tracheal/bronchial wall perpendicularly.

#### Rotate the Ultrasound Image So that It Corresponds to the Endoscopic Images

**i** At a bifurcation (e.g. the opening of the right upper lobe bronchus), we can line up the direction so that the balloon is not in contact with the bronchial lumen

on the endoscopic image, with no echo on the EBUS image.

**ii** For example (Figure 1.23), in the left ultrasound image below, the direction has no echo, because the balloon is not in contact with the bronchial lumen, and direction is from 4 to 6 o'clock. In the right endoscopic image, the balloon is not in contact with the bronchial lumen and direction is from 2 to 4 o'clock. To match up the images, we need to rotate the EBUS image anticlockwise 45°.

**iii** Rotate the EBUS image according to the relative positions of the bronchial tree and the esophagus and great vessel.

When scanning from the lower part of the trachea to the left main bronchus, the esophagus is located at the 6 o'clock direction (Figure 1.24 left). The right pulmonary artery runs anteriorly to the right main bronchus and right middle lobe bronchus, from 10 o'clock to 2 o'clock (Figure 1.24 right). Identify the position of these structures, and rotate the EBUS image accordingly.

### To Assess the Depth of Tumor Invasion, Obtain Images with the Ultrasound Pulse Penetrating the Tracheal/Bronchial Wall Perpendicularly

If the first layer (marginal echo, reflected at the boundary between tissues) is highly echoic, the image can be said to be derived from an ultrasound pulse penetrating the tracheal/bronchial wall nearly perpendicularly (Figure 1.25).

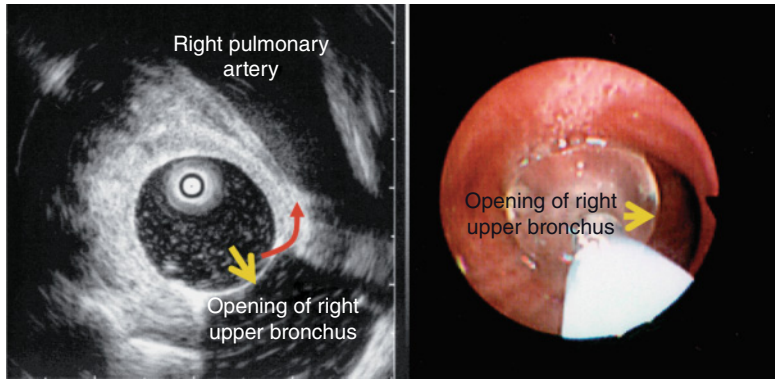


**Figure 1.23** Tips for achieving optimum ultrasound images. Rotation of the ultrasound image so that it corresponds to the endoscopic images.

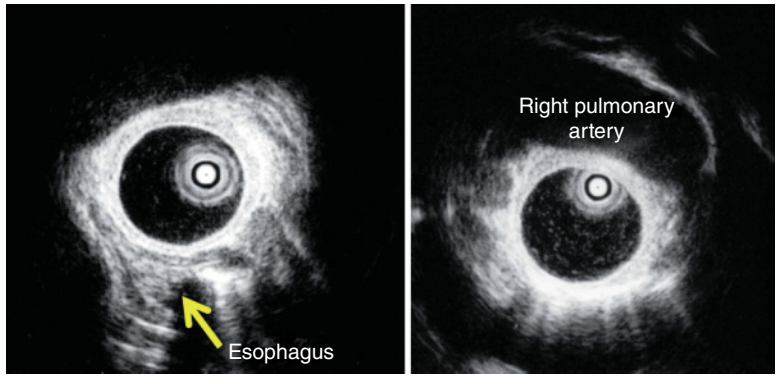


**Figure 1.24** Tips for achieving optimum ultrasound images. Rotation of the EBUS image according to the relative positions of the bronchial tree and the esophagus and great vessels.

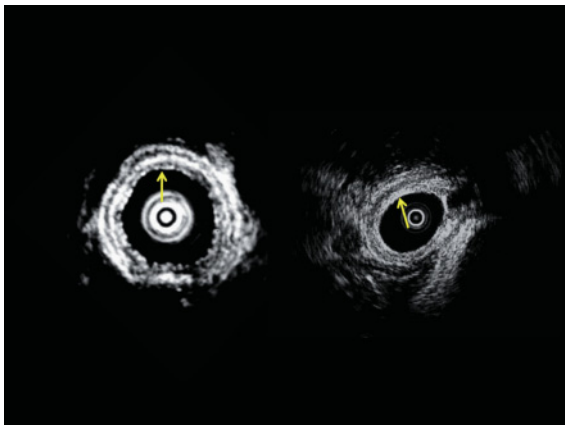

**Figure 1.25** Tips for achieving optimum ultrasound images. To assess the depth of tumor invasion, obtain images with the ultrasound pulse penetrating the tracheal/bronchial wall perpendicularly. The arrows in the figures indicate a highly echoic first layer, with a clearly lineated layer structure in that region.

**Figure 1.26** Ultrasonic bronchoscope (BF-UC160F, Olympus).

## Equipment of EBUS Guided Transbronchial Needle Aspiration (EBUS-TBNA)

The curved array transducer is combined at the tip of the bronchoscope for EBUS-TBNA (Figure 1.26, BF-UC160F, Olympus). This convex bronchoscope consists of an oblique forward viewer with a convex transducer mounted in front of the lens. The convex transducer is 7.5 MHz and covered by a balloon. The

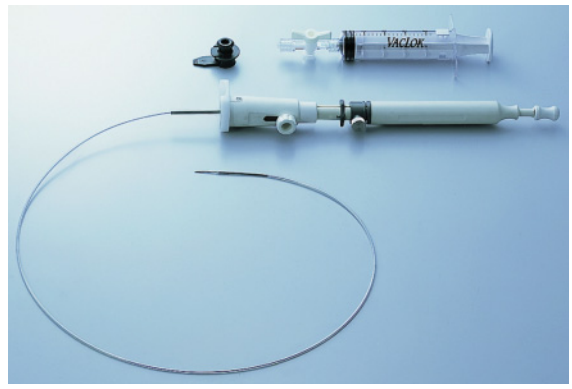


**Figure 1.27** Aspiration Needle (NA-201SX-4022, Olympus).

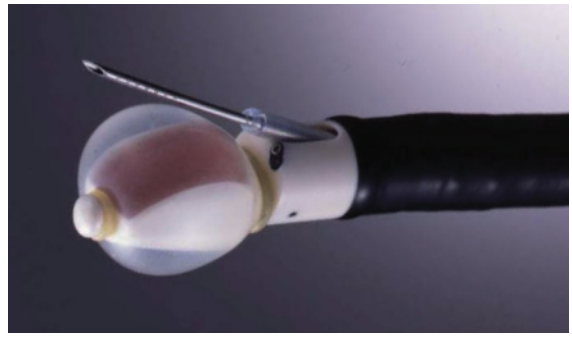

**Figure 1.28** Ultrasonic bronchoscope with needle.

bronchoscope has a working channel with a diameter of 2.0 mm; we can insert the disposable biopsy instrument with a 22 G needle (Figure 1.27, NA-201SX-4022, Olympus) through the working channel (Figure 1.28).

After the convex probe is covered by the balloon, saline is injected into the balloon, filling its inner space.

This bronchoscope is connected to the ultrasound unit (EU-C60) and the power switch turned on (Figure 1.29).

The scope shows us the target lesion for TBNA beyond the bronchial wall. The transducer provides longitudinal planes of peribronchial areas, and the ultrasonographic image shows us real-time movement of the TBNA needle.

As this convex bronchoscope has an oblique forward viewer, there is a little difficulty when inserting this scope through the vocal cord. Observing the 12 o'clock direction of the vocal cord, the tip of the scope is straight and it is easy to enter the trachea.

**Figure 1.29** Ultrasound processor (EU-C2000).

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## Frequently Asked Questions

**1** Which generation of the bronchial tree needs the balloon to visualize the bronchial wall using EBUS?

**A:** From trachea to sub-sub or sub-sub-subsegmental bronchus, the balloon is necessary to obtain excellent images using EBUS.

**2** Could the miniature probe reach the subpleural area?

**A:** Yes, the miniature probe of 1.4–2.5 mm in diameter expands to the subpleural area

**3** Which probe could penetrate the tissue deeper, a 20 MHz probe or 30 MHz probe?

**A:** 20 MHz probe could. As the frequency decreases, the depth penetration of the ultrasound pulse is increased.

**4** What are tips for achieving satisfactory visualization of EBUS using the radial probe?

**A:** The probe should be located at the center of the lumen of the bronchial tree. As the ultrasonic waves penetrate the bronchial wall perpendicularly, excellent images are visualized.

# 2 Anatomy of Mediastinal and Hilar Area

## Overview of Ultrasound Imaging of the Right and Left Bronchi While the Radial Probe is Being Pulled out

EBUS images are cross-sectional images of planes perpendicular to the long axis of the tracheobronchial tree. These images are used to assist endoscopic treatments, so ultrasound images are generally displayed looking from the rostral direction, so that left and right match with endoscopic images.

The positional relationship between the peribronchial organs in EBUS images taken from the trachea corresponds to those in a reversed CT image (CT scans are cross-sectional images looking from the caudal direction). EBUS images taken distal to the bifurcation of the left and right main bronchi, however, are cross-sectional images of planes perpendicular to the long axis of the bronchus, and therefore have a different positional relationship between the peribronchial organs from the CT images.

In clinical practice, when EBUS is performed for centrally located lesions, the balloon is inflated distal to the lesion, and images are obtained while pulling the probe proximally (superficially). The reasons for this are that it is difficult to push the probe distally (deeper) with the balloon inflated, and by pulling the probe proximally, cross-sectional images of planes perpendicular to the long axis of the bronchus can be obtained without bending the probe.

In this part of the chapter, using schematic diagrams and ultrasound images, we will describe the positional relationship between the peribronchial organs and the bronchial tree, as seen when we pull the probe from the right and left lower lobe bronchi up to the left and right main bronchi, respectively. To fully understand EBUS, it is essential to understand the positional relationship between the peribronchial organs during visualization while the probe is being pulled out.

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## Right Bronchi (Figure 2.1)

### Right Lower Lobe Bronchi

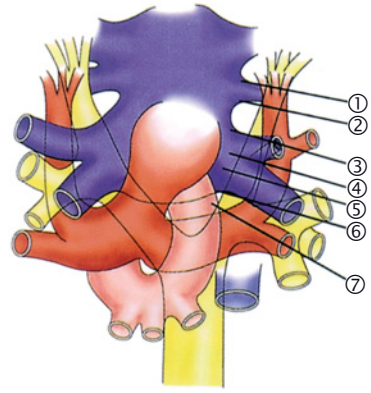
When the balloon is inflated in the right basal bronchus, the inferior pulmonary vein (V6) passes on the dorsal side of the bronchus (1), whereas anterior to the bronchus the pulmonary artery divides into A8, A9 and A10, positioned between 9 o'clock and 2 o'clock.

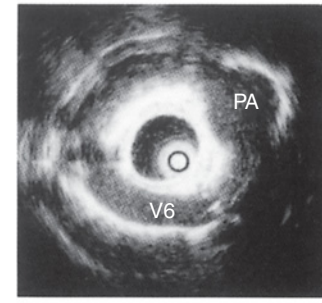
As the probe is pulled back, A8, A9 and A10 meet at the 12 o'clock direction and the direction of the pulmonary artery changes gradually to 3 o'clock (2, 3). When the probe is pulled further back, it approaches the bifurcation of B6. An area that does not contact the balloon appears on the bronchial wall, from where the ultrasound is reflected. As a result, the image of the layer containing the bifurcation of B6 at 5 o'clock is lost.

Pulling the probe back further, the opening of the middle lobe bronchus, indicated by reflection of the ultrasound pulse (because the balloon loses contact with the bronchial wall at the bifurcation), appears at 12 o'clock. The pulmonary artery has gradually moved round to the 2 o'clock position (4).

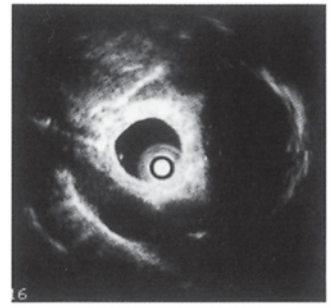
### From the Right Intermediate Bronchus to the Right Main Bronchus

As the probe is pulled from the distal intermediate bronchus to a point immediately below the origin of

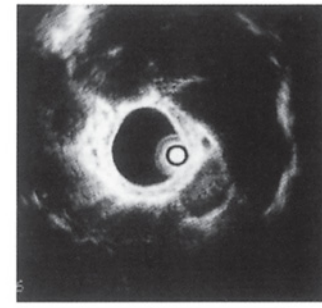


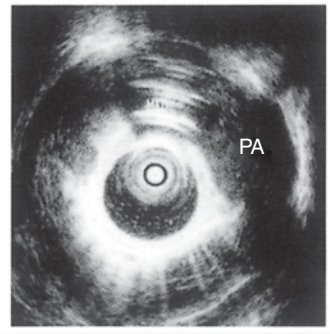

① V6



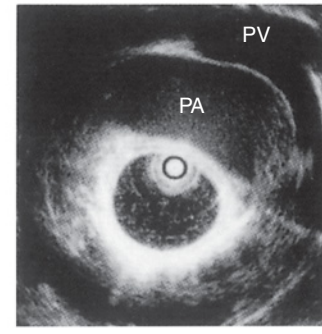
② Upper part of V6



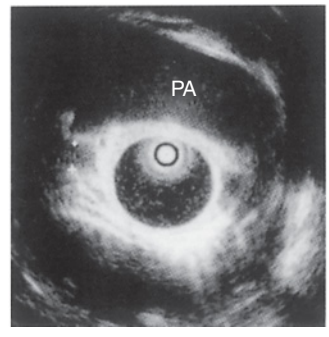
③ Right lower bronchus



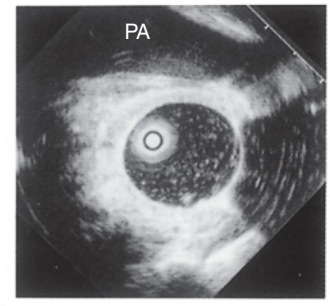

④ Opening of right middle lobe




⑤ Center of intermediate trunk




⑥ Upper part of intermediate trunk




⑦ Right main bronchus
(opening of upper bronchus)

**Figure 2.1** Right bronchi.
PA: pulmonary artery; PV: pulmonary vein;
V6: pulmonary vein for segment 6.

the upper lobe bronchus, the pulmonary artery crosses the bronchus from the right to the left (5, 6, 7). In the central section of the intermediate bronchus, the superior pulmonary vein can sometimes be seen anterior to the pulmonary artery (5).

When the probe is pulled further back, the origin of the upper lobe bronchus is indicated by reflection of the ultrasound pulse (because the balloon loses contact with the bronchial wall at the bifurcation) at 3 o'clock (7).

Pulling the probe back further, A1+3, originating from the pulmonary trunk, can be seen crossing horizontally anterior to the right main bronchus. Retracting the probe further, the origin of the left main bronchus at the carina is indicated by reflection of the ultrasound pulse at 9 o'clock.

The key to reading EBUS images is to recognize the anatomy of the peribronchial organs as the probe is retracted from the right lower lobe bronchus to the right main bronchus.

### Right Side

Right basal bronchus: inferior pulmonary vein, V6 (6 o'clock); PA7-10 (2 o'clock).

Right lower bronchus: PA6-10 (2–3 o'clock).

Right intermediate bronchus: right pulmonary artery (12 o'clock).

Right main bronchus: right upper lobe pulmonary artery (12 o'clock).

PA: pulmonary artery.

**1** V6.
**2** Upper part of V6.
**3** Right lower bronchus.
**4** Origin of right middle lobe bronchus.
**5** Middle part of intermediate bronchus.
**6** Upper part of intermediate bronchus.
**7** Right main bronchus (origin of right upper lobe bronchus).

## Left Bronchi (Figure 2.2)

### Left Lower Lobe Bronchi

When the balloon is inflated in the left basal bronchus, the inferior pulmonary vein (V6) passes on the dorsal side of the bronchus, whereas the A8, A9 and A10 branches of the pulmonary artery meet at 9 o'clock (1, 2).

As the probe is pulled back, it approaches the bifurcation of B6. An area that does not contact the balloon appears on the bronchial wall, from where the ultrasound is reflected. As a result, the image of the layer containing the bifurcation of B6 at 7 o'clock is lost.

Pulling the probe back further, the opening of the upper lobe bronchus, indicated by reflection of the ultrasound pulse (because the balloon loses contact with the bronchial wall at the bifurcation), appears at 11 o'clock (3). The pulmonary artery is located below the origin of the upper lobe bronchus.

### Left Main Bronchus

The distal section of the left main bronchus is characterized by the left pulmonary artery at 10 o'clock, the descending aorta at 7 o'clock, and the left atrium from 1 o'clock to 3 o'clock (4, 5). As we enter the central section of the left main bronchus, the left atrium disappears, and the esophagus appears at 6 o'clock. The subcarinal (#7) lymph node is often visible medial to the esophagus (6).

When the probe is pulled further back, the origin of the left main bronchus at the carina is indicated by reflection of the ultrasound pulse (because the balloon loses contact with the bronchial wall at the bifurcation) at 3 o'clock.

The key to reading EBUS images is to recognize the anatomy of the peribronchial organs as the probe is retracted from the left lower lobe bronchus to the left main bronchus.

### Left Side

Left basal bronchus: inferior pulmonary vein, V6 (6 o'clock); PA8-10 (9 o'clock).

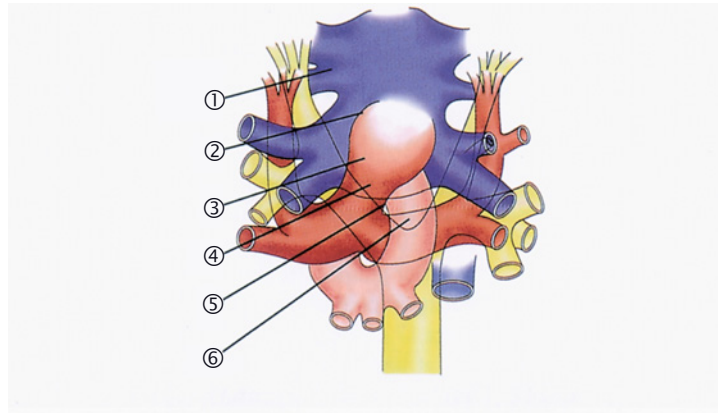
Left lower bronchus: PA6-10 (10 o'clock); superior pulmonary vein (1–4 o'clock)

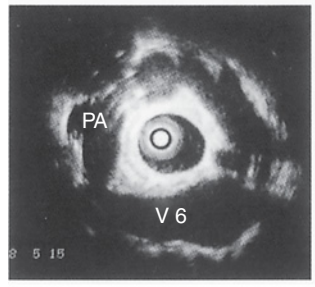
Left main bronchus (distal): left pulmonary artery (10 o'clock); aorta (7 o'clock); left atrium (1–3 o'clock).

Left main bronchus (proximal): left pulmonary artery (10 o'clock); aorta (7 o'clock); left atrium (1–3 o'clock); esophagus (6 o'clock).

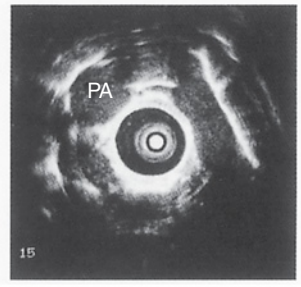
PA: pulmonary artery.

**1** Left V6.
**2** Left lower bronchus.
**3** Origin of left lower bronchus.
**4** Lower part of left main bronchus.
**5** Left main bronchus (LA, PA, Ao).
**6** Left main bronchus (esophagus, #7LN).

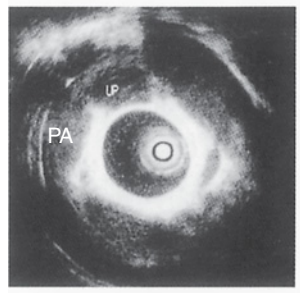


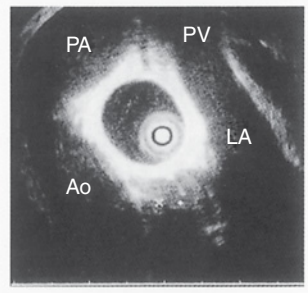

① Left V6



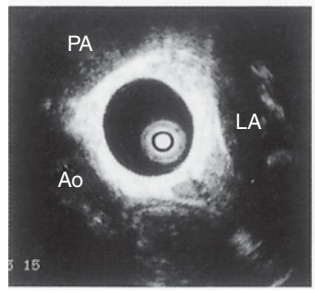

② Left lower bronchus



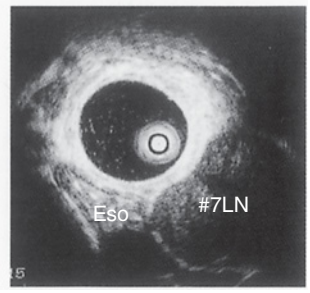

③ Opening of left upper bronchus




④ Lower part of left main bronchus




⑤ Left main bronchus (LA, PA. Ao)




⑥ Left main bronchus, (esophagus, #7LN)

**Figure 2.2** Left bronchi.
Ao: aorta; Eso: esophagus; LA: left atrium; LN: lymph nodes; PA: pulmonary artery; PV: pulmonary vein; V6: inferior pulmonary vein.

## Ultrasound Imaging of Mediastinal and Hilar Lymph Nodes for EBUS-TBNA by the Convex Bronchoscope

To carry out EBUS-TBNA procedures successfully, the bronchoscopist should have a good understanding of ultrasonographic images of the peribronchial vessels and lymph nodes.

### #7 LN: Subcarinal Lymph Node (Figure 2.3)

For approaching #7 LN, the convex bronchoscope is inserted into the right main bronchus. While scanning at the 9 o'clock direction, we can confirm the largest area of the #7 LN. While rotating right handed and scanning at the 11 o'clock direction, we can observe the right main pulmonary artery.

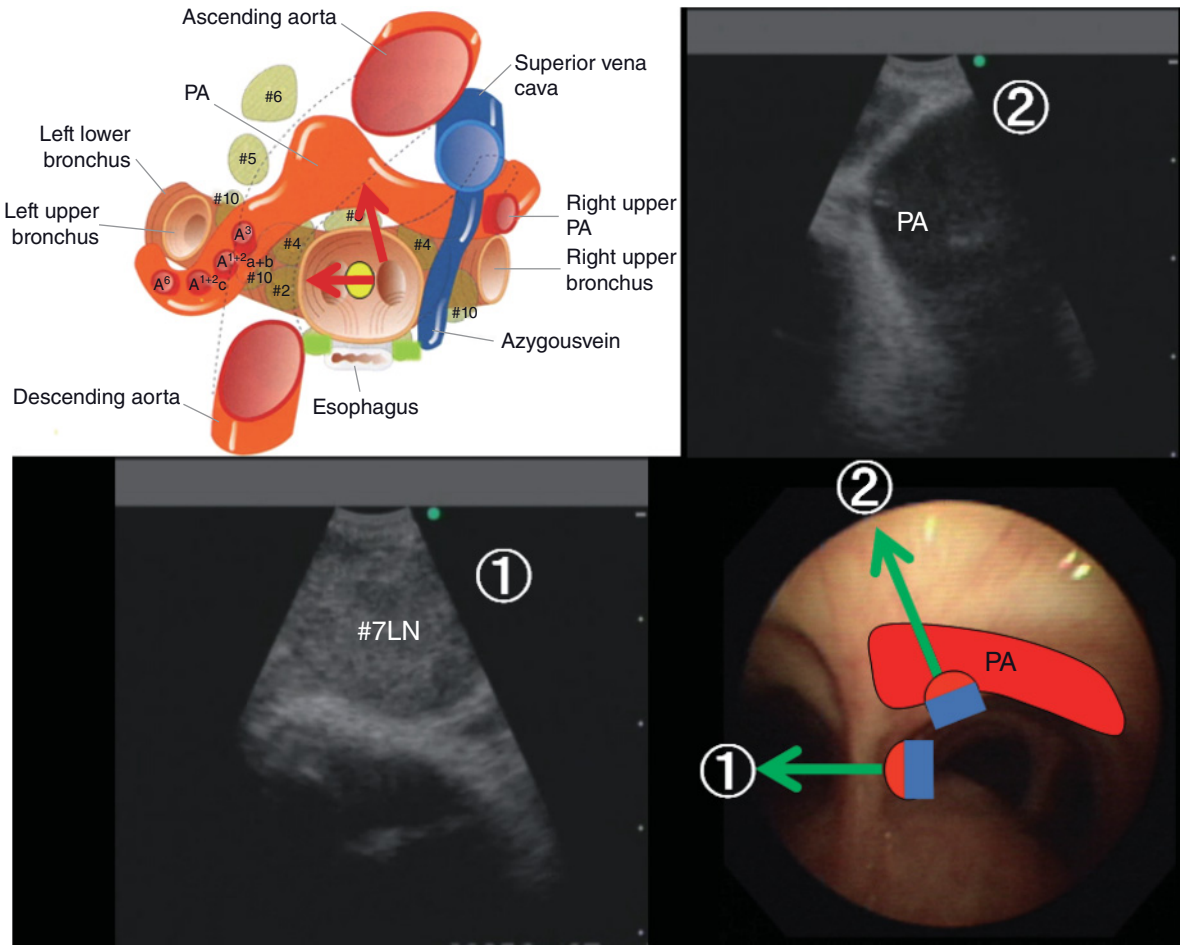



**Figure 2.3** Subcarinal lymph node. PA: pulmonary artery. (From Bronchoscopy, 1st ed. Tokyo, IGAKU-SHOIN, 1998, p. 45 with permission.)

### 11R LN: Right Intralobar Lymph Node (Between Right Lower Lobe Bronchus and Right Middle Lobe Bronchus) (Figure 2.4)

For approaching #11R LN, the convex bronchoscope is inserted into the right basal bronchus. While scanning at the 12 o'clock direction, we can confirm the largest area of the #11R LN. While rotating right handed and scanning at the 3 o'clock direction, we can observe the right pulmonary artery.

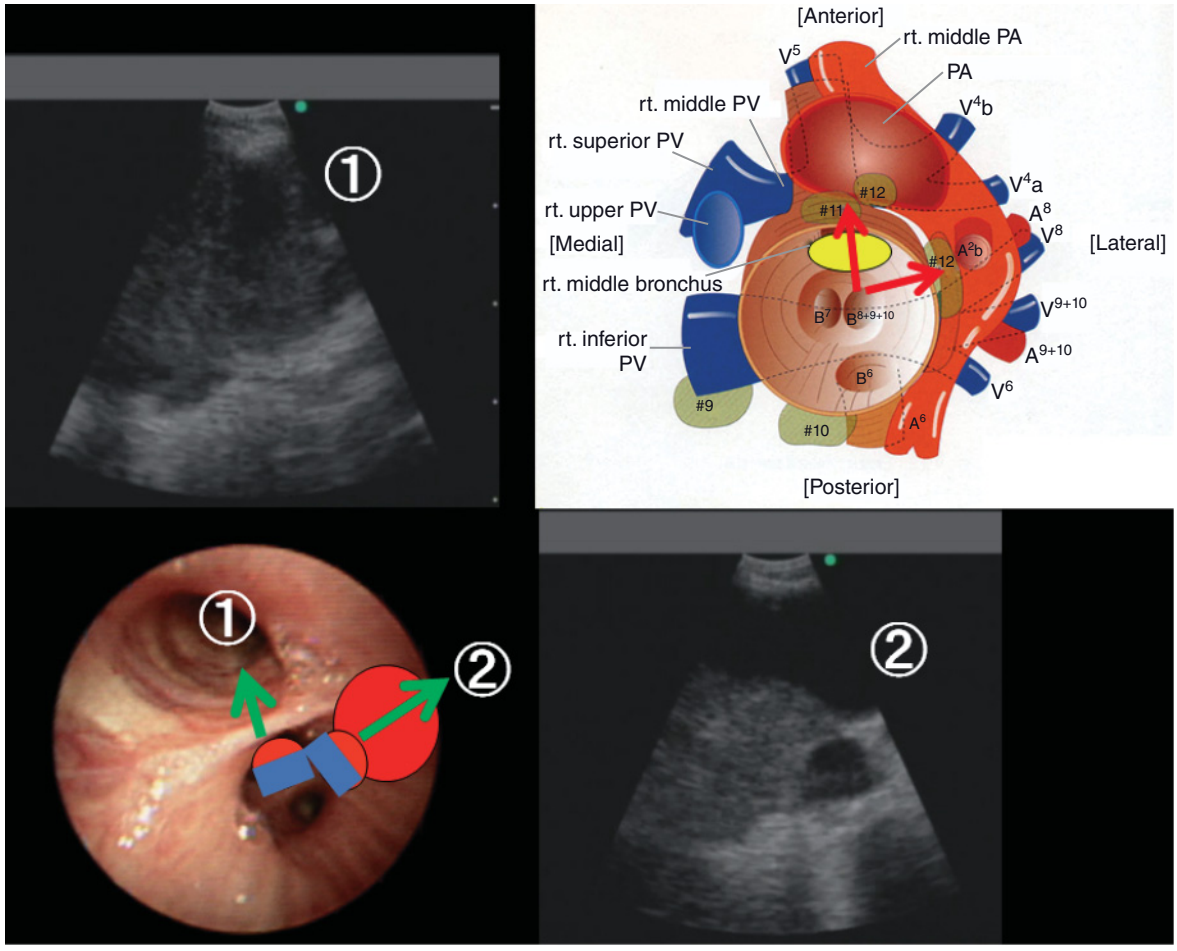



**Figure 2.4** Right intralobar lymph node. PA: pulmonary artery; PV: pulmonary vein. (From Bronchoscopy, 1st ed. Tokyo, IGAKU-SHOIN, 1998, p. 48 with permission.)

### 11R LN: Right Intralobar Lymph Node (between the Right Intermediate Trunk and Right Upper Lobe Bronchus) (Figure 2.5)

For approaching #11R LN, the convex bronchoscope is inserted into the right intermediate trunk. On the bronchoscopic findings, the right upper bronchus is located at the 12 o'clock direction from the intermediate trunk. While scanning at the 12 o'clock direction, we can confirm the largest area of the #11R LN. While rotating left handed and scanning at the 9 o'clock direction, we can observe the right main pulmonary artery.

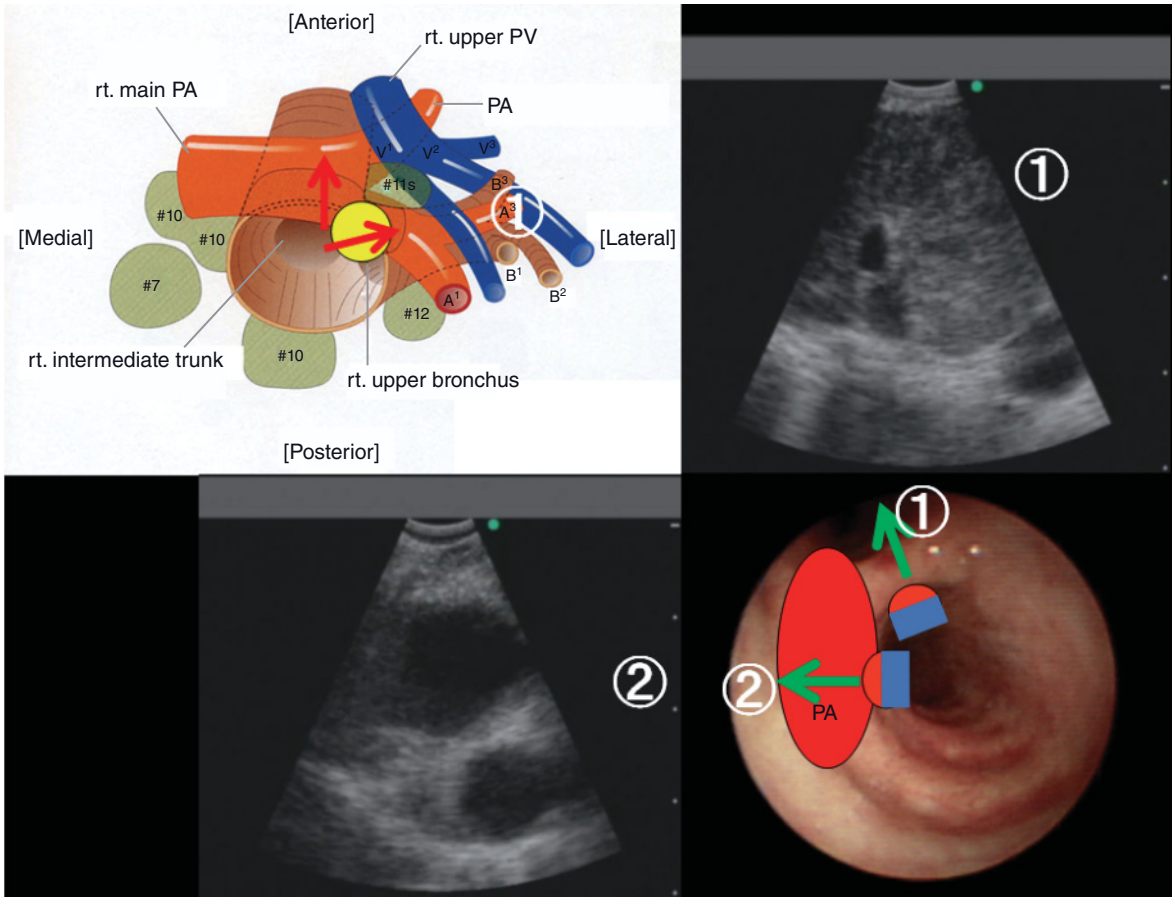



**Figure 2.5** Right intralobar lymph node. PA: pulmonary artery; PV: pulmonary vein. (From Bronchoscopy, 1st ed. Tokyo, IGAKU-SHOIN, 1998, p. 47 with permission.)

## 11L LN: Left Intralobar Lymph Node (Figure 2.6)

For approaching #11R LN, the convex bronchoscope is inserted into left basal bronchus. On the bronchoscopic findings, the left upper lobe bronchus is located at the 12 o'clock direction from left lower lobe bronchus. While scanning at the 12 o'clock direction, we can confirm the largest area of the #11L LN. While rotating left handed and scanning at the 10 o'clock direction, we can observe the right pulmonary artery.

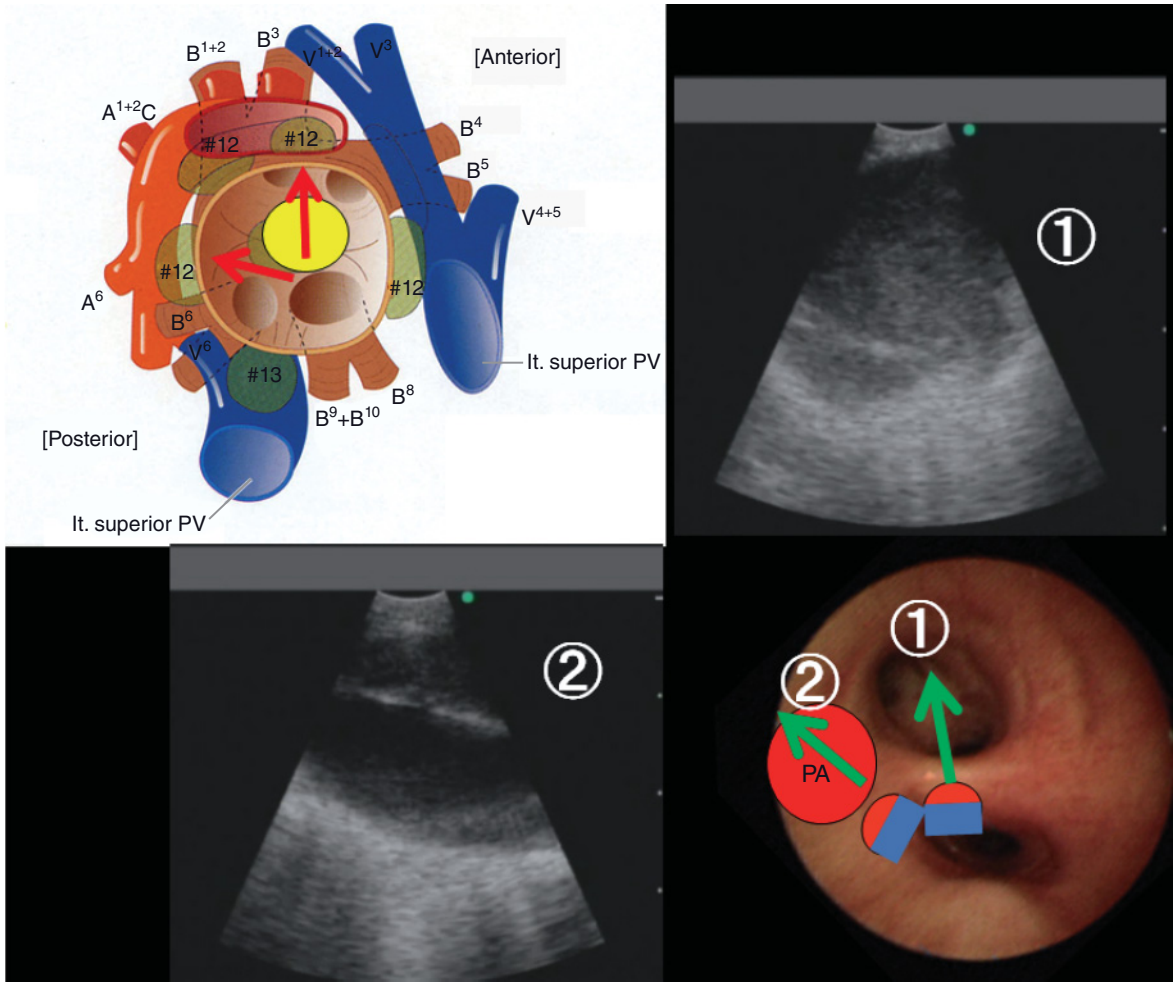



**Figure 2.6** Left intralobar lymph node. PA: pulmonary artery; PV: pulmonary vein. (From Bronchoscopy, 1st ed. Tokyo, IGAKU-SHOIN, 1998, p. 46 with permission.)

### 4L LN: Lymph Node (Figure 2.7)

For approaching #4L LN, the convex bronchoscope is inserted to the distal site of the trachea. On the bronchoscopic findings, the left side of the trachea is located at the 12 o'clock direction. While scanning at the 12 o'clock direction, we can confirm the largest area of the #4L LN. While pushing the scope to the distal site about 1–2 cm, we can observe the left main pulmonary artery. While pushing the scope to the proximal site about 1–2 cm, we can observe aortic arch.

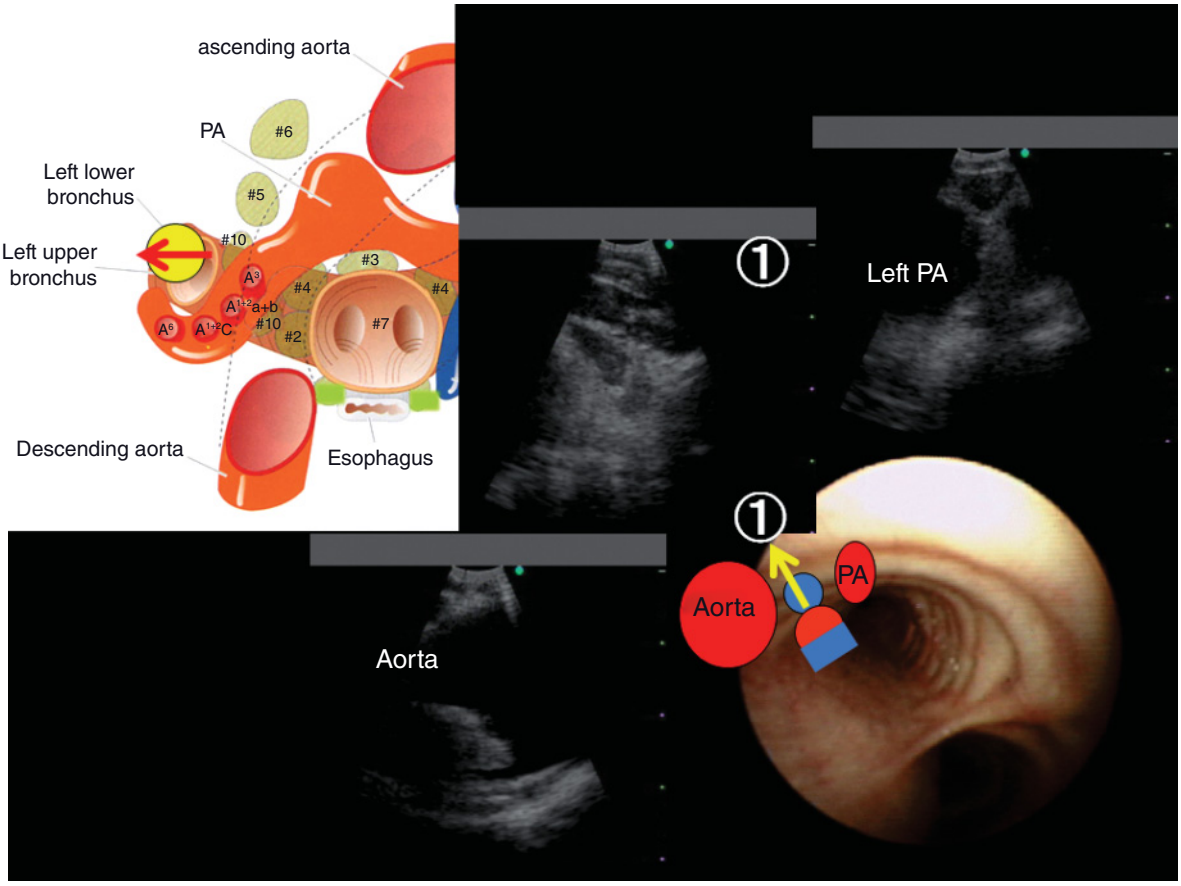



**Figure 2.7** Left lower paratracheal nodes. PA: pulmonary artery. (From Bronchoscopy, 1st ed. Tokyo, IGAKU-SHOIN, 1998, p. 45 with permission.)

### 4R LN: Lymph node (Figure 2.8)

For approaching #4R LN, the convex bronchoscope is inserted to the distal site of the trachea. On the bronchoscopic findings, the membranous portion of the trachea is located at the 6 o'clock direction. While scanning at the 2 o'clock direction, we can confirm the largest area of the #4R LN. While scanning 4R LN, we can observe the superior vena cava (SVC) just below. While pushing the scope to proximal site about 1–2 cm, we can observe the aortic arch #4R LN.

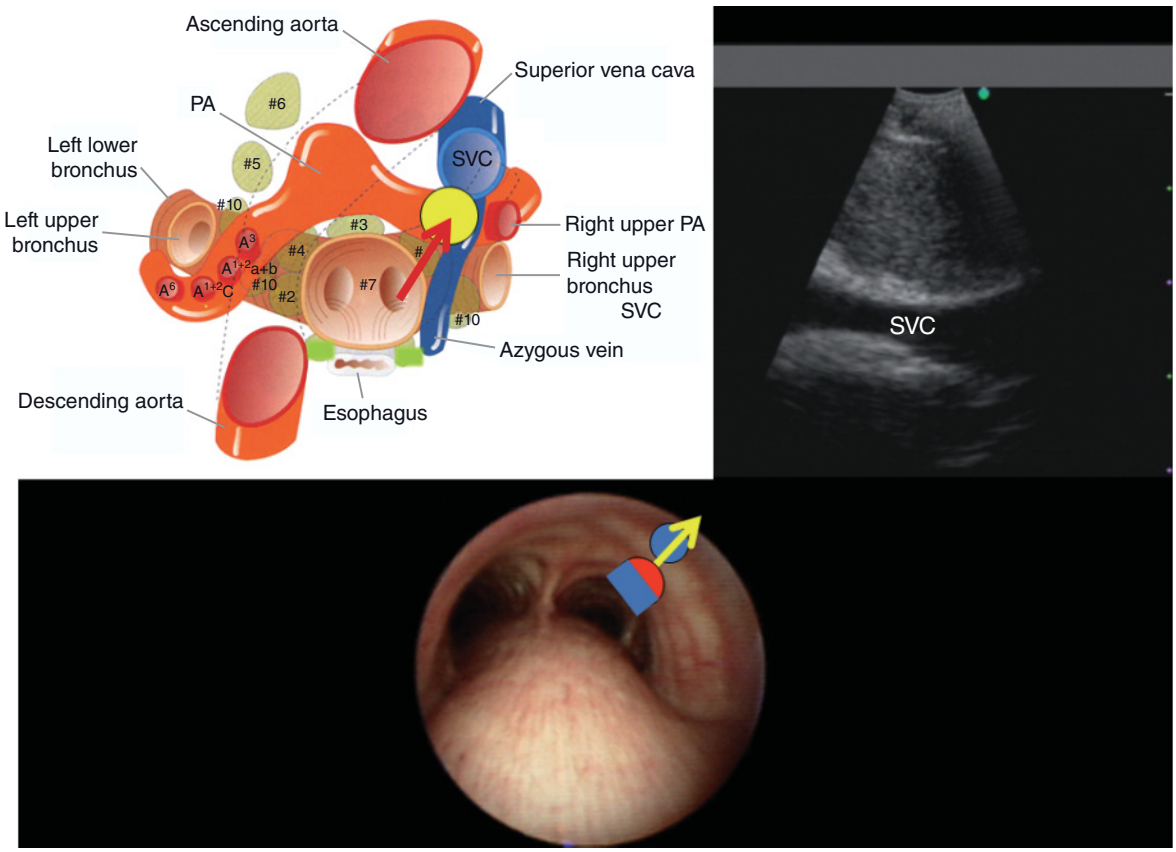



**Figure 2.8** Right lower paratracheal nodes. PA: pulmonary artery; SVC: superior vena cava. (From Bronchoscopy, 1st ed. Tokyo, IGAKU-SHOIN, 1998, p. 45 with permission.)

## Frequently Asked Questions

**1** On the right bronchus, what is most useful for recognizing the direction of the peribronchial organs?

**A:** At the intermediate bronchus and the right main bronchus, the right pulmonary artery is located at the 12 o'clock direction.

**2** On the left bronchus, what is most useful for recognizing the direction of the peribronchial organs?

**A:** At the left main bronchus, the esophagus is located at the 6 o'clock direction.

**3** How can one differentiate a lymph node from vessels during EBUS-TBNA?

**A:** By rotating the convex probe right-handed or left-handed, the margin of a lymph node may not be continued. By rotating the convex probe right-handed or left-handed, the margin of a vessel may be continued. Power Doppler mode is also useful to differentiate a lymph node from vessels.

**4** How do you avoid bleeding during EBUS-TBNA?

**A:** We should avoid puncturing the great vessels (PA, PV, or aorta) and the bronchial artery, particularly when the bronchial artery is located between the bronchial wall and the target lymph node. I recommend checking the route of the needle before puncturing.

# 3 How to Perform Endobronchial Ultrasonography

## Introduction

I commenced endobronchial ultrasonography (EBUS) in August 1994. Initially, I performed EBUS using a radial probe without a guide sheath for the diagnosis of peripheral pulmonary lesions. Guide sheaths became available in 1996 to aid in the accurate identification of the location of peripheral pulmonary lesions. Another early application of EBUS was the radial probe with a balloon to visualize the layer structures of the tracheobronchial wall. In recent years, the use of convex probes combined with the bronchoscope for EBUS guided transbronchial needle aspiration (EBUS-TBNA) has rapidly expanded in many countries. Here I will describe the equipment used for EBUS using a radial probe and EBUS-TBNA, and some tips for various procedures.

## Balloon Probes for Central Lesions

Air always inhibits the visualization of ultrasound images. Beyond the subsegmental bronchi, the outer surface of the probe fits snugly to the bronchial surface. A balloon probe is needed to obtain ultrasound images of central lesions located between the trachea and subsegmental bronchi using EBUS.

### Equipment (Figure 3.1)

For some time, I used a 20 MHz mechanical radial ultrasonic probe (UM-3R, Olympus Optical Co., Ltd, Tokyo, Japan) with a balloon-tip sheath (MH-246R, Olympus). The diameter of this sheath is 3.6 mm, however, and must be used with a bronchoscope with a big channel (BF-ST40, working channel diameter: 3.7 mm). In recent years, I usually use a thinner 20 MHz mechanical radial ultrasonic probe (UM-BS-20-26R, Olympus) with a balloon-tip sheath (MH-676R, Olympus) through the 2.8 mm diameter working channel of a flexible bronchoscope (BF-1T260, Olympus). These probes are able to connect with the Endoscopic Ultrasound System (EU-M 30 and EU-M 2000, Olympus).

### Preparation of the Balloon Probe

(Video clip 3.1)

The ultrasonic probe is inserted into the balloon sheath. The probe and sheath are fixed in place by the connecting unit. A 25 mL syringe containing about 15 mL of saline is connected to the injection port in the connecting unit. Most of the air between the inner surface of the sheath and the outer surface of the probe is removed in two or three aspirations using the 25 mL syringe. Saline is injected from the syringe into the sheath and the balloon at its tip, inflating the balloon to a diameter of about 15 mm with saline filling the balloon. When the tip of the balloon is slightly compressed, a small amount of air is collected in the uppermost part of the balloon and withdrawn into the sheath. This completes the preparation of the balloon probe.

### Performing EBUS Using A Balloon Probe

We use flexible bronchoscopes (1T-40, 1T-240R, Olympus) with a working channel 2.8 mm in diameter for all EBUS procedures using a balloon probe. Sufficient local anesthetic is applied to the bronchi that the balloon probe will make contact with, to avoid the patient coughing during the procedure. The balloon probe is inserted into the working channel of the bronchoscope, advanced beyond the lesion, and then inflated with the minimum amount of saline required to obtain an EBUS image of the entire circumference

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By Noriaki Kurimoto, David I. K. Fielding and Ali I. Musani.
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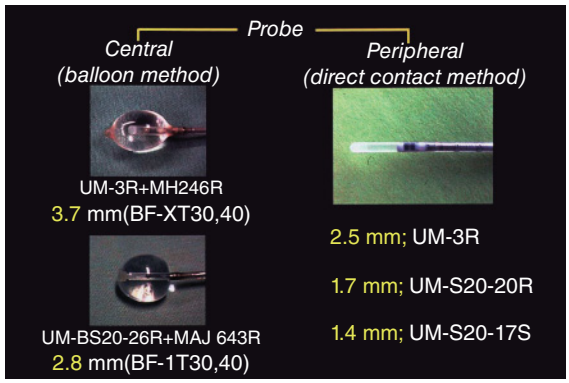


**Figure 3.1** Radial probes for EBUS. Balloon method for central lesions: we use a thick ultrasonic probe (UM-3R, 20 MHz, 2.5 mm diameter) covered by a balloon sheath (MH-246R), or a thin ultrasonic probe (UM-BS20-26R, 20 MHz, 2.0 mm diameter) covered by a balloon sheath (MAJ-643R). Direct contact method for peripheral pulmonary lesions: we use a thick ultrasonic probe (UM-3R, 20 MHz, 2.5 mm diameter), a thin ultrasonic probe (UM-S20-20R, 20 MHz, 1.7 mm diameter), or thinner ultrasonic probe (UM-S20-17S, 20 MHz, 1.4 mm diameter).

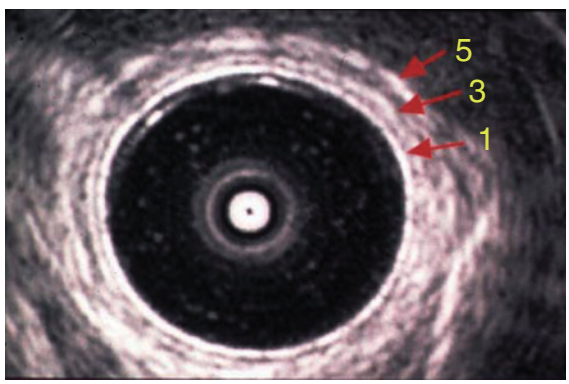


**Figure 3.2** EBUS image obtained using a balloon probe. The balloon probe is inserted into the bronchoscope working channel, and inflated with the minimum volume of saline needed to obtain an EBUS image of the entire circumference of the bronchial wall. The cartilaginous portion of the extra-pulmonary bronchus is visualized as five layers (arrows indicate the first, third and fifth layers).

of the bronchial wall (Figure 3.2). Scanning is performed while retracting the probe slowly from deep (distal) to superficial (proximal). Advancing the probe from superficial (proximal) to deep (distal) can cause damage to the probe, and should be avoided.

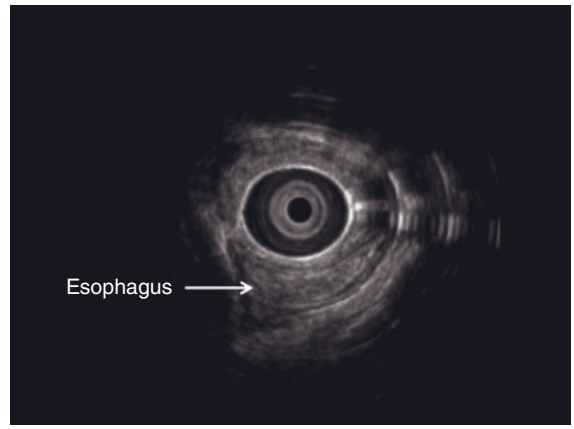


**Figure 3.3** Orientation of the radial probe. Orientation of the 12 o'clock position does not correspond to the bronchoscopic 12 o'clock orientation. The peribronchial anatomy gives us the correct angle to rotate the EBUS image. On this image at the left main bronchus, the location of esophagus is located posterior to the left main bronchus, providing the correct orientation for the radial probe.

Orientation of the 12 o'clock position does not correspond to the bronchoscopic 12 o'clock orientation. Comparison of bronchoscopic images and the EBUS image makes it expedient to rotate the EBUS image (Video clip 3.2). The peribronchial anatomy gives us the correct angle to rotate the EBUS image (Figure 3.3). We therefore routinely rotate the EBUS image to give the same orientation as the bronchoscopic image. The balloon probe is withdrawn gradually to enable acquisition of EBUS images in the short axis of lesions and the tracheobronchial wall.

## Tips for Successful EBUS Using A Balloon Probe

**1** Keep the probe in the center of the balloon.

**2** Assess the depth of the tumor center at a site where the first layer is a thick hyperechoic layer.

Keeping the probe in the center of the balloon allows the ultrasound wave to enter the bronchial wall perpendicularly. The layers of the bronchial wall can be visualized clearly where the first layer is a thick hyperechoic layer, with the ultrasound pulse penetrating the bronchial wall perpendicularly [1].

Because the balloon covers the lesion, it is sometimes difficult to ascertain whether an often thin bronchial lesion, visible bronchosopically, has been actually been

covered by the balloon to allow successful ultrasound scanning. There are two ways of solving this problem. The first is to place the deflated balloon directly against the lesion to confirm its presence, then re-inflate the balloon and scan the entire 360° circumference to accurately identify the position of the lesion. The other method is to inflate the balloon and make a 360° circumferential scan, then pull back the balloon slightly into instrument channel, moving the bronchoscope tip so that it indents the balloon, directly observing through the saline-filled balloon the positions of the probe transducer and lesion, and then identifying the lesion in the ultrasonic images (Video clip 3.3).

## Performing EBUS Using a Guide Sheath (EBUS-GS) for Peripheral Pulmonary Lesions

Fluoroscopy is not able to confirm whether forceps have reached the site for endobronchial brushing and transbronchial biopsy (TBB). EBUS cannot create images of normal air-filled lungs, but it can delineate peripheral pulmonary lesions because only small amounts of air come into contact with the probe. The exploration of some bronchi with the miniature probe allows us to determine, more definitively than with fluoroscopy, which bronchus should be selected for endobronchial brushing and TBB. EBUS is also useful for examining lesions that are difficult to visualize by fluoroscopy (e.g. lesions behind the mediastinum or diaphragm, ill-defined opacities, small lesions, and lesions behind other TBB). EBUS clearly identifies which bronchus is most closely related to the lesion and should be subjected to biopsy. Using fluoroscopy, the probe appears at a slight distance even when it is adjacent to the lesion, as demonstrated by the definitive diagnosis of adenocarcinoma by endobronchial brushing at the site using EBUS. This suggests that the area at the margins of the lesions contains more air, so the margins may appear normal on fluoroscopy, leading to underestimation of the size of the lesion.

Since 1996, we have deployed the ultrasonic probe in a guide sheath with the active part of the probe protruding from the tip, identified the location of the lesion ultrasonically, and then passed instruments such as brushes and biopsy forceps down the guide sheath to collect cytology or tissue specimens [2].

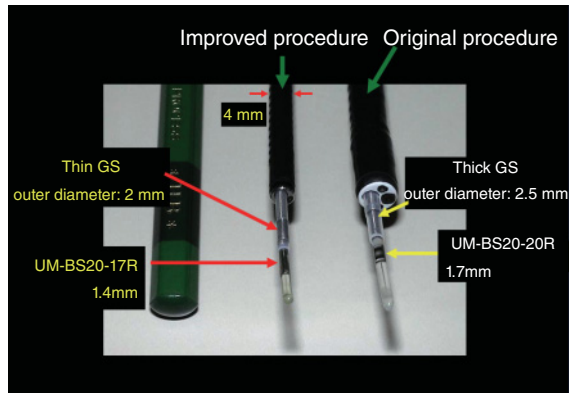


**Figure 3.4** Equipment used in EBUS using a guide sheath (EBUS-GS). In the original procedure, we used a thick guide sheath 2.5 mm in diameter and an ultrasonic probe 1.7 mm in diameter. In the improved procedure, we use a thin guide sheath 2.0 mm in diameter, an ultrasonic probe 1.4 mm in diameter, and a thin bronchoscope 4 mm in diameter.

### Equipment (Figure 3.4)

We use two miniature ultrasonic probes (UM-S20-20R, UM-S20-17R; 20 MHz, mechanical radial, Olympus) with outer diameters of 1.7 mm and 1.4 mm, respectively. Probes are connected to an Endoscopic Ultrasound System (EU-M30, EU-M2000, Olympus). The Guide Sheath Kit (K-201-202, K-203-204, Olympus Optical Co., Ltd.) contains a guide sheath (1.95 mm, 2.55 mm outer diameter, respectively), a disposable brush (BC-204D-2010, BC-202D-2010: 1.4 mm, 1.8 mm outer diameter, respectively), and disposable biopsy forceps (FB-233D, BC-231D-2010: 1.5 mm, 1.9 mm outer diameter, respectively).

### Preparation for EBUS-GS (Video clip 3.4)

**1** A bronchial brush (BC-202D-2010, BC-204D-2010, Olympus), or biopsy forceps (FB-231D, FB-233D, Olympus) for transbronchial biopsy (TBB), is introduced into the specially made guide sheath, so that the tip of the forceps reaches the far end of the sheath to facilitate manipulation. The forceps are marked at the near end of the sheath using the stopper during bronchoscopy.

**2** A miniature probe is introduced into the guide sheath (SG-201C, SG-200C, Olympus) until the tip of the probe including the 2 mm long transducer just protrudes from the far end of the sheath. Then, the probe and the sheath are bound together at the proximal

end of the sheath with the stopper so that the tip of the probe remains positioned at the far end of the sheath.

## How to Perform EBUS-GS

We use a flexible fiberoptic bronchoscope (BF 1T-30, 40, 240R, 260, P260F) for all procedures.

After the bronchoscope is advanced beyond the vocal cords, all segments of the bronchial tree are visualized. Based on the radiographic findings, the miniature probe with the guide sheath is negotiated into the bronchus of interest. That is, by careful study of the CT and the segment where the lesion lies, the subtending bronchus is chosen. With small lesions, choosing the correct bronchus can be difficult and a list of possible 5th or 6th order candidate bronchi can be made by the bronchoscopist before the procedure.

The probe is advanced until it reaches a point where the operator feels resistance, and is then pulled back for scanning (Figure 3.5 – 1). Once an EBUS image of the lesion has been obtained and the location of the lesion has been identified precisely using EBUS, the probe is withdrawn, leaving the guide sheath in place (Figure 3.5 – 2).

Biopsy forceps or a bronchial brush is introduced into the sheath until the point marked by the stopper reaches the proximal end of the sheath (Figure 3.5 – 3). A few vigorous back-and-forth movements of the brush are made under fluoroscopic guidance to collect a sample on the brush.

After the brush is withdrawn, the biopsy forceps are once again introduced into the sheath until the stopper on the surface of the forceps reaches the end of the sheath. The forceps cusps are opened, the forceps are advanced 2 or 3 mm into the lesion and the cusps closed under imaging guidance. After an adequate biopsy specimen is obtained, it is placed in formalin.

The guide sheath is left in place for about 2 minutes to put pressure on the biopsy site to control bleeding. The procedure is concluded after confirmation that haemostasis has been achieved.

## Evaluation of the Diagnostic Yield Using EBUS-GS for Peripheral Pulmonary Lesions [2]

We found that the diagnostic yield for EBUS-GS (thick guide sheath, outer diameter: 2.5 mm) was 77% (116/150 patients) overall, 81% (82/101) for malignant lesions, and 73% (35/45) for benign lesions.

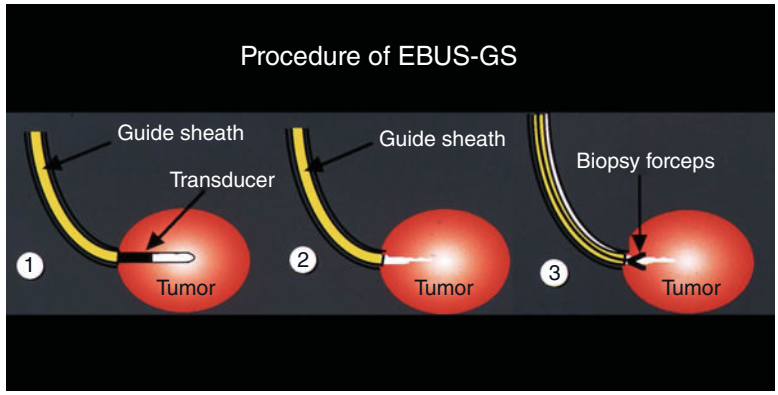


**Figure 3.5** Procedure for EBUS-GS. (1) The probe is advanced until it reaches a point where the operator feels resistance, and is then pulled back for scanning. Once an EBUS image of the lesion has been obtained, the probe is withdrawn and a guide device is inserted into the guide sheath. After searching for the lesion using the guide device under fluoroscopy, the guide device is withdrawn and once again the probe is inserted into the guide sheath and another attempt made to obtain an EBUS image. (2) Once the location of the lesion has been identified precisely using EBUS, the probe is withdrawn, leaving the guide sheath in place. (3) Biopsy forceps or a bronchial brush is introduced into the sheath until the point marked by the adhesive tape reaches the proximal end of the sheath. A few vigorous back-and-forth movements of the brush are made under fluoroscopic guidance to collect a sample on the brush.

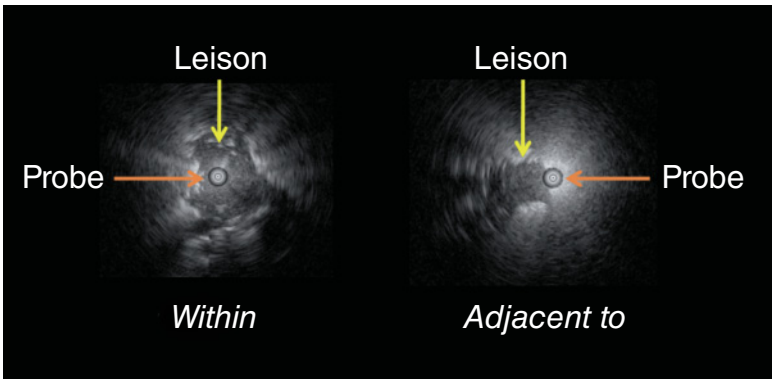


**Figure 3.6** Location of the probe in EBUS-GS for peripheral pulmonary lesions. The diagnostic yield when the probe was within the lesion on the ultrasound image was 87% (105/121), better than that of 42% (8/19) when the probe was adjacent to the lesion.

The diagnostic yield was 60% (90/150) for brushing cytology, and 70% (89/128) for transbronchial biopsy. The diagnostic yield when the probe was within the lesion on the ultrasound image was 87% (105/121), better than that of 42% (8/19) when the probe was at the periphery of the lesion (Figure 3.6).

No difference was seen in diagnostic yield according to lesion size, with 76% (16/21) for lesions ≤10 mm, 76% (19/25) for lesions >10 and ≤15 mm ($p = 0.99, \chi^2$), 69% (24/35) for lesions >15 and ≤20 mm ($p = 0.41, \chi^2$), and 77% (33/43) for lesions >20 and ≤30 mm ($p = 0.96, \chi^2$). In other words, EBUS-GS can diagnose large and small lesions with equal accuracy. A high diagnostic yield of 74% (40/54) was also achieved with lesions ≤20 mm, that cannot be detected using fluoroscopy.

We are now achieving favorable diagnostic results with the introduction of ultrasonic probes in smaller gauge guide sheaths via smaller diameter bronchoscopes, following the route to the lesion determined by virtual bronchoscopy using a CT-based navigation system.

## Tips for Successful EBUS-GS

These comprise tips for using a guide sheath, and tips for introducing the probe into the lesion.

**1** Use of signal attenuation caused by the guide sheath (Figure 3.7). This is a method of accurately placing the guide sheath within a peripheral pulmonary lesion. Once a peripheral lesion has been delineated using EBUS, at the point the lesion appears at its largest and clearest, the assistant should keep the guide sheath stationary and after undoing the connection of the ultrasound probe to the guide sheath withdraw the ultrasonic probe 1 mm at a time until the probe transducer enters the sheath. When the transducer completely enters the guide sheath, the ultrasonic pulse will be blocked by the guide sheath, and the ultrasound image will suddenly become darker. If the site of this phenomenon is within the lesion, the guide sheath will be placed precisely within the peripheral pulmonary lesion.

**2** Moving the guide sheath from adjacent to the lesion to within the lesion (Figure 3.8). Diagnostic yield has been reported to be superior when the probe is within the lesion than when it is adjacent to the lesion [2]. With 4 mm diameter bronchoscopes as commonly used presently, when we introduce the probe into the selected sub-subsegmental bronchus to delineate a lesion using EBUS, the probe is sometimes placed adjacent to the lesion. In that case, the probe should be introduced into another sub-subsegmental bronchus in an attempt to place the probe within the lesion.

When a lesion cannot be delineated using EBUS, the ultrasonic probe should be removed without moving the guide sheath, guiding device introduced into the guide sheath until their tips protrude (Figure 3.9). The tip of the guiding device (a hinged curette) is bent in the direction of the lesion, and the guiding device is then withdrawn slowly, looking for a point at which they move slightly towards the lesion under fluoroscopic guidance. The aim is to enter a bronchus leading to the lesion branching off from the initial bronchus point, and if the tip of the guiding device is advanced in this direction the guide sheath will follow, reaching the lesion. Sometimes such a branch point can be felt as a slight "crank" as the curette drops into a bronchial

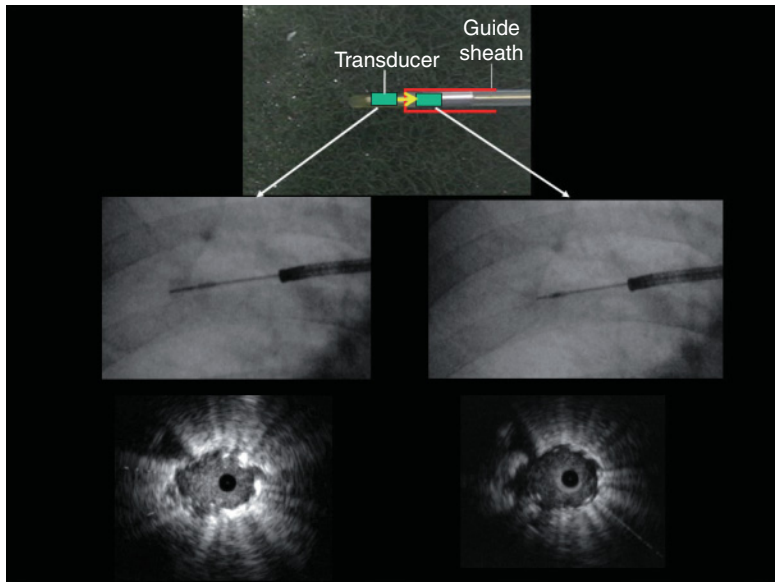


**Figure 3.7** Confirmation of the location of the guide sheath within the lesion. This is a method of accurately placing the guide sheath within a peripheral pulmonary lesion. Once a peripheral lesion has been delineated using EBUS, at the point the lesion appears at its largest and clearest, the assistant should withdraw the ultrasonic probe about 2–3 mm at a time until the probe transducer enters the guide sheath. When the transducer completely enters the guide sheath, the ultrasonic pulse will be reflected by the guide sheath, and the ultrasound image will suddenly become darker. If the site of this phenomenon is within the lesion, the guide sheath will be placed precisely within the peripheral pulmonary lesion.

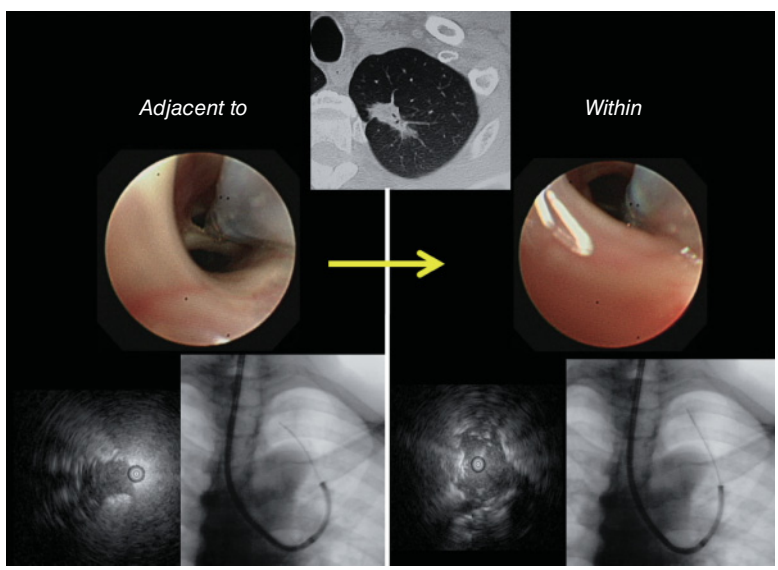


**Figure 3.8** Moving the probe from adjacent to the lesion to within the lesion – method 1. When we introduce the probe into the selected sub-subsegmental bronchus to delineate a lesion using EBUS, the probe is sometimes placed adjacent to the lesion. In that case, the probe should be introduced into another sub-subsegmental bronchus in an attempt to place the probe within the lesion.

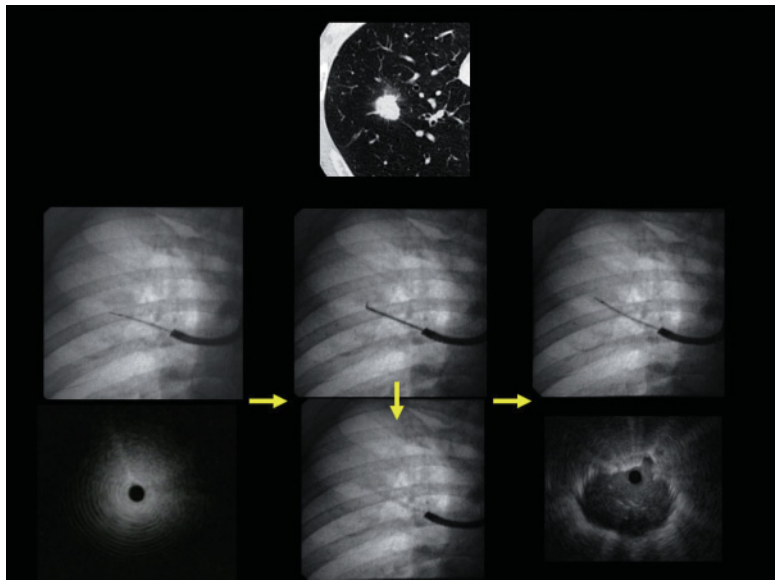

**Figure 3.9** Moving the probe from adjacent to the lesion to within the lesion – method 2. Top: the lesion was located in right upper lobe. Left: When a lesion cannot be delineated using EBUS, the ultrasonic probe should be removed without moving the guide sheath, guiding device introduced into the guide sheath until their tips protrude. Middle: The tip of the guiding device is bent in the direction of the lesion, and the guiding device is then withdrawn slowly, looking for a point at which they move slightly towards the lesion. A bronchus leading to the lesion branches off from this point, and if the tip of the guiding device is advanced in this direction the guide sheath will follow, reaching the lesion. This allows accurate placement of the guide sheath within the peripheral pulmonary lesion. Right: The guiding device is then removed, the ultrasonic probe is reintroduced, and the lesion can be delineated.

opening. This allows accurate placement of the guide sheath within the peripheral pulmonary lesion. The guiding device is then removed, the ultrasonic probe is reintroduced, and the lesion can be delineated.

The main benefits of EBUS-GS are as follows:

**1** The position of lesions can be accurately determined.
**2** Forceps can be introduced any number of times to the same bronchial segment.
**3** The internal structure of lesions can be analysed.
**4** There is very little post-transbronchial biopsy bleeding.

## EBUS Guided Transbronchial Needle Aspiration (EBUS-TBNA)

### Equipment (Figure 3.10)

We use a convex bronchoscope (BF-UC260F, 7.5 MHz, Olympus) with an outer diameter of 6.9 mm. The

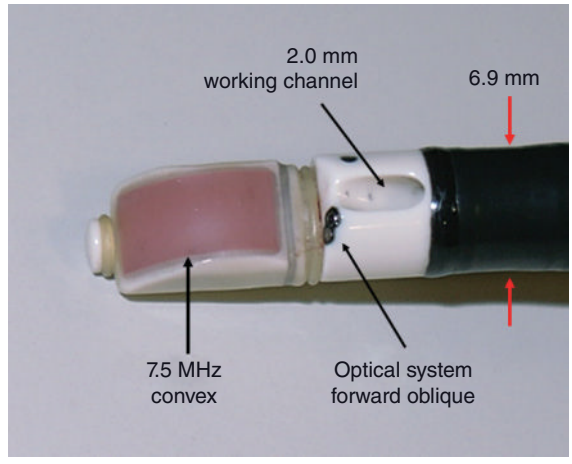


**Figure 3.10** Bronchoscope used in EBUS-TBNA (BF-UC260F, 7.5 MHz, Olympus Optical Co., Ltd., Tokyo, Japan).

probe is connected to an Endoscopic Ultrasound System (EU-C2000, Olympus).

## How to Perform EBUS-TBNA

We usually carry out EBUS-TBNA with topical pharyngeal anesthesia, and sedation (e.g. midazolam).

The assistant elevates the patient's jaw to maximize the pharyngeal space. The convex bronchoscope is inserted into the pharynx. We should observe the 12 o'clock position of the vocal cord in order to pass the larynx smoothly, as this scope has an oblique forward view.

Another way of introducing the bronchoscope into the trachea is to insert an endotracheal tube, leaving this in place for the duration of the procedure. An 8.0–8.5 Fr endotracheal tube is placed over the commonly used bronchoscope, and the tip of the bronchoscope introduced into the trachea. With the tip of the patient's jaw elevated, the endotracheal tube is then introduced into the trachea using the bronchoscope as a guide. Intubation in this way has the advantage that emergency treatment for hemorrhages can be given even if the visual field is obscured by blood on the bronchoscope lens.

During assessment of the location of the lesion on chest CT, the inflated balloon containing the probe is in contact with the bronchial wall adjacent to the lesion.

The target lesion is clearly outlined by EBUS. By rotating the bronchoscope on its axis slightly in both directions, the transducer at its tip will scan and delineate the entire target lesion. In this way, the bronchoscopist measures the size of the target lesion (Figure 3.11). First, B mode scanning determines whether the internal echoes of the lesion to be punctured are homogenous or heterogenous. Scanning in power Doppler mode should be performed for the target lesion as well as the path that the needle is expected to traverse. This additional information should help avoid unintended puncture of interposed small vessels and bronchial arteries located between the bronchial wall and the target lesion. Sometimes the target lesion is a lymph node with some necrotic areas, in which case optional power Doppler mode scanning will show the necrotic areas with reduced blood flow to be avoided, and allow identification of the region with tortuous blood flow (1 mm vessels) within the target lesion that is to be punctured.

The transducer must constantly be held in firm contact with the tracheobronchial wall during puncture. The needle is prepared immediately before puncture is to be performed, and is inserted into the working channel of the bronchoscope. We take care that the edge of the outer sheath just protrudes from the bronchoscope. The stylet is withdrawn a few centimeters to expose the sharp needle. A problem with

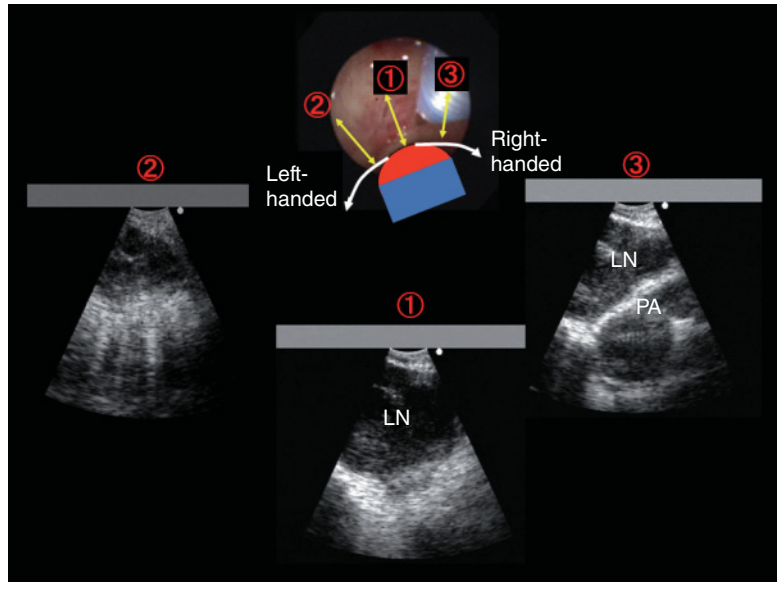


**Figure 3.11** Rotating the bronchoscope for the target lesion. The target lesion is clearly outlined by EBUS. By rotating the bronchoscope on its axis slightly in both directions, the transducer at its tip will scan and delineate the entire target lesion.

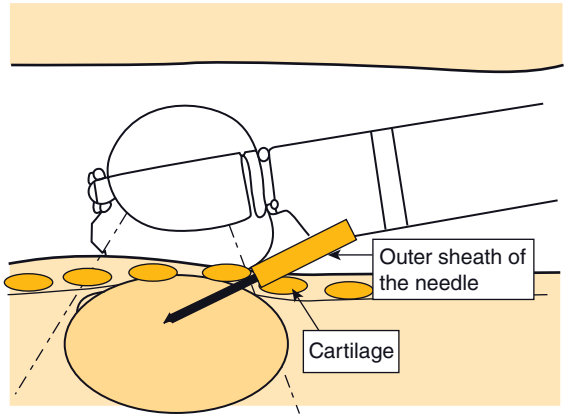


**Figure 3.12** The tip of the puncture between cartilages. The tip of the outer sheath is then pushed toward the bronchial wall, aiming for the membranous part between cartilages.

currently available aspiration needles is that when the needle is advanced, its outer sheath often protrudes too far with it. There is a way to overcome this problem (Video clip 3.5). The needle is pushed anteriorly within the bronchus, so that when the needle comes near the tip of the outer sheath the sheath approaches the transducer, and through the bronchoscope we can see the tip of the outer sheath suddenly drop a millimeter or so down. The needle is stopped at this point, and the outer sheath is withdrawn once again until it can just be seen through the bronchoscope. If we advance the needle now, puncture can be performed with almost no movement of the outer sheath. The tip of the outer sheath is then pushed toward the bronchial wall, aiming for the membranous part between cartilages (Figure 3.12). This step is very important for a successful puncture. The needle is placed against the tracheobronchial wall and the target lesion. The needle, containing the partially withdrawn stylet, is then advanced into the lesion under real time ultrasound guidance. The stylet is repositioned before it is withdrawn to remove the primary tissue plug containing superficial layers and bronchial cartilage from the needle (Video clip 3.6). Suction is then applied through the needle using a 10 or 20 mL syringe. The needle is further advanced into the lesion and moved back and forth under ultrasound control, with 5 to 10 strokes within the lesion usually sufficient. Suction is then equilibrated while the tip of the needle is still in the lesion. The needle is now withdrawn, and the needle and the outer sheath removed.

In order to retrieve the tissue sample from the needle, the stylet is inserted into the needle from the tip of the needle, and the sample will emerge from the needle tip. This is piled up on a piece of filter paper to facilitate histopathological examination. Any cellular material remaining inside the needle is then flushed out using air from the syringe, and sent off for cytological examination (Video clip 3.7).

## References

1 Kurimoto N, Murayama M, Yoshioka S, et al. Assessment of the usefulness of endobronchial ultrasonography in tracheobronchial depth diagnosis. Chest 1999;115: 1500–1506.

2 Kurimoto N, Miyazawa T, Okimasa S, et al. Endobronchial ultrasonography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. Chest 2004;126:959–965.

## Frequently Asked Questions

**1** Is it always necessary to use the balloon?
**A:** The balloon is necessary to scan the cartilaginous portion (horse-shoe shape) of extrapulmonary bronchus for avoiding air between cartilages. The balloon is unnecessary for scanning the membranous portion of extrapulmonary bronchus, and intrapulmonary bronchus.

**2** If N1 and N2 nodes are to be sampled how is this managed – should different needles be used for each site?
**A:** Ideally different needles should be used for each site. However, the needle is very expensive and the first puncture should be performed at the more proximal site (ex: N2). The lumen of the needle should be cleaned by flushing with saline.

**3** Is a standard bronchoscopy necessary before doing a convex probe EBUS procedure?
**A:** For checking a bronchial lesion before TBNA, a standard bronchoscopy is necessary. For EBUS-TBNA, a standard bronchoscopy is unnecessary.

**4** How much bleeding usually occurs after a TBNA?
**A:** In most of cases, bleeding is very little (about 0–3 mL). If bleeding is severe, the balloon is useful to press the bleeding point on the bronchus.

**5** What happens if the needle goes into a pulmonary artery branch?
**A:** If the needle goes into a pulmonary artery branch, bleeding is not usually severe. I have experienced no case of puncturing great vessels, but on animal experiments there was a little bleeding after puncturing great vessels. We should check bleeding around the great vessel in the mediastinum by EBUS.

**6** How do you avoid the esophagus?
**A:** From trachea to left main bronchus, the esophagus is located beside the bronchus. We can detect the esophagus containing air in the lumen.

**7** Which nodes are easiest to biopsy?
**A:** The EBUS-TBNA for 11L or 11R is easiest to biopsy, because the bronchial cartilage around 11L or 11R is small.

**8** Should on-site cytology be used?
**A:** On-site cytology is very useful when deciding to end the EBUS-TBNA for a malignant lesion.

# 4 Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA)

## Anatomy

Mediastinal lymph nodes are generally described according to their anatomic location in the United States. In Europe, Asia, and other parts of the world, they are referred to using international nomenclature. The following diagram (Figure 4.1) depicts their names and locations. It is important to learn the international nomenclature of mediastinal lymph node stations (i.e., their numbers) in order to be able to communicate with surgical and international colleagues.

The lymph node stations easily accessible using endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) include the following mediastinal stations: highest mediastinal (station 1), upper paratracheal (stations 2R and 2L), lower paratracheal (stations 4R and 4L), and subcarinal (station 7). The accessible hilar stations are hilar (station 10), interlobar (station 11), and lobar (station 12).

Some commonly encountered discrepancies between the US and international nomenclature are as follows. Lymph node station 4L is often referred to as the AP (aorto-pulmonary) window node in the US, instead of the lower left paratracheal nodes. In reality, the station 5, subaortic node is the "aorto-pulmonary node" and it is not accessible by TBNA (Figure 4.1). Similarly, station 11, rather than station 10, lymph nodes are often referred to as hilar nodes in the US. According to the international nomenclature, station 11 should be called the interlobar nodes, since it is located below the upper lobe take-off, and station 10 should be referred to as the hilar nodes. Station 8 should be called para-esophageal nodes, and should be distinguished from the subcarinal nodes, or station 7.

In addition to the lymph node stations, the locations of major vascular structures in relation to airways and lymph nodes should be committed to memory. As shown in Figures 4.2, 4.3, 4.4, 4.5, and 4.6 the ascending part of the aorta lies anteriorly, along the left side of the trachea. It then descends, making a curve around the left hilum, heading posteriorly. The main pulmonary artery lies in front and just to the left of the distal trachea and carina. It bifurcates into left and right pulmonary arteries that travel anterior to the left and right mainstem bronchi, respectively. At the level of each hilum, the pulmonary arteries further divide, following the branching of the airways. At each potential transbronchial needle aspiration (TBNA) site, the location of the vessels may vary, as shown in. It is helpful to post a chart of these figures in the bronchoscopy room and review it prior to the procedure.

## Transbronchial Needle Aspiration

Transbronchial needle aspiration (Figure 4.7) has been used for decades, but with very inconsistent yield. Low yield may be related to multiple factors, including the expertise of the bronchoscopist and the variation in size and location of the target lymph nodes. Fear of vascular punctures, often due to inadequate training in the technique, is probably the most common reason for the low yield of TBNA.

In order to use EBUS-TBNA to its maximum potential, the bronchoscopist must first hone his or her standard TBNA skills. Endobronchial ultrasound merely provides real-time images to prevent non-nodal needle insertion. Good samples ultimately depend on

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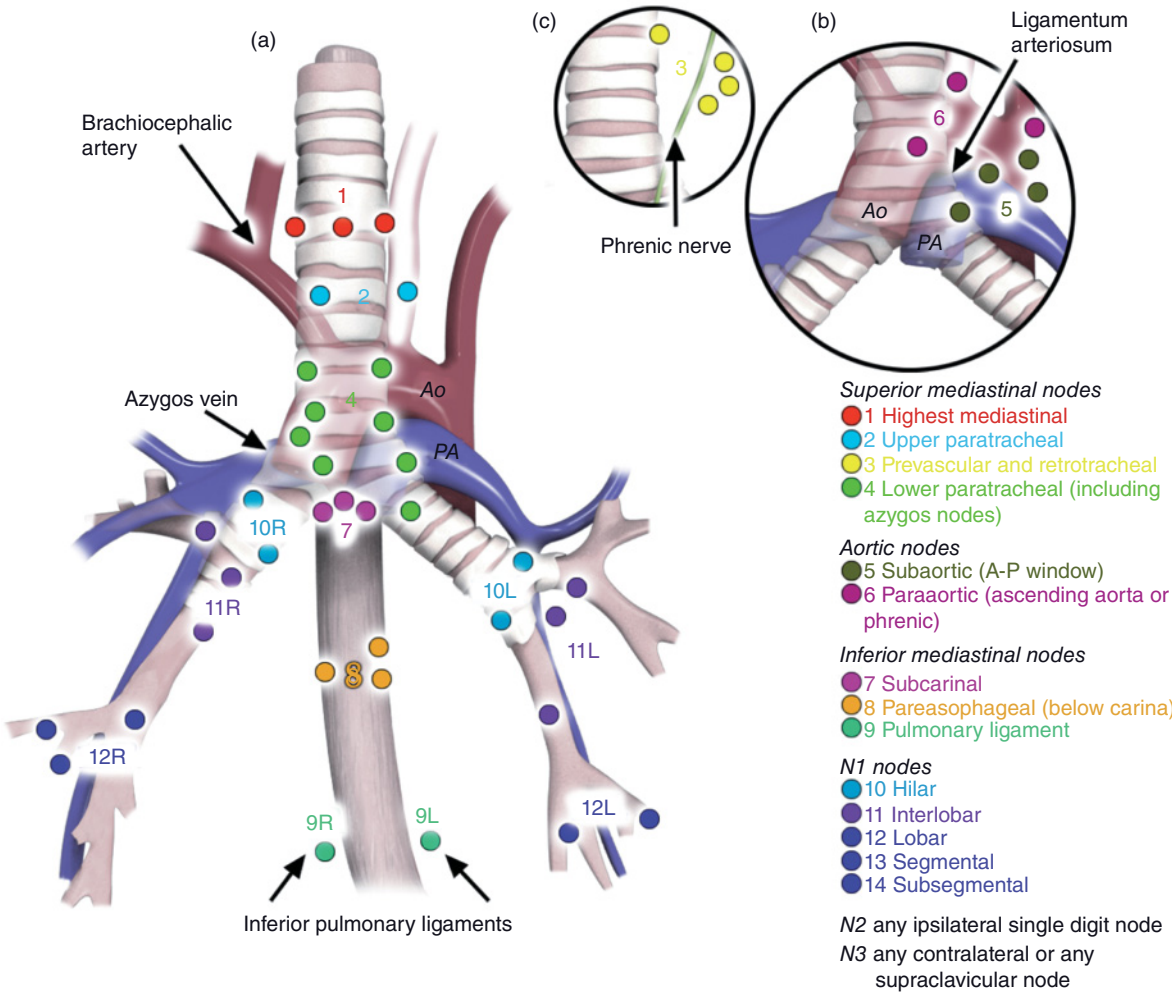


**Figure 4.1** (a) Anterior view of mediastinal lymph node stations in relation to major airways and vascular structure. (b) Lat view of station 5 and 6 in relation to aorta and main pulmonary artery. (c) Station 3 node along trachea with close proximity to phrenic nerve.

good TBNA technique, and the feeling of EBUS-TBNA is very similar to standard TBNA with the added benefit of visualization. Being comfortable with standard TBNA removes much of the "mystery" about EBUS-TBNA, and makes clear the intuitive aspects of the design of the EBUS-TBNA needle. In the following section, the knowledge and instruments necessary for successful TBNA are briefly reviewed.

## Needles

TBNA needles range in size from 19 to 22 gauge (G). Their length usually varies between 13 to 15 mm. Some are little stiffer than the others, depending upon the manufacturer (Figure 4.8).

Generally, the first pass should be performed with a small needle, such as a 22 G, to minimize the risk of inadvertent vascular puncture. Once the safety of the puncture site is established with the 22 G needle, one may use a larger bore (19 G) or histology needle. Larger bore needles are generally required to adequately sample lymph nodes in diseases such as lymphoma or sarcoidosis, because tissue architecture plays a pivotal role in their diagnosis. Alternatively, there is a double needle that has a 21 G inner needle with a

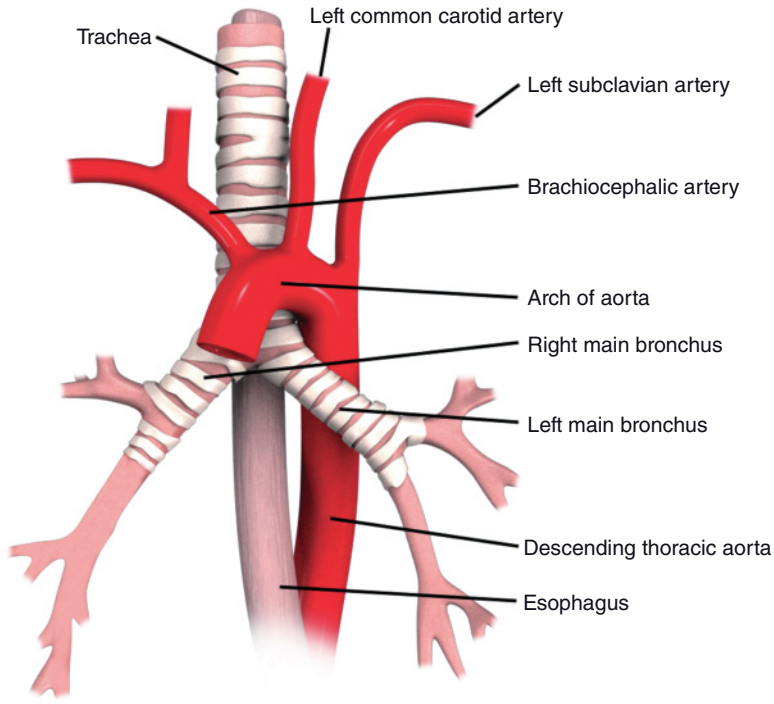


**Figure 4.2** Anatomy of trachea and major airways in relation to the arch of aorta and its main branches "anterior view".

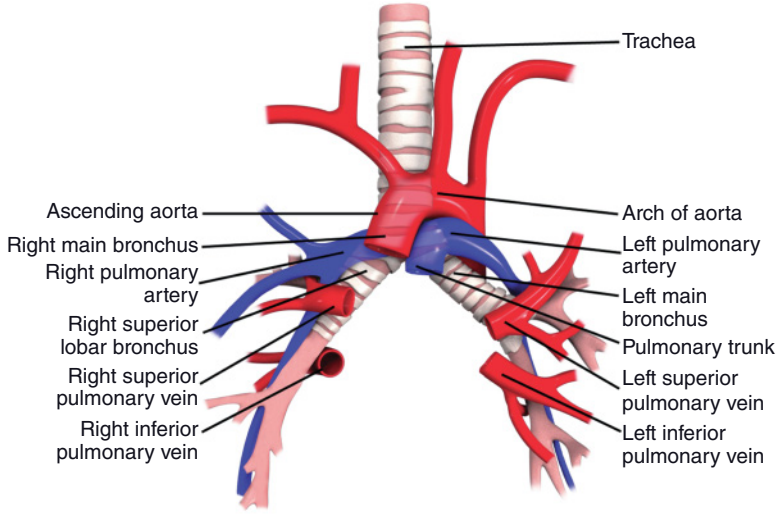


**Figure 4.3** Anatomy of major airways in relation to aorta, pulmonary artery, pulmonary vein and their branches.

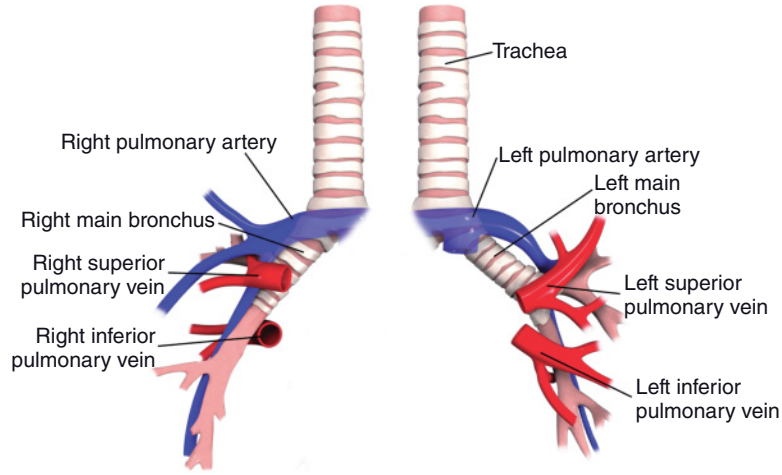


**Figure 4.4** Anatomy of trachea and bilateral main stem bronchi with major vessels.

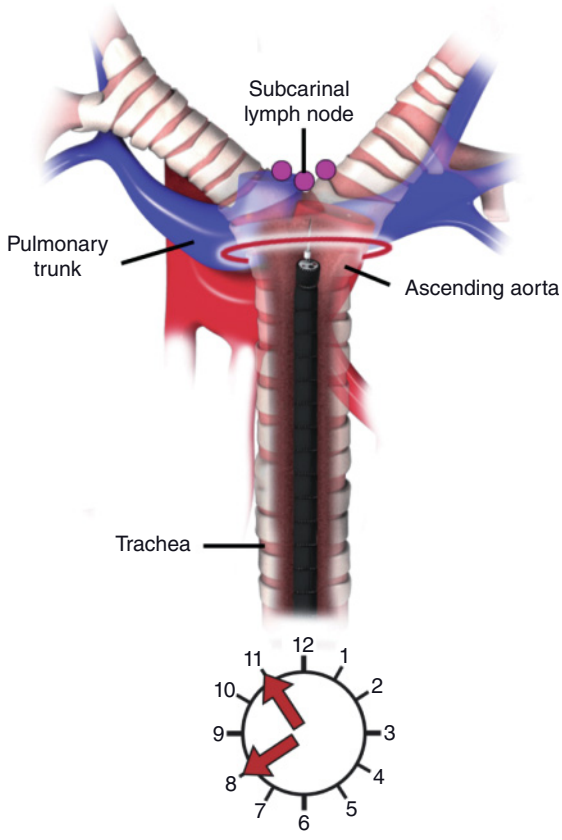


**Figure 4.5** Locations of sub-carinal (station 7) lymph nodes in relation to trachea, main stem bronchi, aorta and pulmonary artery. The anatomical clock at the bottom shows unsafe areas for needle insertion by red arrows pointing in that direction.

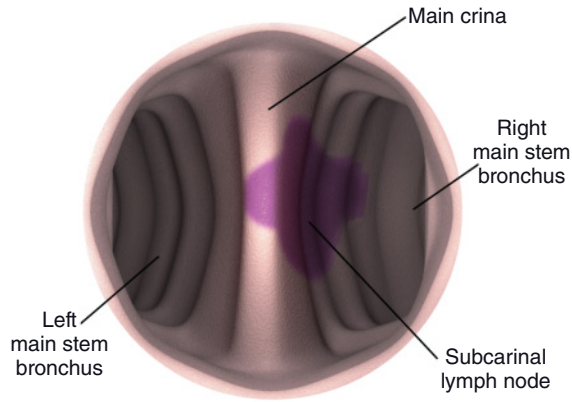


**Figure 4.6** Endotracheal and endobronchial area is highlighted to show the proper site for needle insertion for subcarinal node TBNA.

19 G histology needle that slides over it, from the same catheter.

## Planning the Approach

The chest CT with contrast should be thoroughly reviewed, regardless of whether or not EBUS will also be used. Often, it is helpful to reverse the CT film in order to better visualize the relationship between lymph nodes, airways, and vascular structures, as they will be encountered during the bronchoscopy. All lymph node stations should be thoroughly evaluated on the CT scan, and a strategic plan to approach different stations in the order of preference should be made.

In the event of potential or known malignancy, one should always attempt to sample the node that would stage the disease at its highest level. For example, in a patient with a 1 cm left upper lobe nodule (T1) and adenopathy at left paratracheal, subcarinal, and right paratracheal stations, the first target should be the right paratracheal lymph nodes (N3), which, if positive, would make the disease stage III B. Sampling only the subcarinal (N2) or left paratracheal (N2) nodes would result in staging at a lower level, namely stage III A (Figure 4.9). This approach allows one to diagnose and stage the patient appropriately in a single, minimally invasive, out-patient procedure and precludes unnecessary surgical staging. If the highest station lymph nodes cannot be successfully sampled, one should then move to the second highest station. The issue of changing the needles between different stations is still under investigation.

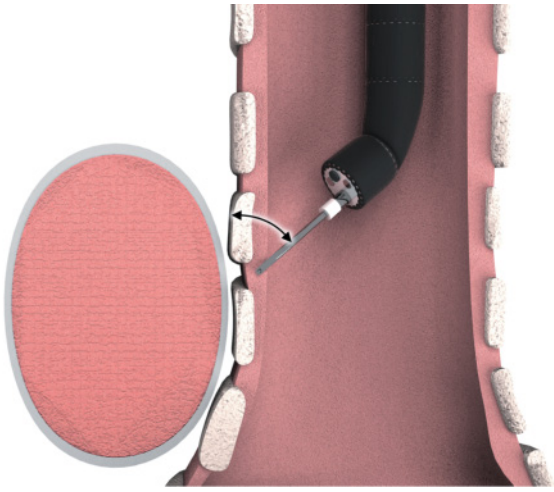

**Figure 4.7** Transbronchial needle aspiration: the needle is passed through the airways wall in between the cartilage with an angle as perpendicular as possible. The lymph node or mass lying outside of the airways is traversed blindly or under ultrasound guidance.

## Insertion Technique

The four most common techniques for standard TBNA needle insertion described in the literature are the so-called hub, jab, piggy-back, and cough techniques. The technique used is purely a matter of personal preference. I prefer the hub technique, mainly because it is safer and easier to teach. The "hub" technique (Figure 4.10) involves placing the hub of the needle/catheter at desired site of insertion and, after watching for needle movement during a few respiratory cycles, pushing the needle out while holding the scope and the hub in place. The "jab" technique (Figure 4.11) involves first advancing the needle out of the catheter and then entering the target area by pushing the catheter down while holding the scope in place. The "piggy-back" technique (Figure 4.12) entails having the needle out of the catheter, with the catheter out of the working channel, at a fixed distance in the airway lumen. The scope is then advanced into the target as one unit.

The "cough" technique (Figure 4.13) requires a relatively awake and cooperative patient. In this technique the patient is asked to cough while the needle coming out from the catheter is held in a steady position on the airway wall. The cough brings the airway wall onto the needle allowing it to penetrate the tissue.

In whichever technique is chosen, once the needle is inside the target area, suction is applied first to confirm the avascular nature of the insertion site. Generally when within a lymph node suction on the

**Figure 4.8** A typical transbronchial needle and attached catheter.

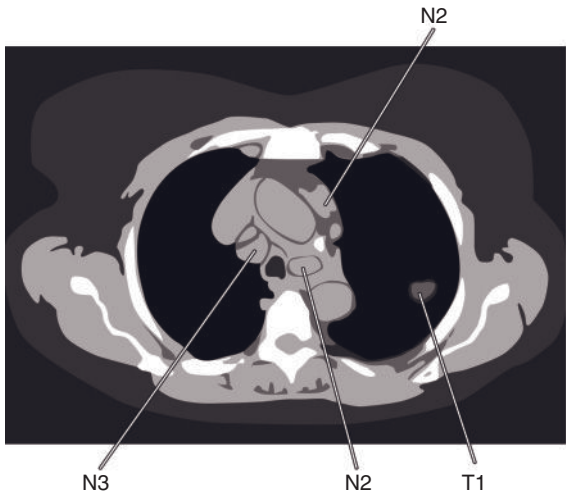


**Figure 4.9** A CT slice depicting a left upper lobe nodule (T1) and a mediastinal adenopathy at stations 4L (N2), 4R (N3) and prevascular area (N2).

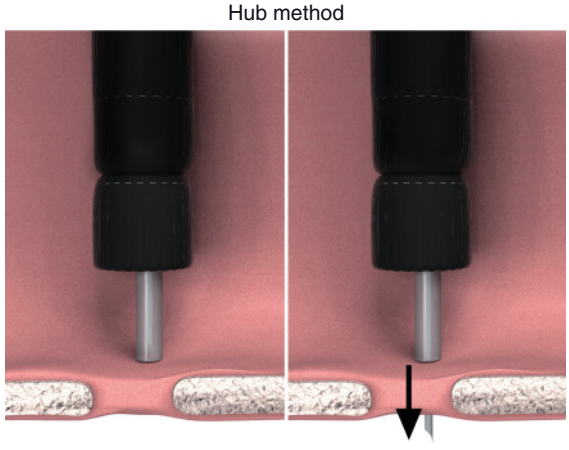


**Figure 4.10** Hub technique – by placing the hub of needle at desired site of insertion, the needle is pushed out while holding the scope and the catheter in place.

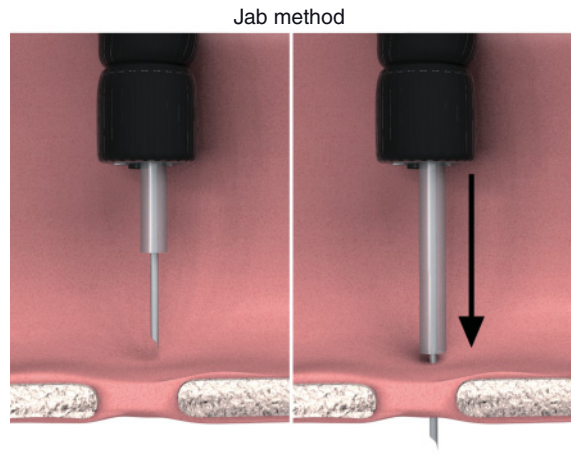


**Figure 4.11** Jab technique – having the needle out of the catheter and then entering the target area buy pushing the catheter down while holding the scope in place.

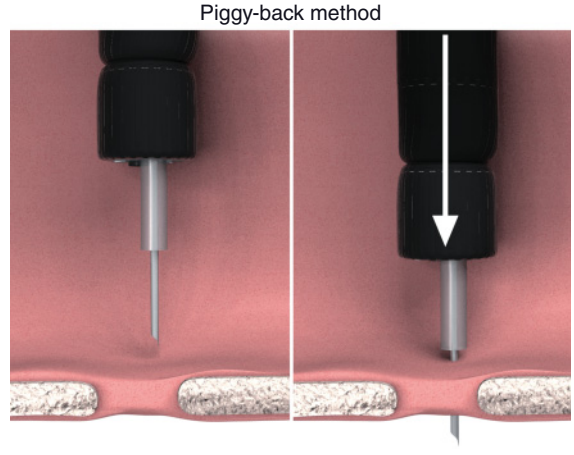


**Figure 4.12** Piggy back technique – having the needle out of the catheter while holding the catheter out of the working channel at a fixed distance in the lumen of the airway. The scope is then driven down into the target by the operator as one unit.

needle should meet with firm resistance. In case of bloody return, suction should be turned off immediately and the needle should be retracted and removed from the working channel. Any blood from the puncture site should be suctioned. In general, bleeding in these situations is minor and stops spontaneously. Significant bleeding is very rare. Once the bleeding stops, another attempt can be made in different location.

Once the needle's location outside of a vascular structure is verified, a rapid and shallow in-and-out motion is used to obtain the sample, while keeping the bronchoscope fixed at the patient's nose or mouth. An assistant may help to limit the scope motion. The

motion should be deliberate and swift. Attention should be paid to keep the scope straight between the patient and the operator's hand. If there is slack in the scope, much of jabbing motion is lost before reaching to needle. I usually jab between five and ten times. The suction should be slowly released before pulling the needle back in the catheter, to prevent aspirating bronchial cells on the way out. Once the needle is fully inside the catheter, the catheter should be removed from the working channel. Care must be taken to make sure that the needle is fully inside the catheter when going in and out of the working channel, otherwise the scope can be lacerated. The bronchoscopist should deliberately pause at this time to clear any secretions from the tip of the bronchoscope to allow as clear a view of the tip of the TBNA needle as possible to ensure that the sharp needle has been completely retracted.

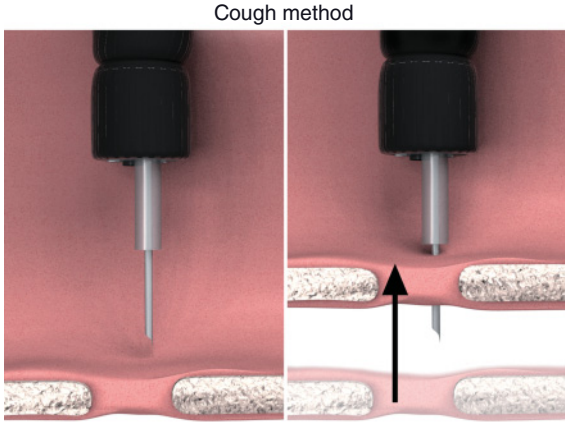


**Figure 4.13** Cough technique – in this technique the patient is asked to cough while the needle is held in a steady position on the airway wall. The cough brings the airway wall onto the needle allowing it to penetrate the tissue.

## Sample Handling

Rapid on-site cytology (Rapid On Site cytologic Evaluation – ROSE) allows for differing additional biopsy with outloss in diagnostic yield, likely lower procedural risk and is cost effective [1]. If on-site cytology is available, the sample from the needle should be transferred directly to the slides. We usually make at least two slides from each pass, one for Diff-Quick and the other for hematoxylin and eosin (H & E). The usual air drying method is employed for the preparation of these slides. The remaining sample is pushed into a container filled with the saline for a cell block. The needle/catheter is purged with air and saline to prevent clotting. The entire process can be repeated in the event of a negative yield on the first pass.

## Endobronchial Ultrasound

Endobronchial ultrasound was created by modifying and miniaturizing the endoscopic ultrasound used by gastroenterologists. Please refer to Chapter 1 of this book for a review of the physical principals of ultrasound. The initial version was a radial ultrasound probe (radial probe) (Figure 4.14). This probe passed

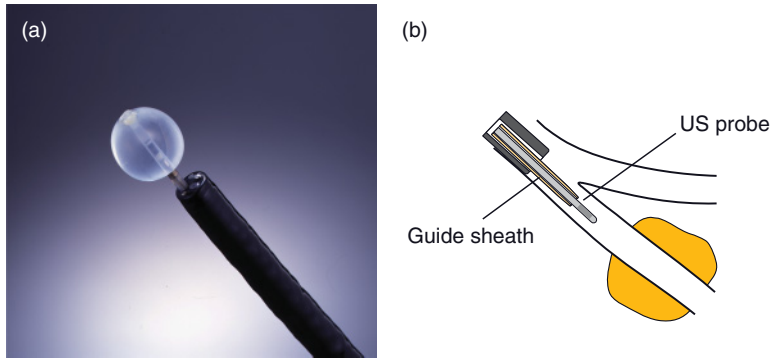


**Figure 4.14** (a) Endobronchial ultrasound balloon probe (UM-BS20-26R) extending out of the working channel of a flexible bronchoscope. The balloon over the probe is inflated with normal saline. (b) Endobronchial ultrasound probe is extended in the lumen of the airway through the working channel of a flexible bronchoscope. Once the balloon is inflated, the probe can pick up the sonographic features of a mass around the airways.

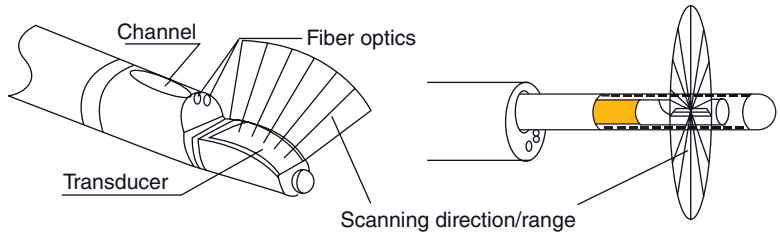


**Figure 4.15** Comparative structures of EBUS scope and radial probe. The EBUS scope (XBF-UC260F-OL8, Olympus, Tokyo, Japan) has a convex/linear transducer (7.5 MHz) extending ahead of the light source and camera. The outer diameter of the scope itself is 6.7 mm whereas that of a tip is 6.9 mm. The angel of the view is 90° and the direction of the view is 30° forward oblique. The radial probe can pass through the working channel of the bronchoscope into the lumen of the airway. It rotates 360° and gives a circular image of objects all around it.

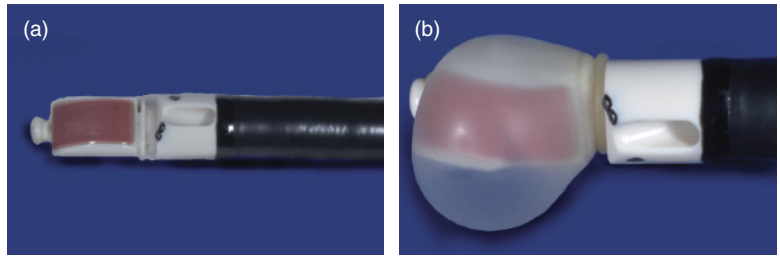


**Figure 4.16** (a) The EBUS scope (XBF-UC260F-OL8, Olympus, Tokyo, Japan). (b) The balloon is over the transducer is inflated with saline.

through the working channel of the bronchoscope into the airway lumen and could rotate 360°. A balloon sheath over the probe was inflated with saline to fill up the airway lumen. The saline-filled balloon provided a good medium for sonic coupling between the probe and the target tissue. Once the images were captured and recorded, the probe was pulled out of the scope's working channel to allow for insertion of the TBNA needle/catheter. As a result, the operator needed to make a mental picture of the potential needle insertion site in reference to the airway and vascular structures. Hence, this was a "blind" technique, (not real-time) which limited its utility and popularity. It did however allow for more confidence in less commonly needled sites such as hilar or left paratracheal.

In early 2000, a real-time EBUS device was introduced. The major difference between the EBUS scope (linear scope or convex scope) and the radial probe is its capacity to provide real-time images during TBNA. The EBUS scope (BF-UC260F-OL8, Olympus, Tokyo, Japan) (Figure 4.15) has a convex/linear transducer (7.5 MHz) extending ahead of the light source and camera. The outer diameter of the scope is 6.7 mm, whereas the tip is 6.9 mm (Figure 4.16). The angle of the view is 90°, and the direction of the view is 30° forward oblique. The convex surface should be in direct contact of the airway wall, or the space between them should be filled with a good sound-conducting medium, such as saline. The ultrasound image is processed in the ultrasound scanner (EU-C2000, Olympus, Tokyo, Japan). A small balloon (Figure 4.17) mounted over the linear /convex probe is filled with saline once the probe is in the airway lumen. An extra opening under the working channel, below the handle of the scope (Figure 4.18), allows for saline to be instilled

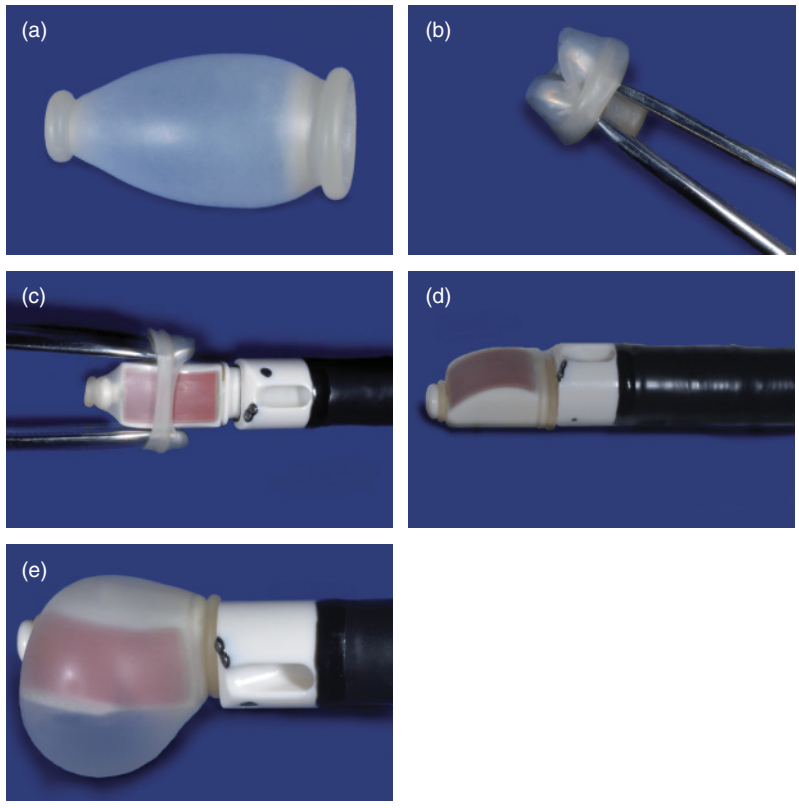


**Figure 4.17** (a) Balloon to go over the convex probe. (b) The balloon is held between the two arms of the application forceps at half length and reversed over it. (c) The balloon is applied over convex probe with the wider opening of the balloon sitting in the crease on the distal aspect of the convex probe. (d) Smaller opening of the balloon is pushed down with the pad of index finger over the tiny knob at the distal most aspect of the convex probe. All the bubbles should be released from the tip of the balloon after first inflation with saline before pushing the tip of the balloon onto the tip of the convex probe. (e) Inflated balloon on the convex probe without any air bubbles.

into and removed from the balloon. Because the camera faces 30° forwards and upwards, maneuvering the scope in the airway can be somewhat challenging. I think of it as lying on one's back in a tunnel looking up and ahead while dragging forward.

The needle set-up of the EBUS scope appears rather complex at first, and requires a good understanding of its operation. The needle comes out at a 45° angle from the working channel of the EBUS scope, passing above and away from the balloon on the probe (Figure 4.19). The needle provided with the EBUS system is 22 G. However, the inner diameter of this needle is equal to a 21-gauge needle, which allows larger, histological core samples. The most proximal portion of the needle assembly (Figure 4.20) is a stylet. Just under the handle bar is a white needle lock that controls the length of the needle. The length of the needle is also controlled by a stop bar slightly distal to handle bar. When placed at number three, the stop bar limits the functional length of the needle to 20 mm. Under the stop bar is a white sheath lock. This lock allows the sheath covering the needle to be moved forward or backwards (Figures 4.21 and 4.22). Usually, I advance the sheath to the tip of the working channel so that it appears on the upper right portion of the monitor screen prior to the actual insertion. This prevents the scope from being pushed away from the tissue when trying to introduce the needle in the tissue.

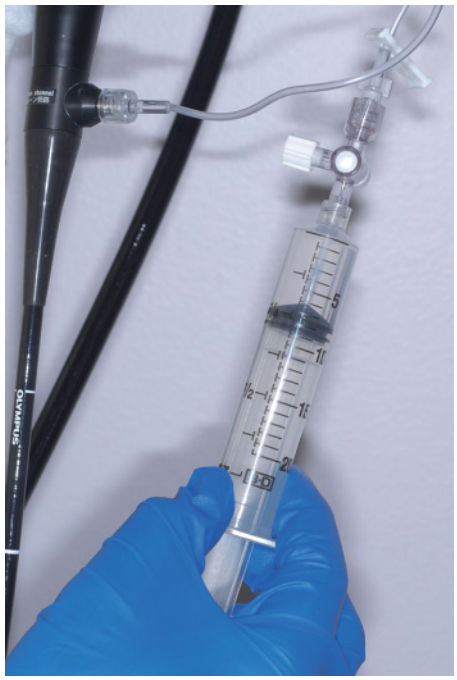

**Figure 4.18** An extra opening under the working channel port of the scope allows for inflation of balloon over the transducer with saline. This opening is connected with the 20 cc syringe filled with saline via IV tubing and a stop cock.

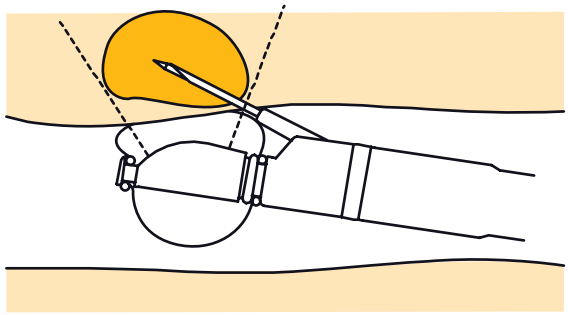

**Figure 4.19** This figure depicts the relationship between the convex probe, balloon covering the convex probe, needle extending from the working channel and penetrating the lymph node behind the airway wall.

Under the sheath lock, there is a safety adaptor to lock the needle handle to the biopsy port. The purpose of this lock is to prevent movement of the needle assembly from the scope.

The EBUS scope set up also includes connecting the scope via a scope cable to the control panel as shown in Figure 4.23. Once connected and secured properly, monitor settings should be chosen for optimal picture quality. Our usual setting are depth 4 cm, penetration mode, and GI2 (contrast 2). The gain is certain at every start up of this ultrasound machine (Figure 4.24).

## Step-by-Step Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

A thorough examination of the airway is performed with a conventional (non-EBUS) bronchoscope prior to EBUS-TBNA. Endobronchial lesions should be excluded which may obviate the need for EBUS-TBNA. An EBUS scope is then inserted through the oral cavity. Some experts go directly to the TBNA site, while others perform a thorough ultrasound examination of the mediastinum prior to proceeding to the pre-selected site. I favor the latter approach, because the ultrasound survey often provides more practical information about the location and accessibility of nodes, compared with the CT scan. However, one should still abide by the predetermined plan to sample lymph nodes that would, if positive, stage the disease to the highest level in the smallest number of attempts.

After the ultrasound-guided mediastinal survey, and before the final approach to the insertion site, the tip of the scope is placed in a large airway, where the catheter and needle are positioned at its tip (Figure 4.25). The catheter is pushed out to the tip of the scope by loosening the catheter lock. The catheter tip should be barely visible on the upper right portion of the monitor screen showing bronchoscopic findings. This can be done either before passing the scope or when inside the bronchial lumen. The needle lock is then loosened and the needle is advanced out to the tip of the catheter. This can be demonstrated by observing a "drop" in the needle apparatus as the needle is advanced with the sheath locked. From this point the sheath is pulled back to its original position just exiting from the channel tip. Once the catheter tip and needle are in place, the locks are tightened and the stylet is pulled back about 2 cm to allow the bevel of the needle to lead. Optionally it is possible to lave the stylet fully in, as some operators report less contamination

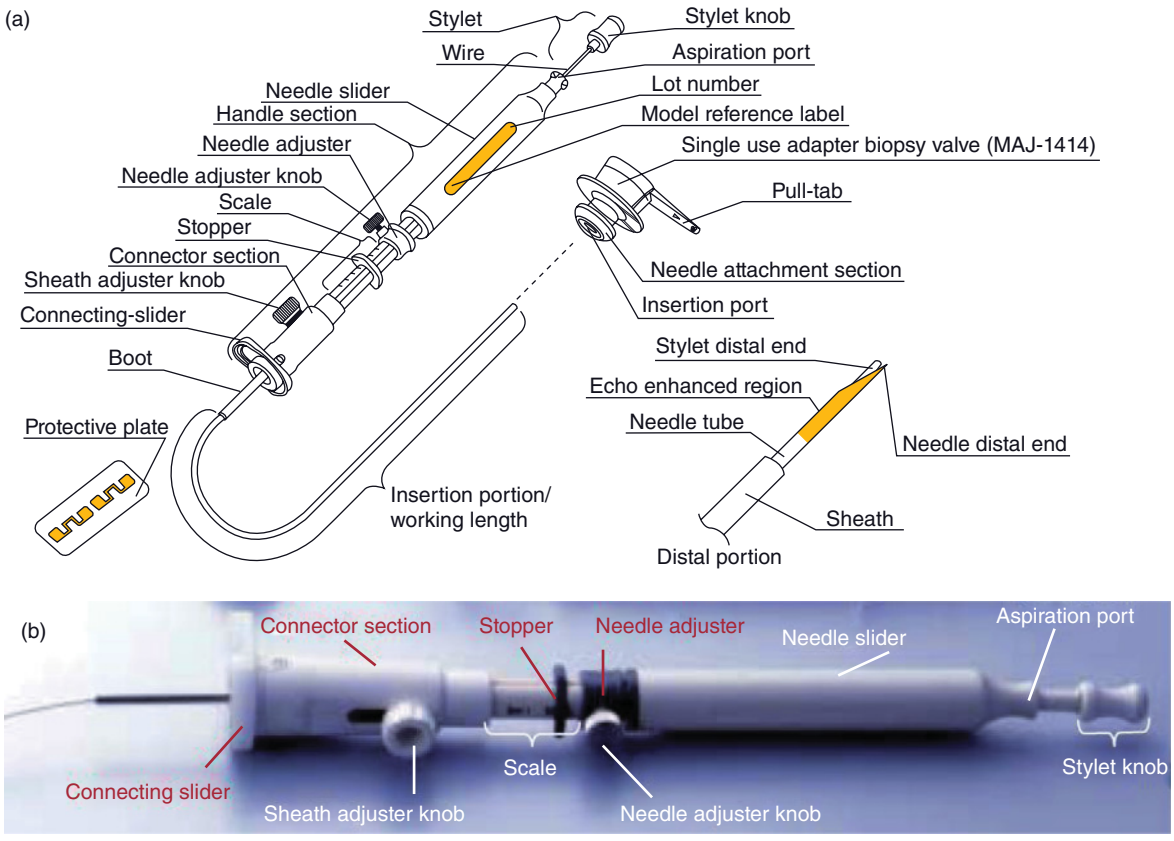


**Figure 4.20** (a) A complete needle assembly system for EBUS-TBNA. (b) Proximal portion of the needle assembly focusing on the needle and sheath adjuster knobs and the needle stopper to determine the functional length of the needle.

with epithelial cells with this method. The target is identified, and the balloon is inflated, allowing ultrasound confirmation of the location. As shown in Figure 4.26 the target is kept in the center of the screen, with the green dot marking the entry point on the right upper edge of the screen. A brief Doppler ultrasound examination is performed at this point, to identify any vascular structures in or around the target. After observing respiratory movement in relation to the EBUS picture for a couple of respiratory cycles, the needle lock is loosened and the needle is advanced into the tissue. An assistant should hold the scope at the patient's mouth while the needle is advanced. Often, an assistant is asked to push the scope down forcefully, yet smoothly, to facilitate penetration. It is not unusual to lose the image of the target while inserting the needle. Once the tissue is penetrated, the picture returns to the screen. This image "blackout" happens because the needle pushes the scope away from airway wall, leading to loss of contact between the balloon and the tissue. This is either because the sheath is pushing the bronchial wall away having extended beyond the tip of the needle, or because the needle has come up against bronchial cartilage preventing penetration. With the latter scenario coming away and re approaching the wall at a slightly altered angle is preferred, particularly aiming at a point "on top of" a cartilage ring to facilitate passage between the rings. Once the scope is pushed down and the needle has penetrated the tissue, the balloon comes back in contact with tissue and the image reappears.

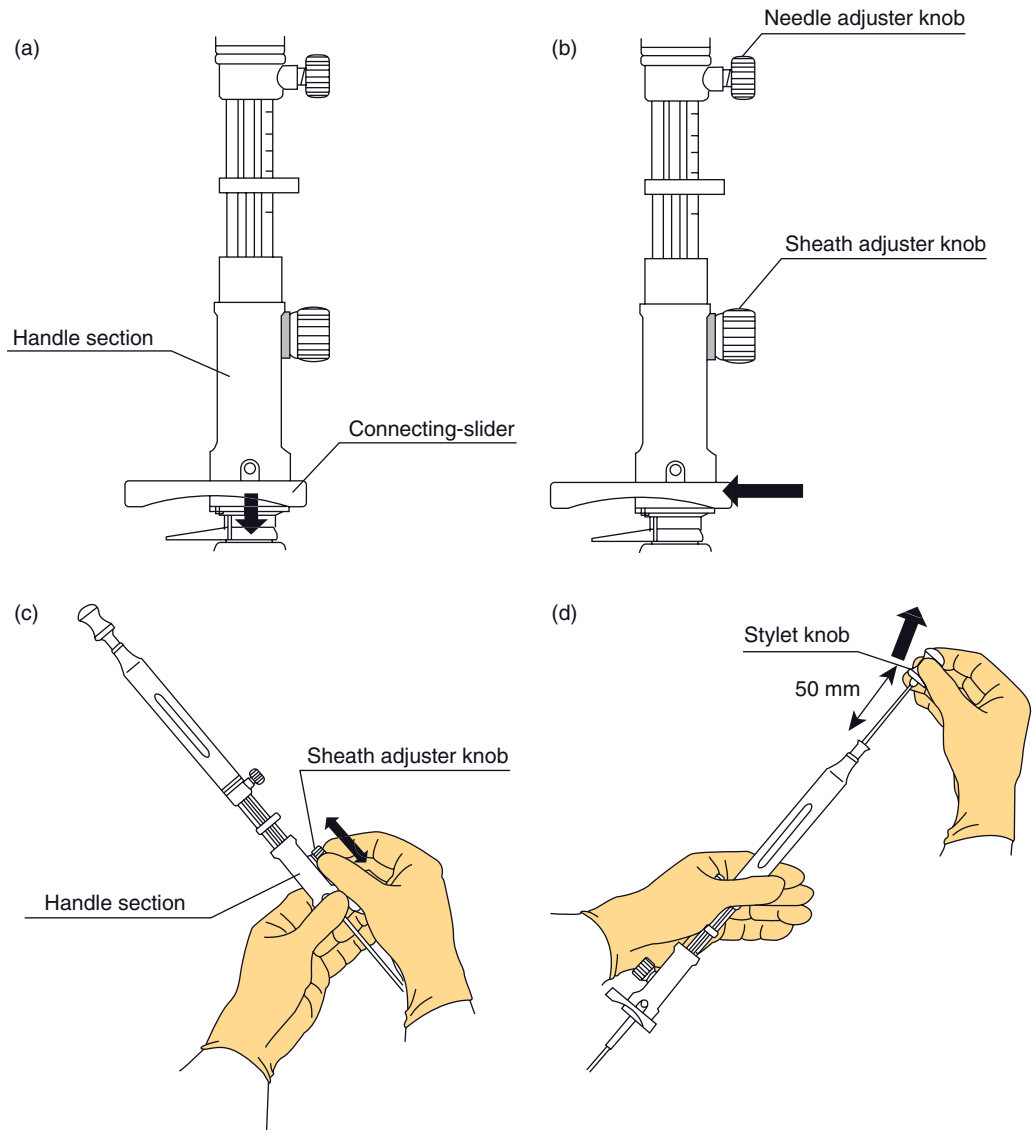


**Figure 4.21** Different parts of a needle assembly system used with EBUS-TBNA scope. (a) The needle assembly's handle section showing how the connecting slider fits on the adaptor attached to the working channel port of the scope. (b) The connector slider is pushed backwards. Needle adjustor knob is located above the sheath adjuster knob. (c) Sheath adjuster knob is loosened by rotating counter clockwise. (d) The stylet is pulled back by holding the stylet knob.

Once the needle is in the lymph node, the stylet is pushed forward a couple of times to force out bronchial cells captured along the way. One can see the tissue and blood being pushed out of the needle on a real-time ultrasound image. The stylet is then removed, the pre-loaded suction syringe is connected, and suction is applied. If no blood is seen in the catheter, gentle jabbing is begun, as previously described, making sure that the needle does not come out of the lymph node. Five to ten long, smooth passes are made,


**Figure 4.22** Proper technique for loading the needle assembly on the scope, step-by-step. (a) The needle is passed through the working channel and the entire needle assembly is loaded in the special working channel cap provided with the needle kit. The tightening knobs should face forward. The sheath and the needle should be completely retraced by pulling their sliders all the way up. (b) Once the needle assembly is tightly fitted in the working channel; the lock should be applied by sliding it backwards. (c) In preparation for needle insertion, the sheath is pushed out by loosening the sheath lock (lower knob on the assembly). (d) Before lowering the needle, the position of the needle length slide lock should be confirmed at 3, allowing only about 20 mm of needle to come out of the scope. (e) The stylet is pulled back a couple of centimeters to allow the bevel of the needle to lead. The needle is then unlocked by loosening the needle lock knob just prior to penetration in the tissue. Once the target is penetrated, the stylet is pushed forward a couple of times to push out the unwanted epithelial cells captured on the way. (f) Suction is applied after removing the stylet with a locking syringe.


**Figure 4.23** (a) Endobronchial ultrasound processor EU-C2000. (b) Endobronchial ultrasound bronchoscope (BF-UC260F-OL8) attached to the processor. (c) Same as (b) seen in close up.

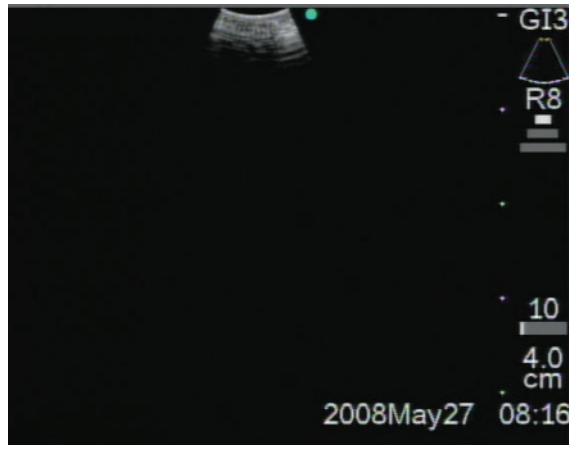


**Figure 4.24** Endobronchial ultrasound monitor. The basic settings and format is shown here. Detailed set up is discussed in Chapter 1.

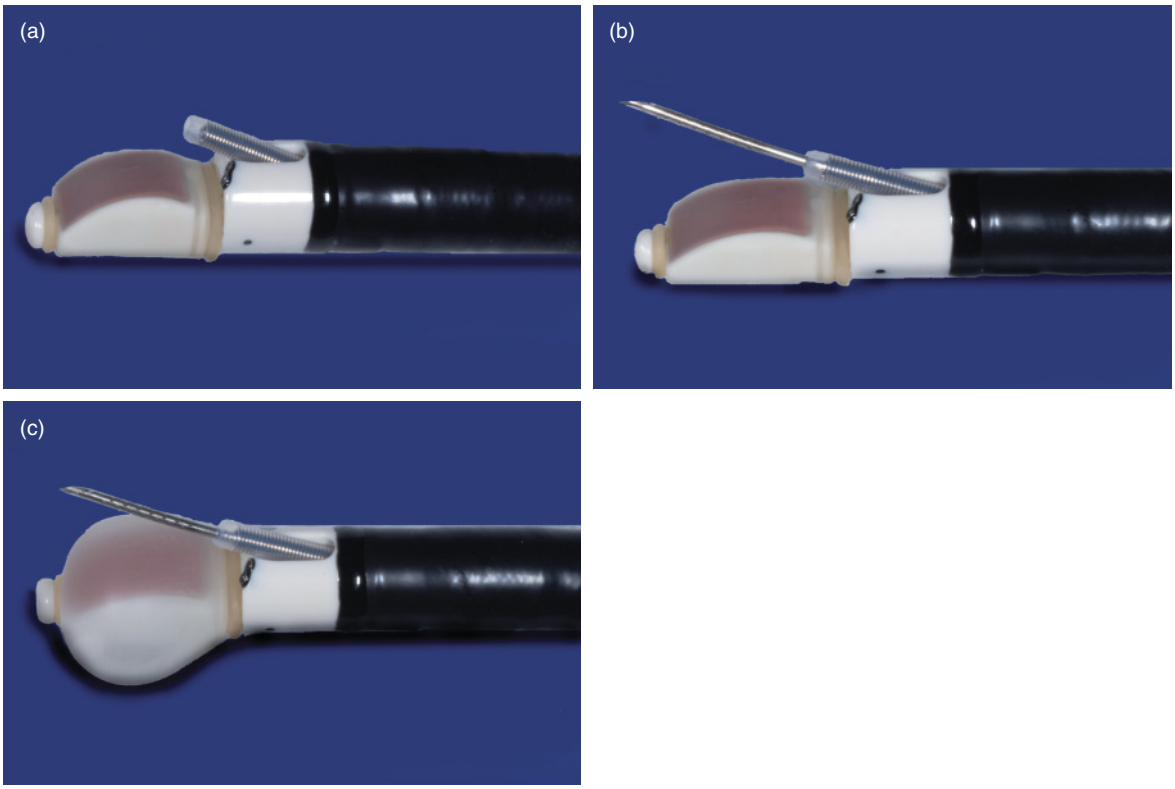


**Figure 4.25** (a) Endobronchial ultrasound convex probe with needle sheath pushed out of the working channel. The balloon is deflated to show the safety margin between the catheter and needle that comes out of it and the probe. (b) Needle pushed out of the catheter pointing at an angle of 45°. Again the balloon is deflated. The angulation of the needle allows for near perpendicular angle between the target and the needle. (c) Needle pushed out of the catheter pointing at an angle of 45°. The needle stays clear of the inflated balloon.

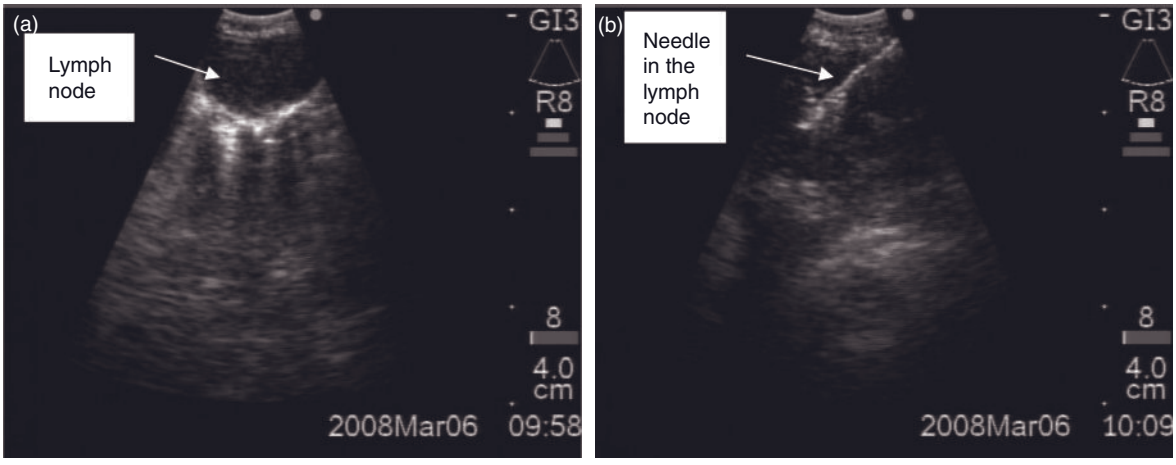


**Figure 4.26** (a) A small mediastinal lymph node is seen on EBUS monitor. (b) A needle is penetrated diagonally across the lymph node. The entry point of the needle is at the green dot on the right upper corner of the ultrasound field.

much like picking ice. Before removing the needle from the lymph node, the suction is turned off to avoid collecting unwanted cells in the needle on the way out. The needle is then retracted into the catheter. The needle assembly is unlocked at the biopsy port and removed from the working channel.

The needle containing the specimen should be taken immediately to the slides, which have been previously laid out, labeled, and numbered. Some bronchoscopists push the specimen out with the stylet onto a filter paper or gauze to absorb blood and separate the core tissue biopsy. The core tissue is then put into formalin for histopathologic examination. Some of the specimen in the needle is pushed out onto the slides for cytologic examination by blowing air through the needle. Sample remaining in the needle is placed into a tube containing normal saline. After the specimen has been pushed from the needle with the stylet, the stylet is cleaned with an alcohol swab to clean blood clots from its surface. Another technique is to push the specimen on the slide with the stylet, then push air and saline to deliver any remaining specimen into saline for later staining and cell blocks. End paper method is used for cell block/histology after the material for slides has been obtained.

If on-site cytology is not available, the specimen retrieved in the needle should be pushed into a tube containing normal saline. However, if on-site cytology is available, the cytologist may help determine whether a second aspirate is needed. If malignant cells, granulomata, or other features reveal a diagnosis, and no more tissue is needed for further confirmation or genetic studies, the procedure can be concluded. However, if the sample contains lymphoid material but no malignant cells or granulomata, one may proceed to another TBNA of the same site or another site. The number of aspirates performed is a matter of personal preference. There are no randomized, controlled trials to suggest that multiple punctures of same lymph node improve the yield. I generally perform at least two TBNAs at the same site before going to the next lymph node station. If lymphoma or sarcoidosis is a strong possibility, I usually insert a 19 G needle at the same puncture site, without EBUS, before proceeding to the next station. Overall, experience with this strategy for EBUS-TBNA has been very good. In general, post-procedure chest radiographs are not needed following an uncomplicated TBNA.

## Acknowledgements

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1 Baram D, Garcia RB, Richman PS. Impact of rapid on-site cytologic evaluation during transbronchial needle aspiration. Chest 2005;128(2):869–875.

# 5 Tips and Difficulties in EBUS-TBNA

## Tips

### Wang's Descriptions of TBNA Positions

The technique of transbronchial needle aspiration has been in the literature for over 25 years [1], and there is much useful material to be obtained from Wang's original description to facilitate transbronchial needle aspiration. The addition of EBUS aids the practitioner in confirming the localization of the lymph node [2], as shown in early studies with an EBUS balloon probe. However, an understanding of the common locations of the lymph nodes adjacent to the trachea and main bronchi as well as their main relationships can be obtained from careful scrutiny of these early papers [1,3]. In his papers, Wang described 11 nodal positions starting at the anterior carina and progressing down the main bronchi, to the subcarina and, ultimately, the hilar positions. At each of these 11 sites, a description of the best point to insert the needle was given in terms of a clock-face with respect to the bronchial lumen. These 11 positions provide an invaluable starting point for the student of transbronchial needle aspiration whether using a standard TBNA needle or using the convex probe and a bronchial ultrasound scope. It should be remembered that these numbered positions are different from the traditional lymph node stations as described by Naruke and the American Thoracic Society in their classifications [4,5]. Even familiarity with two or three of these positions is adequate for the learning practitioner to quickly develop expertise in this technique. The most commonly aspirated sites would be the right paratracheal and subcarinal positions and the anatomical relations of these two sites can be quickly gleaned from the Wang descriptions.

### Radiological Anatomy

The proceduralist needs to become familiar with interpreting the CT scan for the presence of mediastinal and hilar lymphadenopathy. An excellent reference for this is Ko, 2000 [6]. In fact, with EBUS, only the following are accessible: the highest mediastinal (station 1), the upper paratracheal (station 2R and 2L), the lower paratracheal station (4R and 4L), the subcarinal (station 7), hilar (station 10), the interlobar (station 11) and the lobar nodes (station 12). Stations 5 and 6 are the subaortic and para-aortic lymph nodes respectively and neither of these are directly applied to the trachea. Similarly, the number 8 and 9 lymph nodes are too far posterior and inferior to be accessed by the TBNA scope. Both of these can be accessed by endoscopic ultrasound. The number 13 and 14 segmental and subsegmental lymph nodes are usually not able to be biopsied simply because the TBNA scope is too large to proceed further out the bronchial tree towards these nodes. On occasion, a number 13 might be accessible.

Some of the important vascular-relations are described in Ko's paper. The level 1 nodes are only very uncommonly biopsied by EBUS-TBNA. The important vascular relation is that this node is cranial to the brachiocephalic vein where it crosses the trachea. The station 2 para-tracheal lymph nodes are positioned below the top of the left brachiocephaic vein but above the top of the aortic arch. Station 4 lymph nodes can be divided radiographically into a superior and inferior subset. Superior nodes are inferior to the top of the aortic arch and above the azygous

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vein; inferior station 4 lymph nodes are below the horizontal line drawn at the superior aspect of the azygous vein. Of course, lymph nodes in this station 4 para-tracheal position can be contiguous between the superior and inferior positions. In the lower paratracheal position, these nodes can be classified as either 4R or 4L depending on whether they are on the right or left of the lower trachea. The nomenclature is important with respect to 4L as these are separated from the number 5 or aortopulmonary window lymph nodes by the ligamentum arteriosum, with 4L lymph nodes being medial to this structure. Station 10 hilar lymph nodes are anterior and posterior to the right upper lobe bronchus. The demarcation point between station 4 mediastinal and station 10 hilar nodes is the top of the right upper lobe bronchus; mediastinal number 4 nodes are superior to this and station 10 hilar nodes are inferior to this point. Familiarity with these positions and enlargement of lymph nodes at this point obviously brings familiarity with the vascular relations.

In general terms, the anatomy of these major structures is not nearly as variable as is seen in assessing the peripheral airways and small vascular branching at subsegmental levels and therefore it allows the trainee to rapidly develop a concept of pattern recognition [7]. The nodal positions 1, 2R, 4R, 4L, 11L, and 11R and 7 all have fairly constant vascular relations and, as such, a "snap-shot" or pattern recognition image can be used by the trainee [7]. For example, in the commonest position, the number 7 subcarinal location, it is a simple matter of demonstrating the right main pulmonary artery immediately anteriorly at the origin of the right main bronchus and turning away anticlockwise to the subcarinal position at the 9 o'clock location. In the number 2 right paratracheal position, the best known vascular relation deep to the lymph node would be the superior vena cava which can be seen as an elongated vascular structure usually at the 3 o'clock position. (This may be poorly seen if the node is not sufficiently enlarged.) Turning back anticlockwise slightly to the 1–2 o'clock position brings the node into view. In the number 4 lower right paratracheal position, the superior vena cava can be seen in its lower end, whereas at the lower end, more anteriorly, both the azygous vein and right pulmonary artery can be relatively easily seen in a commonly observed pattern. In both the number 11 positions on right and left, the pulmonary artery can be readily seen in the lateral position (3 o'clock on the right, and 9 o'clock on the left). By rotating the scope directly anteriorly, each of these vascular points can be avoided and the node easily visualized in this location just at the origin of the right or left lower lobe bronchus.

The final tip is with hard copy film or even on an electronic copy to flip the film horizontally so that a bronchoscopic type view (standing at the head looking at the feet) is obtained to further visualize the likely direction of needle puncture.

## Which Nodes will be Most Commonly Sampled?

Lymph nodes most commonly sampled will be the right paratracheal and subcarinal lymph nodes and it is suggested to do just 10 or 20 cases at these two sites alone to develop familiarity with the process and needle puncture. The number 4L position can be difficult to access because of the sharper angle of the left main bronchus coming off the lower trachea compared to the right. As such, it is difficult to maintain good application of the EBUS balloon to the tracheobronchial angle and the help of an assistant to hold the bronchoscope in position can be required. To a lesser extent, this can be true at the right tracheobronchial angle in low number 4 or number 10 nodes.

## Setting Up the Scope

The TBNA convex probe dedicated needle made by Olympus (NA-201SX-4022) has a number of moving parts with which the operator can become rapidly familiar.

The needle apparatus is released by unwinding the screw on the gray sleeve. By holding the apparatus above this sleeve between finger and thumb it can be easily pulled down in a controlled fashion to protrude the needle from the tip. Stabilize the hand on the apparatus by winding the fifth finger of the same hand around it below the needle apparatus. Before commencing the procedure, check that the needle moves freely in and out in the same way as one would prepare a simple cannula for venous cannulation. Immediately on completing this simple task and at all times when using the needle, the needle shaft should be pulled back until a click is felt and heard and the screw on the gray sleeve retightened. This ensures that

the sharp needle is fully retracted within the plastic sheath and, as such, the needle tip is unable to damage the biopsy channel of the bronchoscope. Next, the needle apparatus as a whole needs to be calibrated for length against the biopsy channel. The needle apparatus is passed into the channel and the white knob unscrewed to allow inward or outward movement of the plastic sheath. This sheath should be aligned at the end of the biopsy channel; when this plastic sheath just comes into view on the monitor it implies that the sheath has come out the end of the biopsy channel and, therefore, should be fixed in this position so that when the needle is protruded from the sheath it will do so from outside the biopsy channel thereby not damaging it.. The sheath should not be fixed too far out as this will hamper needle penetration attempts by pushing the ultrasound transducer away from the wall and hampering imaging just prior to biopsy. Once this position has been found, the white knob should generally not be adjusted until during the procedure.

Now the balloon can be set up on the transducer tip. Draw up 30 mL of saline into a Leuer lock syringe with flexible giving set and 3-way tap attached. It is best to remove all air bubbles; this is best achieved by drawing up the saline slowly and then expelling the bubbles by holding the syringe in a vertical position with the three way tap uppermost, gently tapping the syringe as required. Having done this, one can prime the balloon channel on the scope with 2 or 3 mL of saline. The three way tap is then closed. The balloon itself then needs to be fitted to the convex probe end of the scope over the ultrasound transducer. There is a dedicated applicator for this. Having applied this to the convex probe, the probe tip is held upwards and the fluid syringe held downwards and 5–10 mL of saline is used to slowly flush through the balloon channel until bubbles are removed from the balloon. Once it appears that this has been complete, the very tip of the balloon can be folded back over the dedicated balloon holder at the tip of the scope. This should only be done once all bubbles have been removed as bubbles can no longer be removed once this has been folded into place.

## Passing the Bronchoscope and Anesthesia

As described in the previous chapter the practitioner needs to adjust for the anterior view of the white light optic and the fact that there is about 1 cm of scope in front of the optic which is not visualized. Therefore to facilitate ease of passage of the scope through the vocal cords it can be helpful for an assistant to provide anterior jaw lift to open up full viewing of the vocal cords. If the anterior commissure is viewed it means the scope itself is pointed at the mid point of the cords and the scope will easily pass through. This part of the procedure requires practice particularly the need to have the scope tip go anteriorly over the arytenoids and not be caught and pushed posteriorly. In patients with crowded upper airways this can be difficult even with anterior jaw lift. Similarly, when in the bronchial tree to pass the main carina one would overcorrect much earlier than with a standard bronchoscope where the viewing optic is at the very end of the scope. For example, 2 or 3 cm before the main carina, the scope would be rotated to the right and very close to the lateral tracheal wall to facilitate passage into the right main bronchus.

Depending on local preference anesthetic support is available in some centers with the ability to intubate the patient either with standard ETT or laryngeal mask airway (LMA). Sarkiss et al. reported their anesthetic technique for EBUS-TBNA [8]. They use a number 4 LMA because it has a large internal diameter and is the most suitable device to secure the airway and provide adequate ventilation around the bronchoscope. The outer diameter of the XBFUC 160F EBUS-TBNA scope is 6.7 mm and 6.9 mm at the tip. These authors used a total intravenous anesthesia (TIVA). TIVA was preferred over volatile anesthetics because frequent suctioning of airway by the bronchoscopist resulted in contamination of the procedure room atmosphere by the anesthetic gases and also causes inconsistent delivery of the anesthetic gas to the patient.

They used propofol infusion at a rate of 75 μg/kg/min once intravenous catheter and standard monitoring for general anesthesia were in place. Small doses of fentanyl or remifentanil were given for induction. An alternative to the LMA is an endotracheal tube (8.5). The indications for ETT placement were difficult laryngeal mask airway placement, obesity, and severe untreated gastro-esophageal reflux. The EBUS can only fit in a size 8.5 or 9.0 mm internal diameter endotracheal tube. These authors used an 8.5 ETT for female patients and a size 9.0 for male patients. To some extent, the endotracheal tube does make it

difficult to oppose the convex probe against the bronchial wall because the tube brings the scope into the center of the lumen. The ETT can be manually "leaned" towards the side of biopsy to some extent.

In general an LMA is preferable because an ETT can at times hinder in access to paratracheal lymph nodes; ETTs may have to be pulled back if this occurs, sometimes repeatedly, to allow free access to the side of the tracheal wall.

## The Reach of the Bronchoscope

Usually, it is difficult to access the segmental bronchi with this 6.4 mm diameter bronchoscope. It is possible to easily access the origins of the right and left main bronchi, both lower lobe bronchi. On the right, occasionally it is possible to enter the right upper lobe bronchus origin to puncture the top end of a number 11S lymph node. Occasionally it is also possible to enter the origin of the right middle lobe bronchus to access anterior lymph nodes at this point. On the left, it is usually possible to access the most proximal parts of the upper division bronchus although the indications to do this are very infrequent and this region is very vascular. Accessing the left upper lobe bronchus and lingula are usually not possible.

## Passing the Needle through the Wall

After inflation of the convex probe balloon a biopsy site is chosen, usually by selecting the most proximal end of the lymph node. Careful Doppler examination at this point should reveal no small bronchial artery; if this is present, simply rotating the scope in an axial plane should be able to remove the vessel from the anticipated needle puncture track. Puncture of the tracheal wall can be done using two different methods. The first and preferred method is to visually determine a mark or minor vascular structure on the tracheal or bronchial wall where the needle will be passed. This is determined by first using ultrasound examination showing the position of the most cranial (near) end of the lymph node. The bronchoscopic white light views are then carefully scrutinized to show a mark at this exact point, obviously just above a cartilage ring. The next step is to flex the bronchoscope a little backwards and away from the bronchial wall so that the needle can be passed more directly straight into the wall at the desired point as described. Having passed the needle into this cartilaginous space, usually on the top of the lower cartilage, the ultrasound balloon can then be flexed back up against the bronchial wall to image the first pass of the needle into the node. Prior to performing puncture, it may be possible to push the plastic sheath in and out allowing visualization of this to occur as it indents the space between the cartilage rings, and makes it easy to pass the needle through.

The second method is to simply hold the bronchoscope with the inflated balloon against the node at its most upper or cranial point and to gently advance the needle into the node without any movement of the scope away from the bronchial wall. The disadvantage of this method is that it is common for the needle to come up against cartilage rings. To overcome this problem it requires re-manipulation or rotation of the scope 5 or 10° in either direction. Again this can be made easier by slightly advancing the plastic outer sheath and visualizing this indenting the top right of the ultrasound image. This method might be easier to use in the more peripheral puncture sites such as the number 11 in the origin of each lower lobe. The obvious reason being the difficulty of flexing the bronchoscope away from the wall at these points given the small bronchial lumen diameter. Also the cartilage rings here tend to be less obstructive.

Before doing either of these methods, it is possible to improve puncture by having the sharp needle come to the tip of the plastic sheath before formally advancing it into the lymph node. Somewhat unexpectedly when the needle is protruded inside the plastic sheath, the sheath is elongated by this action. That is, the sheath will move out in front of the needle even though it has not been specifically released itself. This pushes up against the wall of the bronchus, and can effectively "push" the balloon away from the wall before the needle can be advanced. A quick method to prevent this problem has been recently described by Kurimoto and others: with the scope in the middle of the bronchus lumen away from the wall the needle is protruded and observed closely. The needle will have just reached the tip of the sheath when there is a slight downward movement of the tip of the sheath. The needle shaft is then left in this position and the plastic sheath withdrawn to its original position just outside the biopsy channel.

## Obtaining Samples

It is often helpful to ask an assistant to hold the bronchoscope still at the exit from the mouth as this will prevent slight movements of the scope which can hinder adequate visualization during insertion of the needle. Sometimes as the needle is being inserted, the scope is pushed backwards in a cranial direction and re-advancing the scope the 1 or 2 mm helps to regain the image. Because of the effect of slight movements it helps to have two monitors (one for EBUS and one for bronchoscopic findings) on continuous display rather than alternating the view on one monitor.

It is important to keep the full length of the needle in view on the monitor during the TBNA procedure specifically with reference to the distal tip of the needle.

Occasionally, once the needle has been inserted in the node, it is difficult to push the stylet fully in to remove cartilaginous material from the tip of the needle. This is particularly true when the bronchoscope is more acutely angled and it is sometimes necessary to gently release any angulation on the bronchoscope to allow a more straight passage in of the stylet. Care should be taken to prevent inadvertent bending of the stylet during reinsertions. Occasionally, when two or three insertions are made, it is necessary to ensure any small amounts of blood are wiped off the stylet before it is readvanced as coagulation of blood on it can make it stick in the thin channel.

Sometimes blood comes into the suction syringe in aspirations of vascular lymph nodes. This can reduce the diagnostic yield and therefore it is best to remove the needle without any further passes at that point. Some authors recommend trials of no suction on the needle in this situation just relying on the "cutting" aspect of the needle to obtain the sample. In subsequent passes it may help to just do four or five movements of the needle in and out in the node as opposed to the usual 20.

## How Many Aspirations Per Target Lymph Node Station?

This was reported by Seok Lee et al. and is clearly relevant for those situations where rapid onsite cytopathological examination is not available [9]. In this study, 163 nodal stations in 102 patients with non-small cell lung cancer were punctured. Malignancy was confirmed in 41 stations in 30 patients. Two areas of malignancy as documented by surgery were missed in two patients. Sample adequacy was 90.1% for one aspiration and it reached 100% for three aspirations. The sensitivity for differentiating the malignant from benign lymph node stations was 69.8%, 83.7%, 95.3%, and 95.3% for 1, 2, 3 and 4 aspirations respectively. Maximum diagnostic values were achieved in three aspirations. The negative predictive value of 86.5% for one aspirate and 97.6 for four aspirates respectively. These authors concluded that optimal results could be obtained in three aspirations per lymph node station for mediastinal staging of the potentially operable non-small cell carcinoma. They felt that if a tissue core specimen could be obtained in the first or second aspiration, then two aspirations per lymph node station would be acceptable.

## Side Effects and Risks

Transbronchial needle aspiration biopsy as an alone procedure has been in clinical use for at least 25 years [1]. Tolerance of this technique was summarized in 2000 [10]. The main reported risk at that time was not so much to the patient as damage to the bronchoscope. This occurred when standard TBNA needles were inadvertently deployed whilst still within the biopsy channel, hence causing damage to the channel. [11]. In addition to this, standard TBNA needles can be damaged by the sharp point of the needle going through the plastic sheath [12]. In the review of TBNA, there were two cases of pneumothorax and one case of pneumomediastinum and hemomediastinum [11]. There was one patient with a reported purulent pericarditis after TBNA of a subcarinal mass. One rare complication of standard TBNA has been in advertent liver biopsy in a patient with a right raised hemi-diaphragm [13]. A 2002 report noted a mediastinal hematoma after inadvertent puncture of the aorta; his resolved spontaneously on CT [14].

The convex probe TBNA scope was first reported in 2003 and, to date, very few side effects have been reported [7]. Significant bleeding has not been reported in any patient since the advent of EBUS-TBNA and, indeed, with conventional TBNA, reports have been rare. One case of perihailar hematoma has been

reported from sampling a small node in vicinity of hilar vessels-care with ultrasound examination is needed [15]. There is usually a small amount of blood after removal of the TBNA needle which settles spontaneously within half a minute or so and is usually bleeding from the small bronchial vessels. Occasionally, bleeding can occur from within the node itself, particularly in metastatic lymph nodes from tumours such as renal cell carcinoma or melanoma due to their vascularity. The theoretical increased risk of bleeding in patients with superior vena caval obstruction has previously been raised [16]. As is often seen at EBUS-TBNA, the superior vena cava is displaced out of the way by nodal tissue. The convex probe TBNA needle can be withdrawn should there be any excess of blood come into the needle indicating vascular puncture, however if the node is well imaged, this is exceedingly unlikely to happen. The only caveat may be penetration of a small bronchial artery immediately beneath the tracheal or bronchial wall and this can be quickly ruled out by Doppler imaging at the TBNA site in each case.

Two recent reports concern post EBUS TBNA infections [17,18]. A pericardial infection followed full extension of the needle to 36 mm. Such extension should only be used very infrequently. Another case of pneumonia following sampling of a pulmonary lesion next to a bronchus occurred. In the other report a cystic lesion was sampled in the high mediastinum as part of staging of thyroid disease [18]. An infection ensued with purulent skin discharge; this settled with antibiotics. In both the last 2 cases antibiotics would now be recommended post procedure. Alternatively cystic lesions should be avoided. The author has had one adverse event with respect to the convex probe TBNA needle [19]. This was a case performed by the author in a patient with underlying sarcoidosis. There were large abnormal nodes at the right paratracheal and subcarinal positions, both of which had been aspirated. There had been a strongly positive PET scan prior to the procedure and on site pathology was negative for the presence of any malignancy, hence the patient had four passes before the breakage of the TBNA needle on the fifth pass. In retrospect, this was because the technique of needle penetration was the piggy-back method as described by Wang rather than the two-step or three-step method described above. During the performance of this needle penetration, the patient had coughed very forcibly and because the bronchoscope was being pushed distally with the piggy-back method, it is assumed that with the needle coming against the cartilage and the patient's coughing effort, that there was a shearing force at the point of the needle exit from the plastic sheath. It was apparent that the needle could not be seen advancing on the ultrasound image and needle breakage was immediately suspected. The needle was retracted and a standard bronchoscope was immediately inserted. The broken end of the needle could be seen in the subcarinal position and was removed with standard endobronchial biopsy forceps. The recommendations from this problem were that the piggy-back method should be avoided using this needle, and to use the methods described above. There were no adverse effects with respect to the patient and there was no residual needle seen on chest X-ray immediately following the procedure.

## On Site Pathology

The benefits of rapid on site cytology examination (ROSE) in standard transbronchial needle aspiration are well known [20,21]. Because fewer samples were required the procedure was cost effective and therefore paid for the extra expense of the cytologist's availability.

ROSE also offers benefits in EBUS-TBNA [22]. It is a useful way to not only confirm malignant cells but also where nodes are likely to be benign that abundant lymphocytes can be seen at ROSE. In lung cancer staging with EBUS-TBNA it is usual to start by sampling N3 followed by N2 followed by N1 nodes depending on size and accessibility [22]. In this respect it is very important to not allow positive cytology specimens from one pass to contaminate a subsequent pass. Most authorities consider that simply rinsing a needle is not adequate to prevent such contamination occurring. ROSE clearly can assist with this process. If an N3 sample is positive it would be reasonable to stop the process there. If negative the next step would be to sample N2 nodes. It may be reasonable in these circumstances to use the same needle again for the N2 node, providing the initial ROSE with that needle was negative for malignant cells.

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# 6 Endoscopic Ultrasound-Guided Mediastinal Lymph Node Aspiration for Lung Cancer Diagnosis and Staging

As evident from its name, endoscopic ultrasound (EUS) is performed through a trans-esophageal approach (Figure 6.1). The EUS scope, like the endobronchial ultrasound (EBUS) scope, allows for real-time ultrasound needle aspiration (Figures 6.2 and 6.3). The purpose of this brief chapter is to acknowledge the role of EUS in sampling mediastinal lymph nodes and to compare EBUS and EUS for this particular indication. An in-depth discussion of endoscopic ultrasound for sampling mediastinal lymph nodes is beyond the scope of this book. To learn more about mediastinal sampling with EUS, one should review the gastroenterology literature.

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) of mediastinal lymph nodes to stage lung cancer has been performed since the 1990s. Posterior and inferior mediastinal nodes are easily accessible by EUS-FNA (Tables 6.1 and 6.2). Mediastinal lymph node stations accessible by EUS-FNA include stations 4L (Left lower paratracheal), 7 (subcarinal), 8 (para-esophageal), and station 9 (inferior pulmonary ligament). Superior mediastinal (stations 1, 2, 3, and 4R), N1 (stations 10, 11, 12, 13 and 14), subaortic (station 5) and the para-aortic node (station 6) are not accessible by EUS-FNA.

In comparison, the lymph node stations accessible by EBUS-TBNA include stations 1, 2, 3, 4, 7, 10, 11, and 12. Endobronchial ultrasound-guided fine-needle aspiration (EBUS-TBNA) for lung cancer staging has been performed since the early 2000s.

Because they can access different mediastinal lymph node stations, EUS-FNA and EBUS-TBNA should be considered complementary to each other. When used together, EUS-FNA and EBUS-TBNA allow access to almost all of the mediastinal nodes during one session of conscious sedation. However, when lymph nodes are potentially accessible by both modalities, the EBUS approach is preferred because it also allows examination of the airways for endobronchial disease, which may be easily missed on chest CT scans. Both EUS-FNA and EBUS-TBNA carry a very low risk of complications.

Like EBUS-TBNA, EUS-FNA may be performed as an out-patient procedure. It is usually carried out with the patient under conscious sedation. The needle used for EUS-FNA is typically 19 or 22 G. The 19 G needle provides the benefit of allowing a core biopsy, which improves diagnostic accuracy in diseases such as sarcoidosis and lymphoma. In a meta-analysis, the sensitivity of EUS-FNA was 81–97% and specificity was 83–100% for the diagnosis of posterior mediastinal lymphadenopathy in non-small cell carcinoma lung [1]. The major limitation of EUS-FNA was its high false negative rate. Recent studies comparing PET scan with EUS-FNA for posterior mediastinal adenopathy have shown that the EUS-FNA is better than PET scan in staging lung cancer [2]. These studies suggest that there is a high false positive rate for PET scanning; therefore, EUS-FNA can confirm the benign or malignant status of these lymph nodes.

Endobronchial ultrasound-guided fine-needle aspiration appears to have greater sensitivity and specificity than EUS-TBNA. In a case report of 70 patients with mediastinal (58 patients) and hilar (12 patients) adenopathy, EBUS-TBNA for differentiating benign from malignant nodes had a sensitivity of 95.7%, specificity of 100%, and accuracy of 97.1%, respectively [3].

A recent multicenter trial of more than 500 patients showed EBUS-TBNA to be a very sensitive and specific

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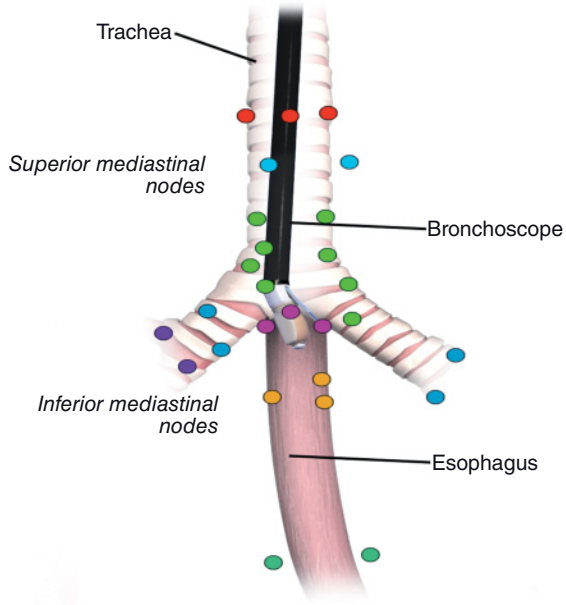


**Figure 6.1** Endoscopic ultrasound scope in the esophagus behind the trachea. The subcarinal and para-esophageal lymph nodes are easily accessible by endoscopic approach with ultrasound-guided fine-needle aspiration.
Colored dots represent lymph nodes.

**Figure 6.2** Endoscopic ultrasound scope (GIF-UC 240P Olympus Corporation).

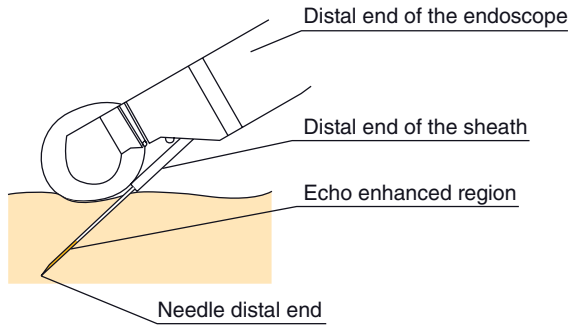


**Figure 6.3** Cartoon depicting endoscopic ultrasound via the esophagus. The real-time images of a mass or node outside the walls of the esophagus allow fine-needle aspiration.

**Table 6.1** Lymph node stations

| Location | Station |
|---|---|
| **Superior mediastinal nodes** | |
| Highest mediastinal | 1 |
| Upper paratracheal | 2 |
| Pre-vascular and retrotrachael | 3 |
| Lower paratracheal | 4 |
| **Aortic nodes** | |
| Subaortic (A-P window) | 5 |
| Para-aortic (ascending aorta or phrenic) | 6 |
| **Inferior mediastinal nodes** | |
| Subcarinal | 7 |
| Para-esophageal | 8 |
| Pulmonary ligament | 9 |
| **N1 nodes** | |
| Hilar | 10 |
| Interlobar | 11 |
| Lobar | 12 |
| Segmental | 13 |
| Subsegmental | 14 |

Adapted from: Naruke T, Suemasu K and Ishikawa S. Lymph node mapping and curability at various levels of metastasis in resected lung cancer. J Thorac Cardiovasc Surg 1978;76:832–39, with permission.

diagnostic modality for sampling mediastinal adenopathy (sensitivity 94% and specificity 100%) [4]. Other studies comparing the sensitivity of PET, CT and EBUS-TBNA for staging of lung cancer showed a higher yield with EBUS-TBNA [5]. The sensitivity of CT, PET and EBUS-TBNA for diagnosing lung cancer in mediastinal and hilar lymph nodes was 76.9%, 80%, and 92.3%, respectively. The specificities were 55.3%, 70.1% and 100%, respectively. The diagnostic accuracies were 60.8%, 72.5% and 98% [6],

**Table 6.2** Accessibility of lymph node stations by different modalities

| Modality | Accessible lymph node stations |
|---|---|
| Standard mediastinoscopy | Superior mediastinal, subcarinal<br>Stations 1, 2, 3, 4 and 7 |
| Extended mediastinoscopy | Aortic nodes<br>Stations 5 and 6 |
| Anterior mediastinoscopy* | Aortic nodes<br>Stations 5 and 6 |
| VATS | Superior mediastinal (right), subcarinal, and aortic nodes<br>Stations 1, 2R, 3, 4R, 7, 5 and 6 |
| TBNA | Superior mediastinal, subcarinal, N1 nodes<br>Stations 1, 2, 3, 4, 7, 10, 11 and 12 |
| TTNA | Superior mediastinal (anterior)<br>Stations 1, 2, 3 and 4 |
| EUS-FNA | Left lower paratracheal, subaortic, inferior mediastinal<br>Stations 4L, 7, 8 and 9 |
| EBUS-TBNA | Superior mediastinal, subcarinal and N1 nodes<br>Stations 1, 2, 3, 4, 7, 10, 11 and 12 |

*Chamberlain procedure.

respectively, for the three modalities. Therefore, EBUS-TBNA has better sensitivity and specificity than either CT or PET scanning in staging mediastinal disease in lung cancer.

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# 7 Qualitative Analysis of Peripheral Pulmonary Lesions Using Endobronchial Ultrasonography

## Introduction

Numerous studies have shown that high frequency, two-dimensional ultrasonography is a useful technique for evaluating the depth of invasion of gastrointestinal tumors, detecting lymph node metastasis, and identifying coronary arterial stenosis and thrombosis [1–5]. Since 1994, we have engaged in the development of endobronchial ultrasonography (EBUS) [6–7], including the localization of peripheral pulmonary lesions during endobronchial brushing and transbronchial biopsy (TBB). In addition to EBUS localizing a lesion the analysis of the images can be useful in terms of suggesting the underlying pathology. Concepts of the qualitative analysis of the internal structure of peripheral pulmonary lesions as visualized by EBUS have been developed by comparing these findings with the histopathological findings (Figure 7.1). The aim of this study is to improve the criteria for distinguishing between benign and malignant peripheral pulmonary tumors.

EBUS uses high-frequency ultrasound (20 MHz) to create detailed images of the internal structure of lesions [8–11], although it cannot delineate tissues external to the lesion. Endoscopic ultrasonography has been used to examine the internal structure of the pancreas, the results correlating well with histopathological findings in cases of cystic tumor, calcification, and pancreatic stones [12,13].

Currently there are few published comparative analyses of the internal structure of peripheral pulmonary lesions as visualized by EBUS and the histopathological findings, so this section will rely largely on our own results.

## Correlation between Preoperative EBUS Scans and Histopathological Examination of Peripheral Pulmonary Lesions

We reviewed the records of patients who underwent diagnostic preoperative EBUS for a peripheral pulmonary lesion where a surgical specimen was available to be sectioned. The histopathological findings were correlated with the internal structure of the lesions as visualized by EBUS.

Most cases of well-differentiated adenocarcinoma showed preservation of blood vessels within the lesion using EBUS (Video clip 7.1). These lesions had homogenous internal echoes overall, but some hyperechoic dots (less than 1 mm in size) were also seen, representing residual air in invaded alveoli. The distribution of the hyperechoic dots was irregular, as were the margins of the lesions. Blood vessels could be seen coursing through the lesions (Figure 7.2).

In some cases of well-differentiated adenocarcinoma, no blood vessels were visualized. These lesions also presented an irregular distribution of hyperechoic dots or arcs around the probe and had poorly defined borders.

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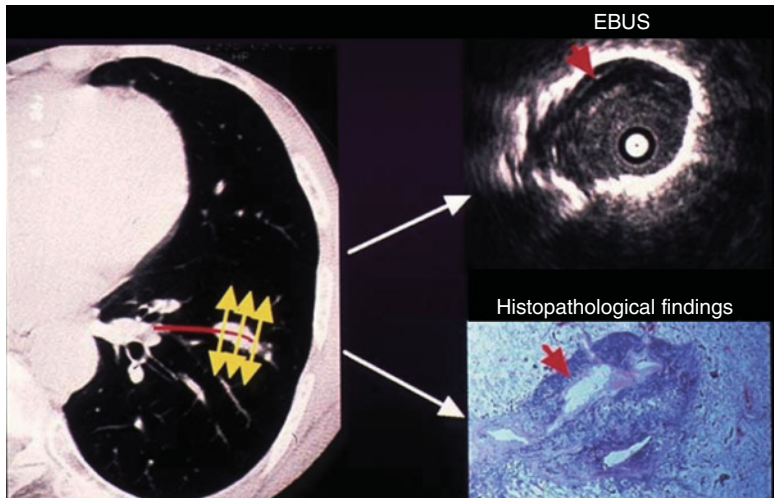


**Figure 7.1** Qualitative analysis of the internal structure of peripheral pulmonary lesions as visualized by EBUS, comparing these findings with the histopathology findings.

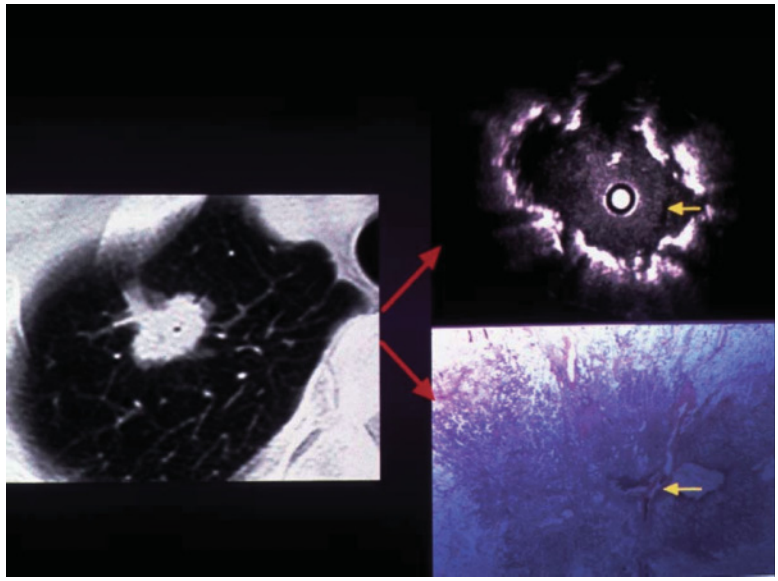

**Figure 7.2** A representative case of well-differentiated adenocarcinoma. Most cases of well-differentiated adenocarcinoma show preservation of blood vessels within the lesion using EBUS. Blood vessels could be seen coursing through this lesion.

In most cases of moderately differentiated adenocarcinoma and squamous cell carcinoma, EBUS images showed obstruction of blood vessels within the lesions, obstruction of bronchi, heterogenous internal echoes, and irregular margins (Figure 7.3, Video clip 7.2). In one case of moderately differentiated adenocarcinoma, numerous very small hyperechoic echoes were observed within the lesion, their distribution identical to that of the multiple calcifications observed histopathologically (Figure 7.4). In some cases of

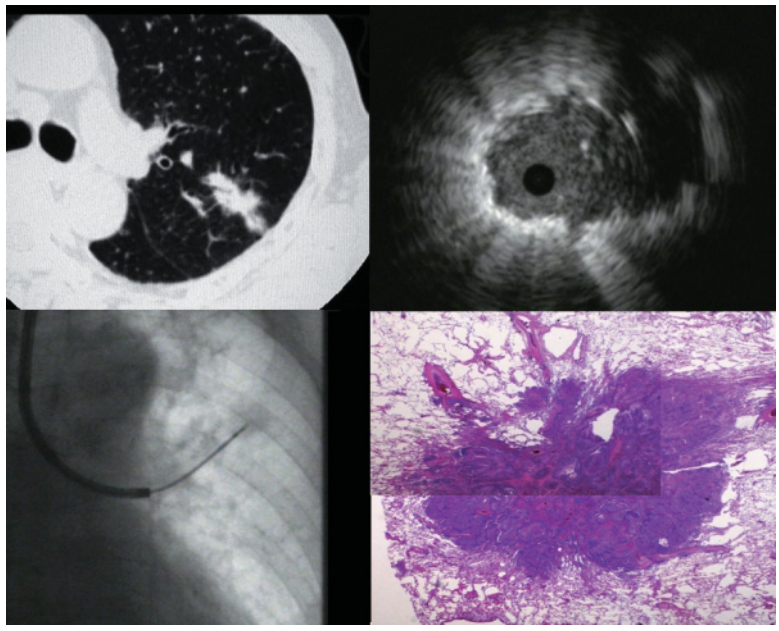

**Figure 7.3** A representative case of moderately-differentiated adenocarcinoma. In most cases of moderately differentiated adenocarcinoma and squamous cell carcinoma, the EBUS images show obstruction of blood vessels within the lesion, obstruction of bronchi, heterogenous internal echoes, and irregular margins.

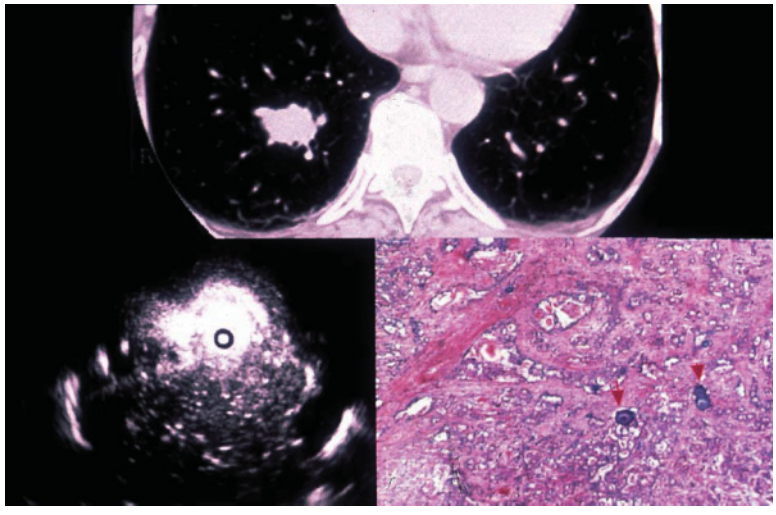

**Figure 7.4** In this case of moderately differentiated adenocarcinoma, numerous very small hyperechoic echoes are observed within the lesion, their distribution identical to the multiple calcifications observed histopathologically.

squamous cell carcinoma, numerous anechoic areas of various sizes were noted, their distribution corresponding to areas of necrosis (Figure 7.5, Video clip 7.3). Squamous cell carcinoma sometimes showed a circumferential hyperechoic line around the probe corresponding to the bronchial wall, caused by tumor growth and outward compression of the bronchial adventitia (Figure 7.6, Video clip 7.4). Most cases of poorly differentiated adenocarcinoma on EBUS showed heterogenous internal echoes, irregular margins, and few patent blood vessels or bronchi.

This small nodular small cell carcinoma has directly invaded the pulmonary artery adjacent to the affected bronchus, resulting in stenosis of the pulmonary artery within the lesion (Figure 7.7, Video clip 7.5). In some cases of carcinoid, the tumor arises in the bronchial wall and grows across the bronchial lumen, resulting in a characteristic snowman-like form, with the neck located at the cartilaginous part of the bronchus. Bleeding within the carcinoid appears as mottled hyperechoic areas on the EBUS image (Figure 7.8).

Homogenous internal echoes are seen in cases of primary malignant lymphoma of the lung, with an appearance similar to that of pneumonia. Large blood vessels remain patent within the lesions, indicating that the lesions are soft.

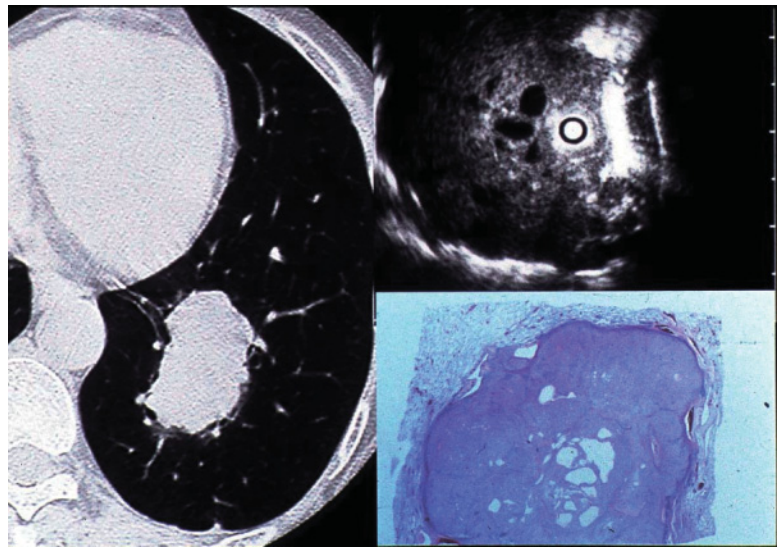

**Figure 7.5** In this case of squamous cell carcinoma, numerous anechoic areas of various sizes are seen, their distribution corresponding to areas of necrosis.

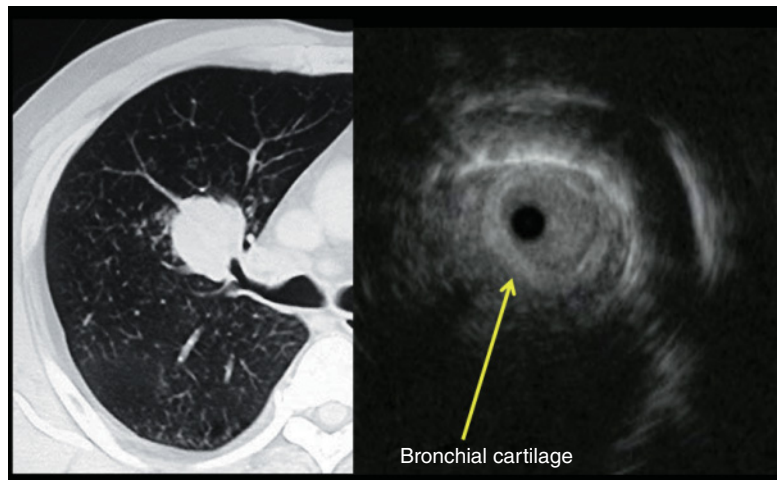


**Figure 7.6** Outward compression of the bronchial adventitia on EBUS image. Squamous cell carcinoma sometimes shows a circumferential hyperechoic line around the probe corresponding to the bronchial wall, caused by tumor growth and outward compression of the bronchial adventitia.

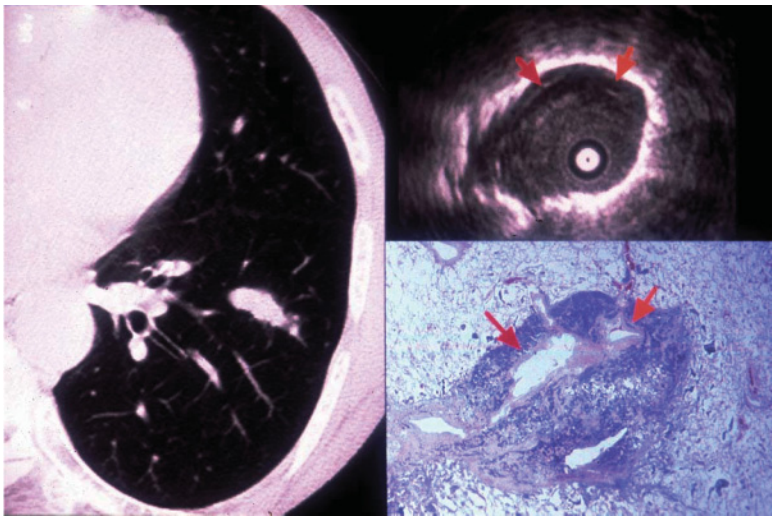

**Figure 7.7** This small nodular small cell carcinoma has directly invaded the pulmonary artery adjacent to the affected bronchus, resulting in stenosis of the pulmonary artery within the lesion.

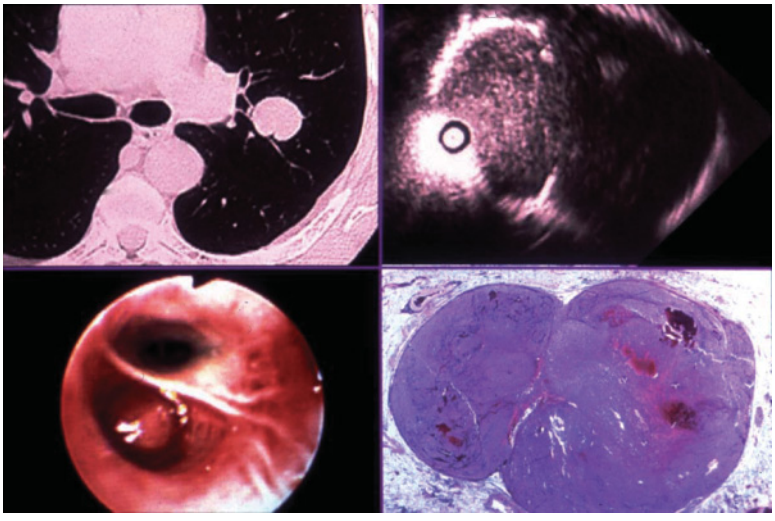

**Figure 7.8** This carcinoid tumor arises in the bronchial wall and grows across the bronchial lumen, resulting in a characteristic snowman-like form, with the neck located at the cartilaginous part of the bronchus. Bleeding within the carcinoid can be seen as mottled hyperechoic areas in the EBUS images.

Anechoic areas with star-shaped margins are visible within the lesion in this case of inflammatory pseudotumor, corresponding to the lumen of the dilated bronchus (Figure 7.9).

In contrast to histopathology, EBUS enables visualization of the internal structures of peripheral pulmonary lesions, such as vessels, bronchioles, bleeding, calcifications, bronchial dilatation, and necrosis (Figure 7.10).

## Internal Structure of Lesions Visualized by EBUS by Histological Subtype

We found that EBUS can clearly visualize internal structures of peripheral pulmonary lesions, including vessels, bronchioles, compressed alveolar air within lesions, calcifications, necrosis, and the homogeneity/

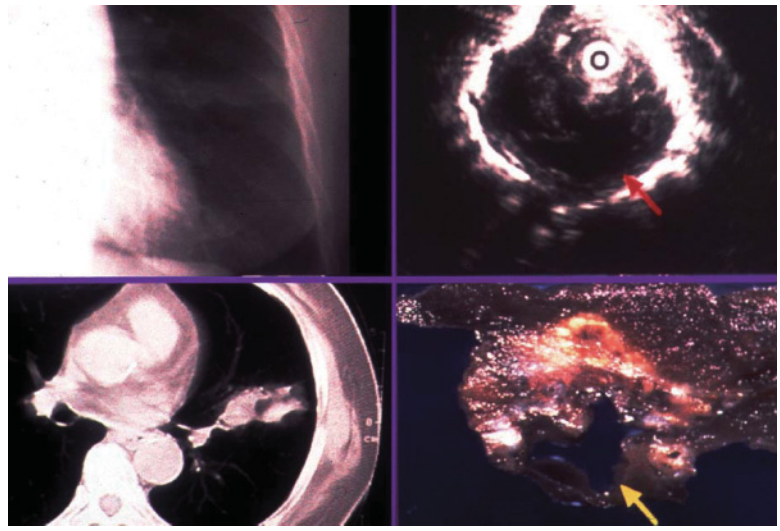

**Figure 7.9** A representative case of inflammatory pseudotumor. Echolucent areas with star-shaped margins are visible within the lesion in this case of inflammatory pseudotumor, corresponding to the lumen of the dilated bronchus.

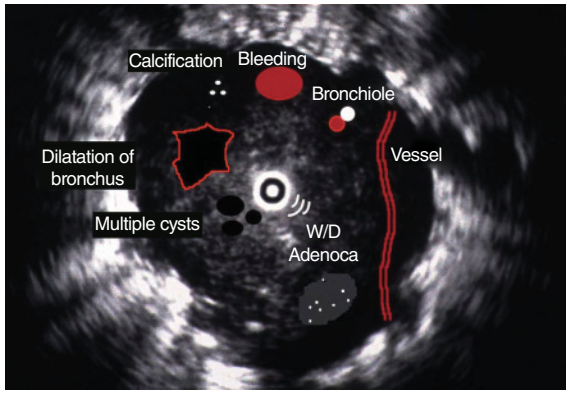


**Figure 7.10** Visualization of the internal structure of peripheral pulmonary lesions. In contrast to histopathology, using EBUS we are able to visualize the internal structure of peripheral pulmonary lesions, including blood vessels, bronchioles, haemorrhage, calcifications, bronchial dilatation, and necrosis.

heterogeneity of the ultrasonic pattern. Tumor typing based on the internal structure as visualized by EBUS can assist in distinguishing between benign and malignant tumors, and assessment of the degree of differentiation. We conducted tumor typing based on the tumor internal structure as visualized by high resolution EBUS.

We were able to visualize the lesion in 143 out of 168 patients (85.1%) with a peripheral pulmonary lesion who underwent EBUS. Of these a definitive tissue diagnosis was obtained in 124 (73.8%). The internal structure of these lesions was analysed, and lesions were typed based on these findings.

Lesions were typed based on internal echo pattern (homogenous or heterogenous), vascular patency, and the morphology of hyperechoic areas (reflecting the presence of air and the state of the bronchi) (Figure 7.11).

## Type I: Homogenous Pattern

### Type Ia: Homogenous Pattern with Patent Vessels and Patent Bronchioles

(Figure 7.12, Video clip 7.6)

The majority of these cases were pneumonia, characterized by exudate-filled alveoli. EBUS images of this type revealed normal blood vessels and bronchi, free of compression or stenosis, within the lesion. The internal echoes were homogenous. There was therefore little ultrasonic attenuation, and even tissue 15 to 20 mm from the probe could be seen clearly. Because lesions extend from one lobule to another, the margins were linear in some areas.

### Type Ib: Homogenous Pattern with No Patent Vessels or Bronchioles (Figure 7.13)

No blood vessels were seen within these lesions using EBUS. Mottled or linear hyperechoic areas were scarce. The internal echoes were homogenous. As with Type Ia, there was little ultrasonic attenuation, and even tissue 15 to 20 mm from the probe could be

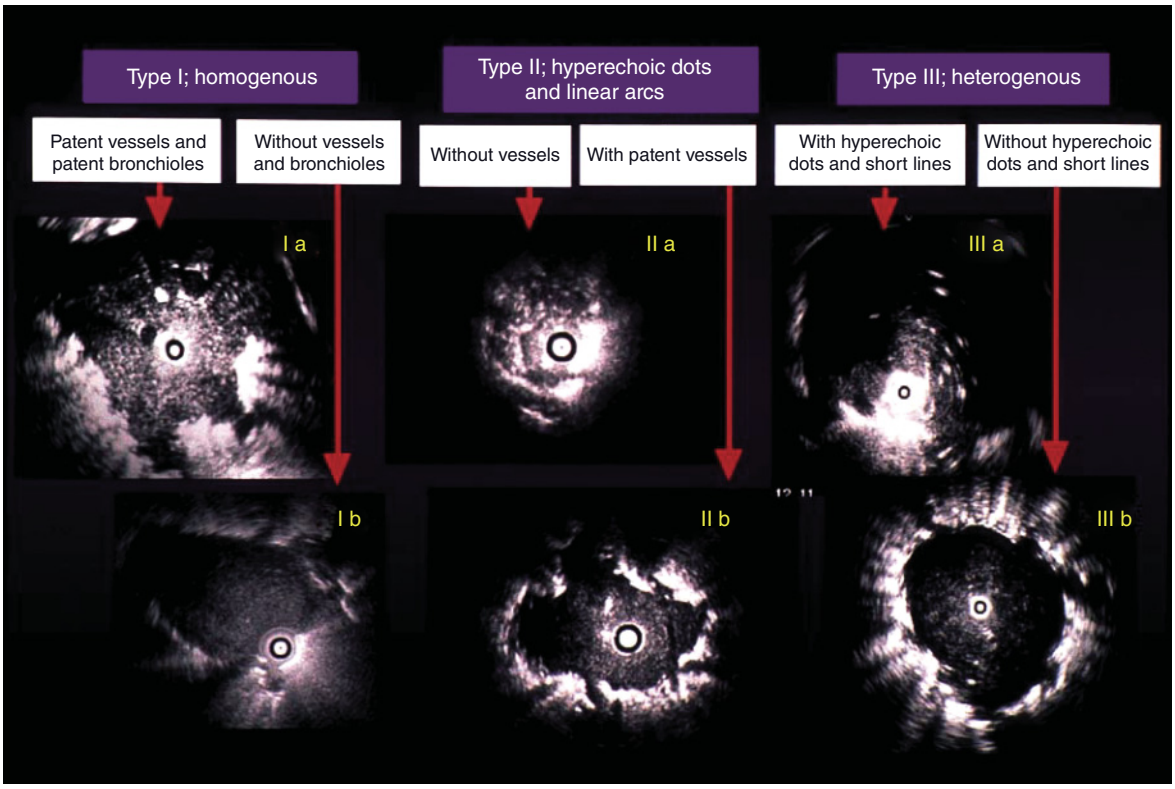


**Figure 7.11** Type classification of peripheral pulmonary lesions. Lesions are typed based on internal echo pattern (homogenous or heterogenous), vascular patency, and the morphology of hyperechoic areas (reflecting the presence of air and the state of the bronchi). Type I: homogeneous pattern; Type Ia: homogenous pattern with patent vessels and patent bronchioles; Type Ib: homogenous pattern with no patent vessels or bronchioles. Type II: hyperechoic dots and linear arcs pattern; Type IIa: hyperechoic dots and linear arcs with no patent vessels; Type IIb: hyperechoic dots and linear arcs with patent vessels. Type III: heterogenous pattern; Type IIIa: heterogenous pattern with hyperechoic dots, and short lines; Type IIIb: heterogenous pattern without hyperechoic dots or short lines.

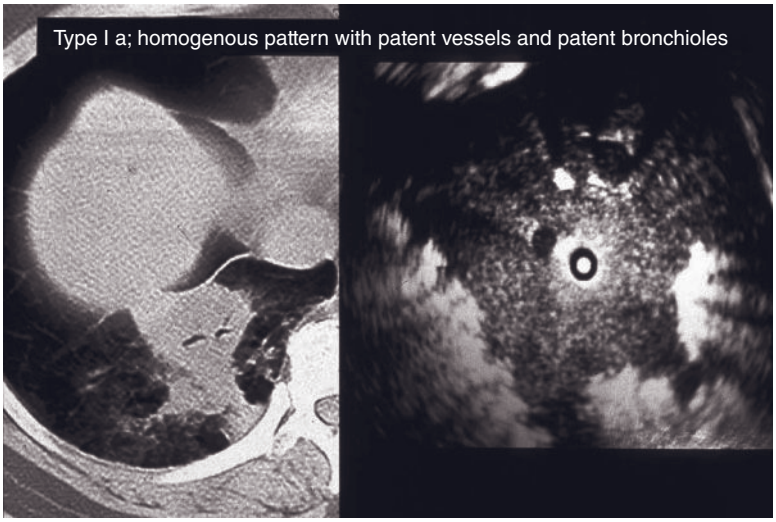


**Figure 7.12** EBUS of Type Ia lesion. This EBUS image shows normal blood vessels and bronchi, free of compression or stenosis, within the lesion. The internal echoes are homogenous.

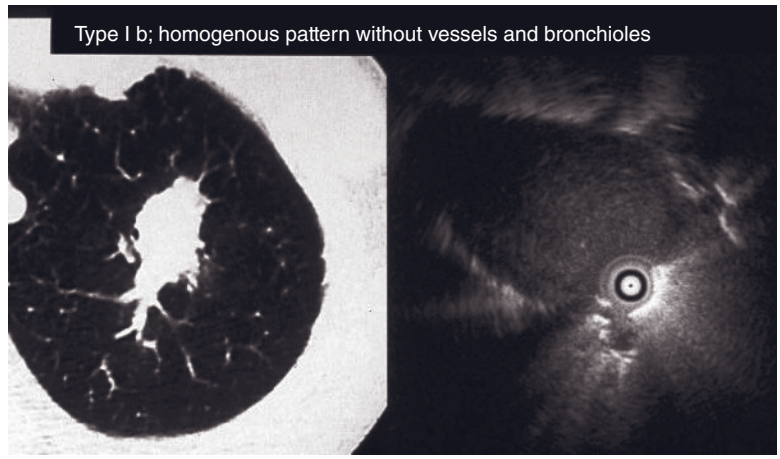


**Figure 7.13** EBUS of Type Ib lesion. In this EBUS image, no patent blood vessels are seen within the lesion. Few mottled or linear hyperechoic areas are visible. The internal echoes are hypoechoic and homogenous.

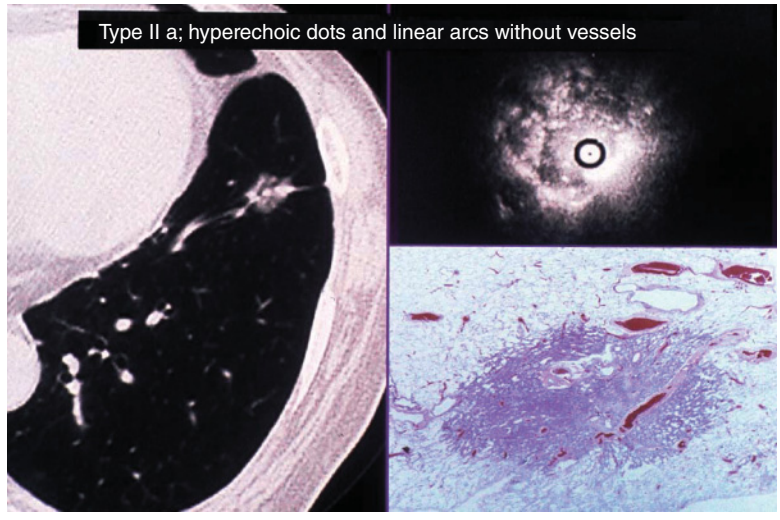


**Figure 7.14** EBUS of Type IIa lesion. In this EBUS image, no blood vessels could be visualized within the lesions. Hyperechoic dots (less than 1 mm in diameter) or hyperechoic linear arcs (primarily around the probe) were distributed irregularly within the lesions.

seen clearly. The Type Ib group mainly included cases of organising pneumonia and tuberculomas.

## Type II: Hyperechoic Dots and Linear Arcs Pattern

### Type IIa: Hyperechoic Dots and Linear Arcs with No Patent Vessels (Figure 7.14, Video clip 7.7)

Most cases were well-differentiated adenocarcinoma which had replaced the alveolar epithelium. No blood vessels could be visualized within the lesions using EBUS. Hyperechoic dots or hyperechoic linear arcs (primarily around the probe) were distributed irregularly within the lesions. The presence of residual air in alveoli is characteristic of well-differentiated adenocarcinoma, which grows to replace the alveolar epithelium. The air remaining in the alveoli hampered visualization of blood vessels within the lesions and obscured the margins of the lesions.

### Type IIb: Hyperechoic Dots and Linear Arcs with Patent Vessels (Figure 7.15, Video clip 7.8)

The majority of cases were well-differentiated adenocarcinoma which had proliferated and replaced the alveolar epithelium while preserving the blood vessels within the lesion. In the EBUS images, the blood

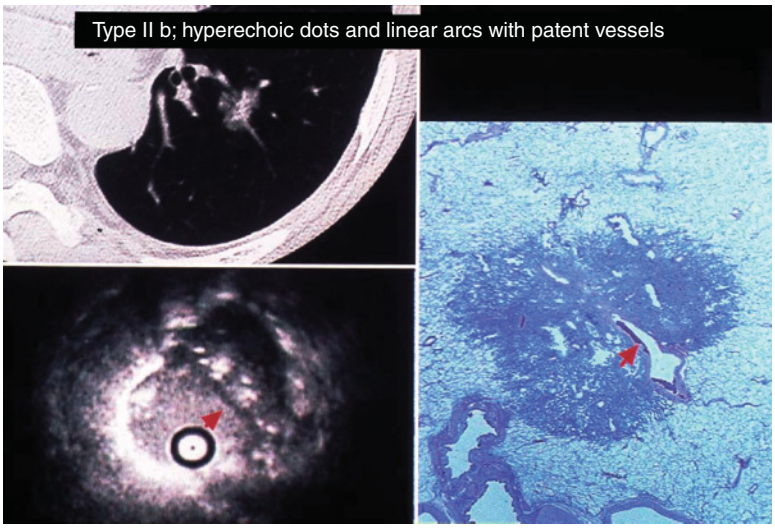


**Figure 7.15** EBUS of Type IIb lesion. In this EBUS image, blood vessels, almost free of compression or stenosis, are visible within the lesion, and the internal echoes are relatively homogenous. Hyperechoic dots (less than 1 mm in diameter) are distributed irregularly within the lesions, corresponding to the presence of residual air in the alveoli.

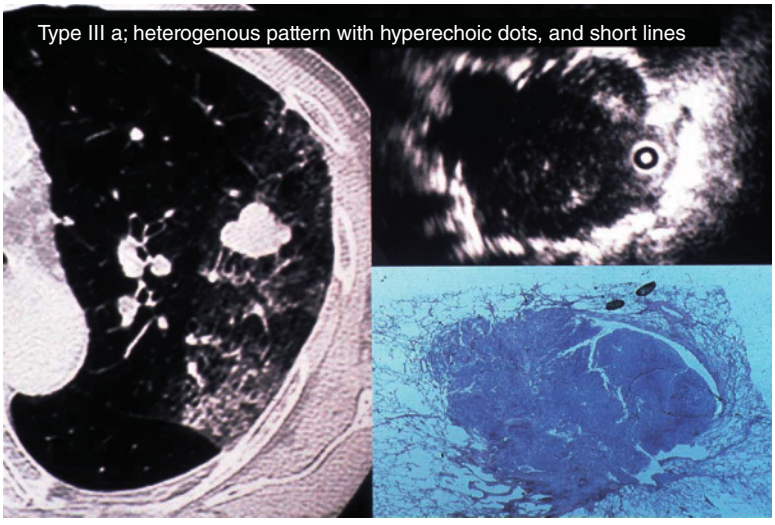


**Figure 7.16** EBUS of Type IIIa lesion. The majority of cases are moderately differentiated adenocarcinomas that grow with a relatively high cell density and form a mass. No blood vessels are seen within the lesion using EBUS. Areas of mottling and linear hyperechoic areas are irregularly distributed within the lesion, corresponding to compressed or stenotic bronchi or alveolar air.

vessels showed little or no compression or stenosis within the lesion, and the internal echoes were relatively homogenous. Hyperechoic dots, distributed irregularly within the lesions, corresponded to residual air in the alveoli, a characteristic of well-differentiated adenocarcinoma. The density of cancer cells was higher and the volume of air remaining in alveoli was smaller in Type IIb than in Type IIa, well-differentiated adenocarcinoma. The margins were irregular because the lesions grew, without any relationship to existing structures.

## Type III: Heterogenous Pattern

### Type IIIa: Heterogenous Pattern with Hyperechoic Dots, and Short Lines (Figure 7.16)

The majority of cases were moderately differentiated adenocarcinoma which had grown with a relatively high cell density and had formed a mass. No blood vessels were seen within these lesions using EBUS. Areas of mottling and linear hyperechoic areas were irregularly distributed within the lesion, corresponding to compressed or stenotic bronchi or alveolar air. The internal echoes were heterogenous, with

markedly attenuated sound wave transmission, so only areas about 6 to 8 mm from the probe could be visualized clearly. Because the lesions spread in a random manner, without extension along lung structures, the margins of the lesions often were rounded. Moderately differentiated squamous cell carcinoma presented numerous anechoic areas corresponding to areas of necrosis within the tumor, which is characteristic of squamous cell carcinoma.

### Type IIIb: Heterogenous Pattern without Hyperechoic Dots or Short Lines (Figure 7.17, Video clip 7.9)

The majority of cases were poorly differentiated adenocarcinoma, which had a high cell density and had formed a mass. The lesions were avascular and showed scant mottled or linear hyperechoic areas. The internal echoes were heterogenous. Since the lesions extend outward, their margins tend to be roundish.

We reported 92.0% of Type I lesions were benign, and 99.0% of Type II and III lesions were malignant. Well-differentiated adenocarcinoma accounted for 88% of Type II lesions, whereas all Type IIIb cases were malignant, including 81.8% poorly differentiated adenocarcinoma.

Some investigators have reported that dynamic magnetic resonance imaging (dynamic MRI) provides information on enhancement patterns of peripheral pulmonary lesions [14,15]. Awaya et al. [16] reported that bronchi and blood vessels can be seen as they cross peripheral pulmonary lesions. The advantage of MRI is that it is less invasive than EBUS, but the images are of poorer quality because the beating heart and breathing introduce motion artefacts.

There have been a number of reports of the use of miniature ultrasound probes for diagnosing peripheral pulmonary lesions. Hürter et al. [10] reported successful visualization of peripheral lung lesions in 19 out of 26 cases, and Goldberg and colleagues [11] reported that EBUS provided unique information that complemented other diagnostic modalities in 18 out of 25 cases (including six peripheral lesions and 19 hilar tumors).

Hosokawa et al. [17] reported that a typical EBUS pattern of neoplastic disease was: (1) continuous marginal echo; (2) rough internal echoes; and (3) no hyperechoic spots representing bronchi, or no longitudinal continuity if present. Kuo et al. [18] assessed the feasibility of EBUS in differentiating between benign and malignant lesions using the following three characteristic ultrasonic features indicating malignancy: continuous margin, absence of a linear-discrete air bronchogram, and heterogenous echogenicity. The negative predictive value for malignancy of a lesion with none of these three echoic features is 93.7%. The positive predictive value for malignancy of a lesion with any two of these three echoic features is 89.2%.

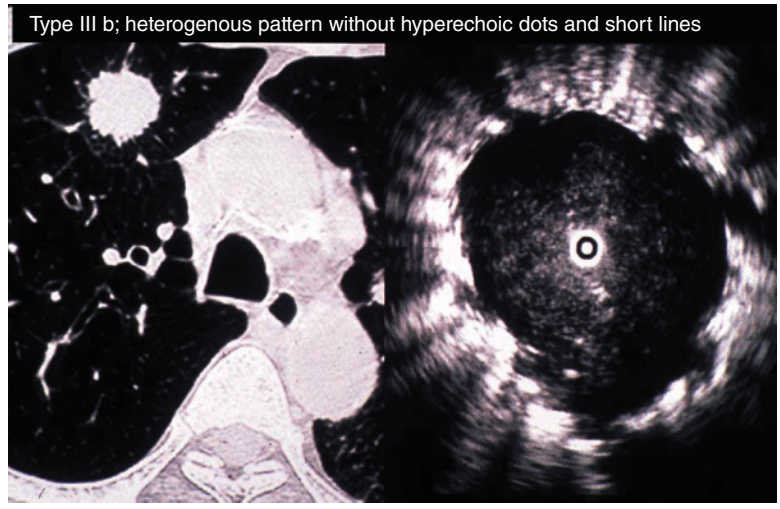


**Figure 7.17** EBUS of Type IIIb lesion. In this EBUS image, the lesion is avascular, and few mottled or linear hyperechoic areas can be seen. The internal echoes are heterogenous.

We developed our classification system with the aim of distinguishing between benign and malignant lesions, identifying the type of lung carcinoma, and determining the degree of differentiation.

Although CT and MRI scans have been used for qualitative diagnosis of peripheral pulmonary lesions, ultrasonograms have the following advantages. The guide sheath can be used to determine the following:

**1** Patency of microvasculature within the lesion.

**2** The distribution of micropneumatosis (small white dots) within the lesion.

**3** The existence of anechoic areas corresponding to necrosis within the lesion.

**4** The echo strength within the lesion.

In particular, the echo strength within lesions visualized by 20 MHz high frequency ultrasonography varies according to factors such as the distribution and density of tumor cells, presence of mucous, and interstitial hyperplasia within the lesion. The echo strength depends on the extent that ultrasound waves are reflected at interfaces between tissue types. Tumors with increased cell density, e.g. poorly differentiated adenocarcinoma, produce a comparatively weak echo. Bronchioloalveolar carcinoma (mucinous type), difficult to distinguish from pneumonia using CT scanning, produces a stronger echo than pneumonia using high frequency ultrasonography at 20 MHz. The reason for this is unclear, but is suspected to be due to viscous mucous, or to increased reflection from neoplastic tissue in the alveolar septa.

EBUS provides a new way to visualize the internal structure of peripheral pulmonary lesions. Classification of the EBUS images suggests the pathology and histology.

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# 8 EBUS-Guided Peripheral Pulmonary Nodule Biopsy

## Introduction

The adaptation of ultrasound miniprobes to bronchoscopic diagnosis was an important step forward in bronchoscopy. It grew out of a need for an improved way to biopsy peripheral lung nodules which traditionally had been performed just with X-ray guidance [1,2]. Ultrasound miniprobes had previously been used in the large airways; however a fluid-filled balloon sheath was required to allow for a probe–tissue interface [3]. An important understanding in allowing the development of the peripheral lung miniprobe was that no balloon sheath was required in the periphery of the lung [4]. This was somewhat counter-intuitive given the air-rated structure of the lung; however, there was an excellent ultrasound image obtained when the ultrasound miniprobe was placed bronchoscopically within peripheral lung lesions. Because of the small caliber of the bronchial airways in the periphery, the ultrasound probe was applied directly to the lesions and no balloon-sheath filled with water was required. It was also noted that when the probe was in a bronchus surrounded by normal air-filled lung, there was just artifact image on the ultrasound monitor and therefore it was easy to discriminate between normal and abnormal tissue. The next step was the use of a guide sheath – into which the thin caliber miniprobe could be deployed. Both the miniprobe and the guide sheath could therefore be inserted as one into the biopsy channel of the standard bronchoscope [5]. This allowed ease of biopsy once the probe had been removed by simply passing forceps and brushes into the location found by the ultrasound miniprobe prior to its removal. Further refinements have included the use of virtual bronchoscopy to aid in tracking the bronchial openings which give the best access to the lesion [6]. Also, whilst the traditional means of performing this type of biopsy has been with X-ray fluoroscopy, with greater experience some authors advocate that fluoroscopy may not be necessary in performing this technique [7]. Finally, the aspect of ultrasound diagnosis by interpretation of the ultrasound images can be useful to give a qualitative impression of malignancy versus benign disease and, in selected situations, may add to the histological samples obtained [8,9].

## Conventional Transbronchial Lung Biopsy

There has always been the need to biopsy lesions beyond the reach of a bronchoscope and the standard method has been to use X-ray fluoroscopy with a brush or biopsy forceps passed under X-ray guidance into the lesion as seen on X-ray fluoroscopy. For best results, the X-ray fluoroscopy is usually performed in two planes and this may be achieved by rotating the fluoroscopy C arm or altering the patient's position during the procedure with the bronchoscope in situ. For lesions of 3 cm or less, there can be considerable misjudgment of the placement of the forceps in respect of the actual lesion. Furthermore, it is not uncommon for small lesions to be totally invisible on X-ray fluoroscopy, particularly those close to the diaphragm and adjacent to the cardiac borders. High apical lesions may also be difficult to visualize. Perhaps for these reasons, there is a wide variation in overall sensitivity

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**Table 8.1** Standard TBLBx studies.

| Reference | Year | *n* | Lesion size <2 cm % | Sensitivity | Pneumothorax % | Bleeding % |
|---|---|---|---|---|---|---|
| Popovich | 1982 | 20 | | 75% | | |
| Fletcher | 1982 | 101 | 6/21(28%) | 36% | 5(5%) | 4(4%) |
| Stringfield | 1977 | 29 | 1/3(33%) | 48% | | |
| Radke | 1976 | 97 | 0% | 56% | | |
| Wallace | 1982 | 143 | 3/65(5%) | 19% | | |
| Hanson | 1976 | 164 | | 57% | 7(4%) | 15(9%) |
| Shiner | 1988 | 71 | 0 | 70% | 1(1%) | 3 hemoptysis(4%) |
| Torrington | 1993 | 30 | | 9% | | |
| Chechani | 1996 | 49 | 6/11(55%) | 72% | | 3(6%) severe, 6/49 moderate (12%) |

of this method with yield between 18 and 75% [10–12]. Because of the requirement to move the C arm of the patient, it can be cumbersome and time consuming, and some radiation is always delivered to the patient, and to a much lesser extent into the bronchoscopy room.

A number of studies have looked at the efficacy of standard transbronchial lung biopsy for peripheral solitary pulmonary nodules (Table 8.1). These predate EBUS guide sheath biopsy, from as early as 1976. One small retrospective study only evaluated a diagnostic efficacy for malignancy which was 9% [13]. The range of diagnostic efficacies no doubt was due to different combinations of malignant and benign disease, variable size and location of the lesions, the extent to which the lesions were biopsied, incorporating some or all of the techniques of bronchoalveolar lavage, bronchial brushings, biopsies, and transbronchial needle aspiration.

Typical sensitivities for lesions of less than or equal to 2 cm in size ranged from 5% up to 55% and most studies commented that there was a significant reduction in diagnostic efficacy below 2 cm in size. Obviously, small size would mean difficulty in visualizing the lesion on X-ray fluoroscopy in two planes. In one study by Chechani, lesions less than 2 cm, less than 3 cm, and greater than 3 cm had positive diagnoses made in six of 11, 12 of 21, and 24 of 30 lesions respectively [2]. Overall, from 49 bronchoscopies, lesions which had a positive diagnosis had a mean lesion diameter of 4.55 cm compared to lesions which were negative on biopsy which had a lesion diameter of 3.14 cm. In peripherally placed carcinomas, Shiner et al. showed that lesions 2–4 cm in size, 4–6 cm, and 6–8 cm had positive diagnoses made in nine of 13, 10 of 15, and two out of three lesions [14]. This series excluded data from lesions less than 2 cm in size.

Fletcher's series lesions 2–4 cm in size had a 40% yield, and those greater than 4 cm had a 63% yield [15].

Chechani et al. commented that certain pulmonary segments of the bronchial tree were difficult to visualize on fluoroscopy. This is the common experience of most bronchoscopists, including when dealing with the basal segments of the lower lobes and the apical segments of the upper lobes [2]. An interesting comment from Chechani et al. was that "lesions which had sharp borders on X-ray had a poorer diagnostic rate (54%) compared to lesions which had fuzzy borders (83%) or cavitating (100%)". They postulated that the reason for this was that the more sharply demarcated lesions were not likely to be intra-luminal. This included both benign lesions and metastatic deposits and with these there was a recommendation that the transbronchial needle aspiration approach

should be used in an attempt to cross the bronchial wall into the lesion. This is mentioned by other authors performing endobronchial ultrasound techniques as discussed below.

With respect to pneumothorax rate, where reported, the incidence was between 1% and 5% [15]. Bleeding complications were not uncommon. In one series by Chechani, three out of 48 patients (6%) had severe bronchial bleeding [2]. In addition to this, moderate bleeding was seen in six out 40 cases that had transbronchial lung biopsies and three of 48 cases that had transbronchial brushes. In another series by Blascow in 169 patients with solitary pulmonary nodules, three patients had bleeding of more than 100 mL after the biopsy [16]. Fletcher et al. also reported a 4% incidence of severe bleeds. There were no mortalities reported; however the extent of the bleeding is quite different from that observed in endobronchial ultrasound as discussed below [15].

## Method and Equipment

### History

The possible role of ultrasound miniprobes in evaluating and biopsying peripheral lung lesions was demonstrated by Hurther [17] and Goldberg [18]. Both recognized the potential for ultrasound miniprobes in the lung which had previously been used in other specialties of gastroenterology and urology. Goldberg demonstrated that 15 out of 25 peripheral lung lesions, most less than 3 cm in diameter, could be localized with an ultrasound probe. The characteristics of the solid tumor, blood vessels within the tumor, and air artifact within normal lung, were demonstrated. In that series, there was no guide sheath used and the biopsy point was simply determined by the position of the ultrasound miniprobe within the lesion and recorded by fluoroscopy. Quite correctly, both authors foresaw the potential for this method in its simplicity and inherent safety. In 2002, there were two publications which further elucidated the benefits of this technique. Herth, Ernst and Becker demonstrated, in a prospective series of 50 patients, the ability of endobronchial ultrasound miniprobe biopsies to yield a similar success rate to fluoroscopic guidance (80% versus 76%) [2]. This demonstrated first the accurate localization of the lesions by EBUS, but also the advantage that far less radiation exposure would be required. Also in 2002, Kurimoto published a detailed account of the ultrasound characteristics of malignant and benign lesions [5]. This included cases analysed preoperatively with an ultrasound miniprobe passed into the lesion bronchoscopically prior to surgical resection. There was close correlation between the ultrasound image and anatomical structures such as bronchi and small blood vessels within the lesion. As discussed below, a detailed scheme of analysis of the internal structures was described and the potential for interpretation of ultrasound images in tissue diagnosis was raised. Both of these series used the 20 MHz miniprobes from Olympus. These were radial probes, either UM-3R or UM-20-26R.

In 2004, Kurimoto published a series describing the addition of the guide sheath, the plastic sheath into which the ultrasound miniprobe was passed prior to insertion down the biopsy channel of the bronchoscope [9]. This was coupled with the introduction of the thinner 20 MHz radial probe (UM-S20-20R). This probe itself had an outer diameter of 1.7 mm and, combined with the guide sheath, meant that it could be inserted into a 2 mm working channel of a fiberscope. This smaller probe demonstrated its flexibility in terms of accessing the subsegments of the smaller upper lobes which had more acute angles; in the previous studies it had been difficult to access these with the slightly larger caliber UM-3R miniprobe. This study also demonstrated the practical benefits of the guide sheath when coupled with the miniprobe with virtually nil evidence of bleeding and facilitation of multiple biopsies at the same site.

The next step was the addition of pre-procedure evaluation of the patient using virtual bronchoscopy CT images [6]. By tracking the path that the bronchoscope and probe would take out towards the lesion with virtual bronchoscopy, it was demonstrated that choice of the correct bronchial segment could be improved.

### Equipment

The most commonly used miniprobe for EBUS directed peripheral nodule biopsy is the 20-20R Olympus Miniprobe, usually the 1.7 mm diameter probe with accompanying guide sheath. Prior to inserting this into the guide sheath, it is necessary to calibrate the biopsy forceps and brush forceps to the length of the plastic guide sheath. This allows the forceps to be inserted up to a pre-marked point when the guide sheath is in situ

in the lesion in the lung. This pre-marked point is simply made by placing adhesive tape on the proximal end of the forceps or brush at the point where the distal end is either just protruding from the end of the plastic sheath in the case of the forceps, or just at the tip of the sheath in the case of the brush. Lastly, prior to commencing the procedure, the ultrasound miniprobe is placed inside the sheath and taped with double-ended adhesive tape. This stops the miniprobe slipping back into the sheath as it is passed out from the end of the bronchoscope into the selected bronchus. The double-ended tape means that the tape can be removed simply once the lesion has been located. Now the guide sheath is available with dedicated rubber markers to simplify this preparation.

A 2.8 mm biopsy channel bronchoscope is required for this procedure. It is very important to select the segmental or subsegmental bronchus which is considered to lead most directly to the lesion in question. This is determined by careful scrutiny of the CT scan prior to the procedure. The ultrasound miniprobe in the guide sheath is passed gently out into this bronchus towards the periphery of the lung until a slight resistance is felt suggesting proximity to the visceral pleura, similar to the procedure of a standard transbronchial lung biopsy. It is possible to perform this part of the procedure with fluoroscopy guidance to prevent the miniprobe being passed out too far. Once this slight resistance is felt, the ultrasound probe is turned on by the foot pedal and slowly pulled back as ultrasound pictures are obtained. Once a clear image is obtained, it is usual to pull the ultrasound probe back to the proximal extent of the lesion. This is so that biopsy forceps, when passed back down the guide sheath, are not passed too far beyond the lesion, rather opening into the middle of the lesion. On occasions, the lesion in question is only imaged peripherally, as opposed to having the lesion fully surrounding the miniprobe. In this situation, it is best to pull the miniprobe back and re-advance into an adjacent subsegmental bronchus, preferably done under bronchoscopic vision. Sometimes only slight adjustment in this way can greatly improve the ultrasound image. Some centers use a curette passed into the guide sheath to facilitate that purpose. To do this, the ultrasound miniprobe must be removed from the guide sheath and the curette passed out with angulation of the curette used under fluoroscopy guidance, in order to turn the guide sheath in the desired direction. Having obtained an improved position in this way, the ultrasound miniprobe is re-inserted and moved to the best position based on the ultrasound image.

Usually the point at which the ultrasound images are best can be saved with a fluoroscopy picture and the C arm kept stationary. If fluoroscopy is used in this way, it is possible to simply leave the guide sheath in place and advance first the brush and then the biopsy into position. Fluoroscopy can be shown to demonstrate the brush and biopsy actually taking the samples, so that it is clear that each of these have exited from the end of the plastic sheath. It is also a further check that the parietal pleura is not being breached by these biopsy methods. Some centers do not advocate doing this to minimize fluoroscopy exposure, given the excellent results of the procedure done completely without any form of fluoroscopy [7,19].

Having taken the necessary samples, the brush and biopsy forceps are removed in turn and the guide sheath is usually left in place for 1–2 minutes. This is an extremely effective way to tamponade any bleeding from the segmental bronchus simply because the caliber of the sheath is usually equivalent to the caliber of the biopsied bronchus. Then, under bronchoscopic vision, the guide sheath is carefully and slowly removed, watching for bleeding in the usual way as one would after completion of a transbronchial lung biopsy. Following the procedure, X-ray fluoroscopy can be used if available to confirm the absence of an immediate pneumothorax, and it is usually desirable to perform a departmental chest X-ray to exclude pneumothorax after an interval of 1–2 hours.

More recent refinements have included the adoption of even smaller miniprobes (1.5 mm diameter with a 1.7 mm bronchoscopic sheath) to go down the biopsy channel (2 mm diameter) of a pediatric video bronchoscope (4–4.9 mm) [20]. This has been shown to further improve access into the smaller subsegments at greater angles. These smaller miniprobes use dedicated smaller caliber biopsy forceps and brushes.

## Clinical Trials

The advent of endobronchial ultrasound transbronchial lung biopsy has been an important milestone in

the expansion of bronchoscopic techniques, in some of the larger studies performed in various methods of bronchoscopy. These studies are summarized in Table 8.2.

The first prospective study was published in 2002 by Herth, Ernst and Becker [4]. The aim of this study was to determine the added benefit of using ultrasound compared to standard transbronchial lung biopsy. Guide sheath was not used in this early study. The study design was to perform both ultrasound and standard fluoroscopy-guided transbronchial lung biopsy in each patient. The results were excellent with EBUS biopsies providing a tissue diagnosis in 40 patients (80%) and showed a significant improvement compared to standard fluoroscopy biopsies in lesions less than 3 cm in size where the overall diagnostic rate was still 80% compared to 57% for fluoroscopically guided biopsies. An important aspect was that the time for the EBUS-guided transbronchial biopsy was close to the time for the procedure performed with fluoroscopy, both being approximately 6 minutes each. The limitation of this investigation was that whereas the methods were applied sequentially in random order, it could not exclude bias in that the location of the lesion may have been established by the respective first method. That is, if the lesion was localized first with fluoroscopy, it could have been an aid to the subsequent EBUS-guided biopsy. However, the authors did not feel that prior fluoroscopy enhanced the ability to locate lesions by EBUS, as three out of four lesions not found with EBUS were previously detected by fluoroscopy. Overall, there was a very high localization of lesions by EBUS.

The next important study was by Kurimoto and reported the introduction of the guide sheath associated with the miniprobe [9]. The overall diagnostic yield in this study once again was very high with 77% of procedures obtaining a tissue diagnosis in lesions which, once again, in general, were quite small. The ultrasound was able to enter the lesion in 87% of cases. The important finding in this study was the uniform high histology rate across lesion sizes, with lesions less than or equal to 10 mm, having a 76% success rate; lesions 15–20 mm in size having a 66% success rate; and lesions 20–30 mm in size having a 77% success rate. There were 81 lesions less than 20 mm in size in this study and standard fluoroscopy was not able to confirm whether the forceps were within the lesion. This is, once again, indicative of the ability of ultrasound to locate these very small lesions. If fluoroscopy was not able to localize the lesion, the yield was still 74% in terms of positive histology; those small lesions where fluoroscopy could detect the lesion had a 67% positive histology rate. The guide sheath was left in place for two minutes after the biopsies in an attempt to prevent any bleeding after the biopsies. Careful quantitation of bleeding was undertaken in this last study and, in only two patients (1%), was there moderate bleeding estimated as between 30 and 50 mL of blood, which was self-limiting and did not affect the patient's oxygenation status. The overall procedure time was not significantly prolonged by the EBUS guide sheath procedure. The total procedure time was 9 minutes with the mean time of use of ultrasound being only 1 minute, and the mean time for use of fluoroscopy also being 1 minute.

Also in 2004 Shirakawa reported 50 cases who had EBUS-guided biopsy of a peripheral lung lesion [21]. These were compared with 42 controls assessed with fluoroscopy only. An important aspect of this study was that 78% of patients had their lesion accessed by endobronchial ultrasound. This meant that changing position of the patient was not required to assist in fluoroscopy. Usually fluoroscopy should be performed in two planes to facilitate lesion location and clearly this was obviated in a large percentage of these patients. Overall, this study showed trends to improve diagnosis with the EBUS guide sheath; however they did not reach statistical significance. Nonetheless the overall yields were high with fluoroscopy alone reflecting a better than usual proficiency with this standard technique.

In the same year, a study using a smaller miniprobe (20R-17R, 1.4 mm outer diameter), was used [6]. This could also be included in a guide sheath and, importantly, could be used with a small caliber 4 mm bronchoscope. This was because access to the upper lobe subsegmental bronchi is often important with these types of biopsies. Often lesions are high in the upper lobes and acute angulation of the bronchoscope is required to access these points. This study demonstrated the ability to localize even very small lesions, with lesions <3 cm in size entered by the EBUS probe. In this study, the diagnostic rate for malignancy was 67%. These authors had prior long experience using

**Table 8.2** Prospective clinical studies: EBUS Guide sheath.

| Author | Year | Reference | Miniprobe | Scope | Biopsy channel calibre | n ebus | comparator | comparator n |
|---|---|---|---|---|---|---|---|---|
| Herth | 2002 | 4 | 20-20 | 1T30/1T40/ XT20 | | 25 | standard TBLBx | 25 |
| Kurimoto | 2004 | 9 | 20-20 | iT30/1T40/ 240R | | 150 | | |
| Shirakawa | 2004 | 21 | UM3R/ UM4R/20-20 | 1T240 R | | 50 | standard TBLBx | 42 |
| Kikuchi | 2004 | 6 | 20-17 | 260F/p240/ p200 | 2 mm | 24 | | |
| Yang | 2004 | 24 | | | | 96 | standard TBLBx | 122 |
| Asahina | 2005 | 20 | 20-17 | p 260f/p240 | 2 mm | 29 | | |
| Paone | 2005 | 22 | 20-20 | bf b3/t20 | | 87 | standard TBLBx | 119 |
| Herth | 2006 | 7 | 20-20 | bf t 160 | | 54 | | |
| Chao | 2006 | 27 | 20-20 | p 260f | | 131 | | |
| Yamada | 2007 | 23 | 20-17 and 20-20 | p 260 f/1T30/1T260 | 2 mm/ 2.8 mm | 155 | | |
| Fielding | 2007 | 29 | 20-20 | 1T40 | 2.8 mm | 140 | CT FNA | 121 |
| Chung | 2007 | 28 | 20-20 | p260f | | 113 | | |
| Dooms | 2007 | 25 | | | | 50 | | |
| Yoshikawa | 2007 | 19 | 20-17 | 260/p240 | 2 mm | 121 | | |
| Asano | 2009 | 26 | 20-17 | | 2 mm | 32 | | |

X-ray fluoroscopy at their hospital in diagnosing small peripheral lesions. In the prior 12 months, simply by using fluoroscopy alone, for lesions less than 20 mm in diameter, fluoroscopy did not allow the biopsy forceps to reach the lesion in 35%, and only 13% were able to obtain a tissue diagnosis. The authors commented that the gap between localizing the lesion and obtaining a tissue diagnosis could have been affected by the small size of biopsy forceps and brushes used with this smaller caliber guide sheath. The authors made qualitative comments that bleeding of any kind was hardly ever seen when the guide sheath was removed. They assumed, as did Kurimoto, that the wedged guide sheath in the bronchus was tamponading any bleeding. As with Kurimoto's study, these authors were adept at using a doubled-hinged curette. This was used to facilitate placement of the catheter in adjacent bronchi if the original pass with the ultrasound probe in the sheath was unsuccessful. Clearly, using this method does require fluoroscopy and does require some skill and practice.

In 2005, Paone reported a large series of 221 patients who were randomly assigned to either EBUS biopsy or transbronchial biopsy for small peripheral lung

| mean lesion size mm | Procedure time | Lesion entered | Yield | Yield malignat | Yield benign | Yield <3 cm | Yield <2 cm | Side effects |
|---|---|---|---|---|---|---|---|---|
| 33.1 | 6 minutes EBUS time | 92% | 80% | | | 80% | | minor bleeding ×2( no guide sheath), px ×1 |
| | 1 min EBUS 9 mins procedure | 87% | 77% | 81% | 69% | | | moderate >30 ml bleeding×2 |
| (33/50 <2 cm) | | 78% | | 71% | | | | |
| 18 mm | | 79% | 53% | 67% | 33% | | 53% | ×1 px |
| | | | | 55–66% | | | 55% | |
| 19 mm | 25 mins whole exam, time to first ebus imaging 12 mins | 80% | 63% | | | | | |
| | 9.8 mins including instrument set up | | 76% | 79% | 69% | 75% | 71% | nil |
| 22 mm | 12.3 mins including biopsies | 89% | 70% | | | | | 1 px, 3 self limited bleeding |
| 44 mm | | | 63% | | | | | |
| 21 mm | | | 67% | | | 76% | 40%((15–30) | |
| 29 mm | 25 mins for all bronchoscopy | | 66% | 63% | 70% | | | 2 px |
| 25 mm | | 72% | 68%-see comments | 73% | 24% | | | ×1 px, ×5 mild bleeding |
| 37 mm | | 74% | 62% | | | | | |
| 31 mm | | | 62% | | | 76%(>20 mm) | 30% | 1 px |
| 31 mm | 22 mins total | 94% | 80% | | | | | |

lesions [22]. Eighty-seven patients underwent EBUS and 119 had transbronchial lung biopsy. Overall, there was a 76% diagnostic rate for EBUS compared to 52% for standard transbronchial lung biopsy without EBUS. As with the other studies, a variety of benign and malignant conditions could be diagnosed. There was no difference in the overall success rate for lesions greater than 3 cm in diameter; however the evaluation of patients with lesions less than 3 cm showed a substantial benefit for EBUS-guided biopsy compared to standard transbronchial lung biopsy. There was a 75% sensitivity for EBUS compared to 31% for transbronchial lung biopsy which was highly statistically significant. This is even allowing for the fact that many centers would probably have difficulty achieving 31% success rate with transbronchial lung biopsy alone. For lesions less than 2 cm in size, a similar improvement was found with 71% sensitivity for EBUS and 23% sensitivity for transbronchial lung biopsy.

In 2005, Asahina reported EBUS-guided sheath biopsy of peripheral lung lesions assisted by CT virtual bronchoscopy [20]. Prior to the bronchoscopy, a fly-through image of the bronchial tree was created using images reconstructed from helical CT data transferred

to a worksite. Images were clear as far as the fifth general bronchi; however for more peripheral zones, virtual bronchoscopy images were generated using pulmonary arterial branches. As in the study of Kukuchi, once again a thin caliber 1.4 mm EBUS miniprobe was used. The bronchoscope was inserted as deeply as possible into the target bronchus under direct vision as suggested by the correct path from the CT virtual bronchoscopy. The miniprobe in the guide sheath was then inserted. Standard radiographic fluoroscopy and EBUS imaging were used. Using this method, EBUS was able to detect 24 of the 30 peripheral pulmonary lesions (80%) with an average diameter of 19 mm. The average time to the first EBUS imaging of the lesion including anesthesia of the bronchial tree and insertion of the bronchoscope and echo probe into the lesion, was 10 minutes. The average time for the first biopsy including the time to the first EBUS imaging and adjustment of the forceps position was 12 minutes. Overall, the complete examination took 25 minutes. This elegant study demonstrated the capacity of virtual bronchoscopy to assist the proceduralist in identifying relevant small subsegmental bronchus into which the guide sheath miniprobe should be passed. The upper lobes can be particularly subject to significant anatomical variations and guidance in probe site selection is clearly of benefit to the proceduralist. Even lesions less than 20 mm in diameter had a 54% success rate in tissue diagnosis.

In a study reported in 2006, Herth et al. presented results in 54 patients with solitary pulmonary nodules that could not be visualized with standard fluoroscopy done at the time of bronchoscopy [7]. These were very small lesions with an average diameter of 2.2 cm. A very high percentage of these patients could be localized with EBUS (89%) and, overall, there was a tissue diagnosis in 70% of these patients. Lesions were distributed quite evenly throughout the lung and there was a slightly better tissue diagnosis rate for malignancy compared with benign lesions. The results indicate the added benefit of ultrasound in that if standard transbronchial lung biopsy is performed and the lesion cannot either be seen or located, the biopsy site becomes the best estimate of the proceduralist. The advantage of EBUS clearly is the definitive localization of the lesion.

In 2007, Yoshikawa reported EBUS to guide a transbronchial lung biopsy without radiographic fluoroscopy in 123 procedures [19]. Once the EBUS confirmed the lesion, the probe was withdrawn and the guide sheath left in place. Brushings and transbronchial biopsies were performed by the guide sheath; when an EBUS image could not be obtained at that stage, the bronchoscopic examination became a standard fluoroscopically guided transbronchial lung biopsy. 62% of lesions were diagnosed by the EBUS method without fluoroscopy. Amongst these lesions, those greater than 20 mm in diameter had a 76% diagnostic rate and this was significantly higher than those with lesion diameters of less than 20 mm where the histology rate was 30%. Two other interesting aspects for the proceduralist were first that when the CT could clearly identify a bronchus leading to the lesion, the overall yield was 79%. In addition, there was a higher diagnostic yield for solid lesions (67%) compared with non-solid lesions (35%). Non-solid lesions such as ground glass opacities often simply surround the small peripheral bronchus without either compressing or invading it. Hence, a transbronchial lung biopsy may have difficulty actually catching the abnormal tissue in these cases. The goal of this study was to demonstrate the ability of EBUS to perform the biopsy without the excessive radiation exposure for patients and medical workers that can occur with the use of fluoroscopy. This study extended the findings of Herth et al. who had shown in their earlier study similar overall success rates for EBUS and fluoroscopically guided transbronchial lung biopsies. The authors commented that the previous studies by Kikuchi and Paone had higher diagnostic rates for lesions less than 2 cm in diameter (53% and 71% respectively) because there could be fluoroscopically guided confirmation of the peripheral pulmonary lesions in those studies. Second, fluoroscopy allows the use of the hinged curette to facilitate repositioning of the probe. Third, fluoroscopic guidance may assist with preventing the probe from moving during respiratory movement. Overall, therefore, the authors concluded that fluoroscopic guidance was not necessary for lesions more than 20 mm in diameter, but probably would be required for lesions smaller than this. With respect to lesion location, the authors made some interesting qualitative comments. First, the diagnostic yields of peripheral pulmonary lesions in the right middle lobe and lingular were significantly higher. The access to these lobes is clearly easier than some of the apical

segments of the upper lobes. Others had previously shown lower success rates for biopsies in the right upper lobes [9]. Negotiating the sharp bends of the bronchus in these airways opening with the tip of the EBUS catheter can be quite difficult. They also felt that the guide sheath seemed to move and slip off more easily from the lesion with deep inspiration in lesions in the lower lobes. With respect to peripheral pulmonary lesions which are aerated and non-solid, the authors recommended that transbronchial needle aspiration could be used.

In 2007, Yamada reported factors which increased the yield of small peripheral pulmonary lesions [23]. As noted from these other studies, there is often a gap between the access to the lesion as confirmed by ultrasound and actually confirming a tissue diagnosis. The first important parameter was the location of the probe with respect to the lesion. There was clearly an improved diagnostic yield (83%) when the probe was positioned within the lesion compared to those where it was positioned adjacent to it (61%) were outside the peripheral pulmonary lesion. These were statistically significant results and indicate the need for the practitioner, possibly with the use of a curette, to facilitate placement of the probe well within the lesion. In this study, once again, very small peripheral lesions (85%) were actually entered with the EBUS probe. Lesions of between 15 and 20 mm, greater than 20 and less than 25 mm and greater than 25 and less than 30 mm had diagnostic yields of 40%, 74%, 72%, and 81% respectively. Other useful data from this paper were that there was an increasing diagnostic yield approaching 97% where the final diagnosis was made after five biopsies. It would therefore seem that at least five biopsies ought to be taken. The importance of the placement of the probe within the lesion was demonstrated in that multivariant analysis showed this to be the most significant factor in overall diagnostic yield, even overcoming small lesion size, as small as less than 15 mm in diameter. The study also demonstrated the lack of any statistical difference between operators in the procedure, all of whom had had more than four years experience in bronchoscopy. Other factors in biopsying lesions most effectively would be to place the guide sheath at the near end of the lesion as gauged by ultrasound. In this way, as the forceps comes out, it will not over-reach the lesion as it may do if the guide sheath is left in the middle of the lesion.

## Analysis of Internal Structure of Peripheral Pulmonary Lesions Using EBUS

In Kurimoto's study of 2002, a detailed analysis of the ultrasound appearance of peripheral pulmonary lesions when accessed by an EBUS probe was presented [5]. This work began in January 1996. The overall question, of course, is whether there is a correlation between ultrasound characteristics and final histological confirmation. Initially, 69 patients with preoperative EBUS images were correlated with histopathological findings of surgical specimens upon surgical resection. This allowed exact correlation with small intra-lesional bronchi and vessels. Subsequent to that, another 124 lesions underwent bronchoscopic biopsy, and EBUS pictures were analysed for their internal structures depending on the final tissue diagnosis. The ultrasound images appeared to have correlation to the lesion in question primarily on the basis of how much the underlying pathology destroyed the usual structures in the lung, namely the bronchi, alveoli, and blood vessels. The more destructive the lesion, such as an aggressive carcinoma, the less were these structures identifiable; conversely, the more benign and less destructive the process, the more identifiable such structures as bronchi were. The former, overall, tend to therefore have a somewhat heterogenous appearance because of the different echodensities of compressed or distorted structures. The latter more benign lesions tend to have a homogenous appearance because of the maintenance of normal lung tissue architecture to some extent within the lesion. Residual air within a lesion was reflected as a hyperechoic dot as air tends to give such an appearance on ultrasound. Blood vessels could often be seen coursing through lesions, sometimes with diameters as small as 0.68 mm when measured histopathologically. These structures tended to be seen more in benign less destructive pathological processes. At a frequency of 20 MHz, the spatial resolution of ultrasound images is approximately 0.38 mm.

Broad groups of three EBUS images were described. Type 3 lesions had a heterogenous appearance and the majority of these were malignant (Table 8.3). No blood vessels were seen within the lesion by EBUS and there were irregular mottled and linear areas distributed in the lesion corresponding to the destructive

**Table 8.3** Differentiation of peripheral lesions on EBUS images

| Kurimoto | Key features | Type 1 | Type 2 | Type 3 |
|---|---|---|---|---|
| | hetrogeneous/homogeneuos | Homogeneous | | Heterogeneous |
| | vessels seen | Type 1a | Type 2b | Type 3a |
| | bronchi seen | Type 1a | Type 2b | Type 3a |
| | hyperechoic points | | Marked | |
| | Malignant | | 99 | 99 |
| | Benign | 92 | | |

Kurimoto N, Murayama M, Shinchikiro S, Nishisaka T. Analysis of the internal structure of peripheral pulmonary lesions using endobronchial ultrasonography. Chest 2002;122:1887–1894.

| Chao | Homogenous/heterogenous | | Hyperechoic dots | Concentric circles | Continuous margin |
|---|---|---|---|---|---|
| Malignant | 4% | 97% | 54% | 2% | 22% |
| Benign | 41% | 59% | 74% | 53% | 9% |
| p | <0.001 | | | <.001 | 0.09 |

Adapted from Chao TY, Lie CH, Chung YH, et al. Differentiating peripheral pulmonary lesions based on images of endobronchial ultrasonography. Chest 2006;130:1191–1197.

effects of the tumor compressing bronchi and alveolar air. The echoes were therefore heterogenous and relatively dense. There was a significant attenuation of the sound waves by the tumor so that only about 6–8 mm of the lesion could be seen clearly, whereas tissue outside this was seen clearly. Most of these were peripheral adenocarcinomas. Some type 3 lesions did not have any hyperechoic dots or short lines, possibly because they were relatively avascular, and remnants of previous structures which caused such features in other type 3 lesions were therefore absent. Therefore, type 3 lesions could be classified as either A or B depending on the presence or absence of these hyperechoic dots and short lines. Overall, however, there was always heterogeneity of internal echoes.

Type 2 lesions had a predominance of hyperechoic dots and linear arcs and these represented the residual alveoli (small points of hyperechoic air) and slightly compressed bronchi. These lesions could be further subclassified as either A or B depending on whether vessels were not, or were, visualized. The histopathological correlate of these residual alveolar structures was that of well-differentiated adenocarcinomas which grow in a lepidic fashion without destroying the underlying alveolar parenchyma. It was thought that some of these lesions did not have blood vessels visualized because of the predominance of the alveolar air pockets which hampered the visualization of the vessels. In those type 2 lesions where vessels were identifiable, there was a greater density of adenocarcinoma cells and presumably this allowed identification of vessels because of more solid tissue surround them as opposed to air pockets.

Type 1 lesions had the unifying characteristic of being homogenous. That is, the internal echoes between any visible structures such as vessels or bronchioles were homogenous. In some of these cases, the vessels and bronchioles were visible and predominantly these included cases of pneumonia where there was a pattern of exudates-filled alveoli demonstrate on histopathology. Because the pneumonia was not causing any compression or stenosis of bronchi or vessels, these were well seen. There was small ultrasound attenuation because of this type of lesion which was not particularly dense and even tissue 15–20 mm from the probe could be seen clearly. Sometimes, where the lesion was up against a fissure, the margins of the lesion could be seen to be linear. There was one case of malignancy amongst this group because the form of metastasis from a pancreatic carcinoma was of

a pneumonic type with respect to the CT scan and histopathology. Some cases of homogenous type 1 pattern did not have vessels or bronchioles visualized; however the important aspect was that mottled or linear hyperechoic areas were absent or scant. These included cases of organizing pneumonia and tuberculomas; it did include one case of moderately differentiated squamous cell carcinoma.

Overall, using this classification, there was an extremely good correlation between the presence of type 2 or 3 lesions and the presence of malignancy (99%). Furthermore, 21 of 24 type 2 lesions (87.5%) were well-differentiated adenocarcinomas. All of the type 3 B lesions were malignant. With respect to type 1 lesions, 25 (92%) were shown to be benign.

In 2006, Chao et al. reported a similar study [27]. They developed a classification involving four particular aspects of the ultrasound image from 20 consecutive patients. In the following 131 patients, this classification scheme was tested. The four points described were: (1) a continuous hyperechoic margin around the lesion; (2) a distinction between homogenous or heterogenous internal echoes; (3) hyperechoic dots in the lesion; and (4) concentric circles along the echo probe. Points 2 and 3 had been a critical part of Kurimoto's earlier classification. With respect to the margin, the thickness of the margin varied among different parts of the lesion. The margin was basically between the lesion and normal aerated pulmonary tissues. From 93 patients, only 16 had a continuous hyperechoic margin fully around the lesion. In 13 of 16 cases of these 16 cases (81.3%) there was malignancy. This did not quite reach statistical significance comparing benign and malignant lesions ($p = 0.09$). With respect to the internal echoes of the lesion, homogenous internal echoes were unanimous in size, echogenicity and distribution, and the echogenicity was invariably slightly lower than that in normal lung parenchyma. Heterogenous internal echoes displayed a mosaic pattern in imaging particle distribution and the particles varied in size. The echogenicity of the lesions comprised both hyper and hypoechogenicity. Overall, there were 16 subjects from the 93 who had homogenous internal echoes and the majority of these (88%) were benign. Ninety-seven percent of neoplastic lesions demonstrated heterogenous internal echoes and this was statistically different ($p < 0.001$). This significance was lost after multivariant analysis combined with concentric circles was included. The third characteristic was hyperechoic dots and here the spots were generally bigger than normal particles. The dots may have merged several variable sized areas or hyperechoic linear arcs. The presence of residual air in the lesions or tiny calcifications could have been the reason for this pattern. Overall, more than half of all the lesions displayed hyperechoic dots including 54% of neoplastic lesions and 73.5% of non-neoplastic lesions. Therefore, it was thought not to be useful in distinguishing lesions. Finally, the presence of concentric circles was analysed. There was a sense of gradation from the inner to the outer parts of the lesion. It was thought to represent the effect of the residual intact architecture of the bronchioles within the lesion. About one half of the non-neoplastic lesions had the characteristics of concentric circles and this was only detected in one case of malignancy. This difference was highly statistically significant and the significance was persistent even by the multivaried analysis combined with internal echoes. Note that it was present in only 53% of the benign lesions. Therefore, this classification system did not use the pattern of vessels or bronchioles to type the lesions. In their scheme, there was unanimity amongst three reviewers in the vast majority of cases. The time taken to perform this analysis was less than four minutes. Overall, the authors concluded that the presence of concentric circles favored the peripheral lung lesion as being benign and that the existence of a continuous hyperechoic margin was suspicious for malignancy. The remainder of the findings at this stage were therefore regarded as qualitative and perhaps used in support of further observation in biopsies where the histology is benign.

Other authors [8] have used image analysis software to determine the presence of underlying heterogeneity or homogeneity of the echoes within an ultrasound lesion. This would facilitate the kinds of distinctions made in both the Kurimoto and Chao classifications and has shown to be useful in a prospective follow-up series.

## Side Effects and Tolerability

Table 8.1 highlights the low incidence of side effects of transbronchial lung biopsy easing into bronchial ultrasound method. Bleeding and pneumothorax are

inherent to transbronchial lung biopsy; however, in all of these series, the overall incidence of these was less than 1%. An important observation is that studies that did not use a guide sheath had a slightly higher incidence of minor bleeding; no incidences of severe bleeding were seen. Nonetheless, this can be disconcerting for the proceduralist at the time and, as described by a number of authors, the most common scenario was to have absolutely no bleeding of any quantity upon removal of the guide sheath and one or two minutes after the last biopsy. A paper by Chung described EBUS guide sheath peripheral mass biopsy without the use of the guide sheath, using the measurement of length of the lesion away from the end of the bronchoscope by fluoroscopy as the ultrasound probe was removed [28]. The biopsy forceps were placed back that same distance out from the end of the bronchoscope to take the samples. Normally, when the guide sheath was used, the end of the guide sheath itself becomes the marker point to which the forceps are passed. There was a significant improvement in the overall diagnostic yield (79% compared to 57%) in patients where this measurement was used. An important finding from the point of view of side effects was that, from these 158 lesions, there were five episodes of mild bleeding. Some of the other studies, however, suggest that the guide sheath does have a protective effect in terms of minimizing any bleeding. With respect to pneumothorax limitation, the important aspect is to prevent excessive passage of the biopsy forceps or brush beyond the tip of the guide sheath. Most, but not all, operators use X-ray fluoroscopy to manage this part of the procedure thereby preventing excessive lengths of the biopsy forceps coming out the end of the guide sheath. Clearly, the localization of the guide sheath at the proximal end of the lesion should prevent this happening. In the author's experience, one case of pneumothorax occurred because the biopsy brush was extended too far. It is an inherent problem of using a biopsy brush that sometimes in taking the specimen, the brush can be advanced 2 or even 3 cm and thereby breach the visceral pleura. Special care should be therefore taken to prevent over-excessive application of the brush length. In a retrospective series, we demonstrated that our incidence of pneumothorax with this technique was much less than our current hospital experience with pneumothorax from CT-guided fine needle biopsy [29]. We demonstrated that we had an incidence of 1% pneumothorax rate from 140 cases of EBUS-guided sheath biopsy. This compared to a 28% pneumothorax rate and 6% rate of intercostal catheter insertion in 121 retrospectively reviewed cases of CT fine needle aspiration.

## Conclusions

Endobronchial ultrasound-guided sheath peripheral biopsy provides a safe, reliable, and technically simple means of extending the bronchoscopist's capacity to obtain tissue diagnosis on small peripheral lung lesions. It has an excellent safety profile, probably safer than standard transbronchial lung biopsy in terms of bleeding, and probably better than usual rates for pneumothorax compared to CT-guided fine needle aspiration biopsy. Not only does it allow the accurate localization of very small peripheral pulmonary lesions, it also allows the qualitative characterization of the underlying lesion by way of assessment of the ultrasound characteristics of the lesion. In a recent recommendation, the American College of Chest Physicians advocated the use of endobronchial ultrasound in lesions less than 2 cm in diameter [30]. In many respects, the biopsy of peripheral lesions larger than this can also be benefited by the use of endobronchial ultrasound particularly in centers not frequently using standard X-ray fluoroscopy for such types of biopsy. Because of its safety and simplicity, it rapidly allows the bronchoscopist to gain access to the lesion without the need to image in two planes by fluoroscopy. It also provides safety advantages over and above the standard transbronchial lung biopsy technique by way of the benefits of the guide sheath.

### The Future of EBUS Peripheral Lung Biopsy

Presently, there are two aspects in development with respect to endobronchial ultrasound. First, there is the ongoing miniaturization of the equipment and the greater use of the 1.4 mm diameter EBUS Miniprobe. This being combined with a 4 mm diameter bronchoscopes has been demonstrated to access very small lesions in two studies from Japanese centers. Better biopsy forceps and brushes for use with these smaller miniprobes and smaller guide sheaths are currently

allowing better diagnostic yields, particularly in very small lesions of less than 1–2 cm in diameter. Such miniaturization can afford the bronchoscopist greater access to very small bronchi in somewhat tortuous positions as experienced with bronchoscopes of standard caliber.

The increasing use of CT virtual bronchoscopy will be an important component in the ongoing development of this technique [31]. Many practitioners do not have the encyclopedic knowledge of small segmental bronchi that surgeons have, nor the knowledge held in some of the Japanese and European centers. Therefore, there will probably always be a need for some radiological assistance of practitioners in identifying the correct bronchus. The development of simplified user interfaces for virtual bronchoscopy is ongoing, and this combined with the use of small caliber miniprobes and bronchoscopes should further increase the user-friendliness of this technique.

In a recent report from Eberhart et al. EBUS was combined with electromagnetic navigation bronchoscopy to determine their relative contribution to biopsy of peripheral lung lesions [32]. Electromagnetic navigation bronchoscopy utilizes a system of navigational guidance to the lesion based on specific hardware and software interfaces, but importantly uses a steerable biopsy forceps. This type of forceps has a guide sheath and is for single patient use. This study was performed in lesions, once again, very small in diameter, ranging between 25 and 28 mm for the two techniques. In this study, navigation to the lesion was first performed by electromagnetic navigational bronchoscopy (ENB). When the lesion was located, the sensor probe was withdrawn and the EBUS probe was inserted through the ENB guide sheath. If the EBUS image confirmed that the sensor was indeed within the target, then the biopsy was performed. However, if no acceptable EBUS image was obtained, re-navigation with ENB and subsequent reconfirmation with EBUS was done. This combined technique had a significantly higher diagnostic yield of 88% compared to EBUS alone (69%) or electromagnetic navigational bronchoscopy alone (59%). The authors felt that ENB enhanced EBUS by providing real time and subtle navigation through the steering mechanism of the locatable guide. They felt that this navigation capability was marginally better than that afforded by either fluoroscopy, curettes, or virtual bronchoscopy. These three techniques have returned yields of 58–73%, 58–77%, and 63% respectively. Interestingly, there was a diminished lower lobe yield of 29% in the ENB alone group and this was thought possibly due to navigational error; navigation in the lower lobes was thought to be more effective by diaphragmatic movement during breathing. This could have hampered the CT images acquired in a single breath hold prior to the actual procedure, with such planning data being used in the navigation process. The overall rate of pneumothorax was 5% in EBUS and 5% in ENB. Fluoroscopy was not used because earlier data had shown that it did not decrease the rate of the iatrogenic pneumothorax after transbronchial lung biopsy. Perhaps this was the explanation for the slightly increased pneumothorax rate.

## Tips for Endobronchial Ultrasound-Guided Transbronchial Lung Biopsy

The techniques are not particularly different from standard transbronchial lung biopsy and hence the procedure is accessible to many. Some simple suggestions may assist in the uptake of the technique.

**1** CT anatomy: becoming more familiar with the common appearances of the takeoff of each of the ten subsegmental bronchi on the right and the nine subsegmental bronchi on the left and their associated fifth border branchings is important. It is relatively easy to become familiar with this over one of two months of repeated study of the CTs. Discussion with the radiologist can also be helpful as can scrolling through the digital images on a PC. This allows tracking of the bronchial segments out to the corresponding lesion. Having done this, it is necessary to make a shopping list of bronchial segments into which the guide sheath can be passed starting from the most likely to the least likely. Even the most experienced bronchoscopist will do this.

**2** Increased familiarity with the numerical system for naming of bronchi as originally described by Boyer and Icheda. This is much more familiar to Japanese and European readers as opposed to readers in the UK, United States and Australasia. The numerical system greatly facilitates an understanding of the inter-relationship of the bronchial appearance to the CT scan appearance. Clearly, there will be variations but improving one's awareness of these and the

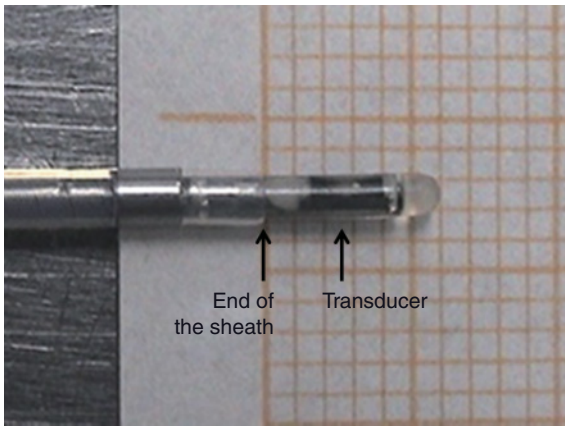


**Figure 8.1** Set up of distal end of EBUS minprobe which is shown exiting from the guide sheath (left).

likely expected bronchial anatomy greatly improves success rate.

**3** Probe preparation: it is important to have the ultrasound part of the miniprobe just outside the end of the plastic sheath (see Figure 8.1). If any part of the processor is hampered by the plastic sheath, interference images will appear. Sometimes as the probe is passed out into the peripheral bronchi, compression from bronchial structures pushes the probe back inside the sheath and such interference patterns can appear. As such, it is important to ensure that the proximal end of the probe is firmly taped to the guide sheath.

**4** The biopsy forceps and brushes need to have a tape mark placed at the proximal end prior to starting the procedure such that, in particular with the biopsy forceps, the end corresponds to the point of the EBUS miniprobe transducer.

**5** Use an assistant. This is important because small changes in position of the bronchoscope or the miniprobe can affect biopsy yield and it is often helpful to have an assistant hold the bronchoscope in place while the main proceduralist actually takes the biopsies.

**6** With the use of an image intensifier, it is often helpful to save the image of the point of the guide sheath on one screen and have another screen to show the actual live passage of the biopsy forceps. This can allow a very accurate positioning of the biopsy forceps; however this is not essential as keeping the guide sheath in place once the ultrasound confirms positioning may be all that is required.

**7** Use separate monitors for white light bronchoscopic findings and for ultrasound findings. There is the facility to have a picture display on the monitor, one showing ultrasound and the other showing bronchoscopic findings, or the facility to swap between the two images on one monitor. In the author's experience, it is always better to have both showing constantly and simultaneously on two separate monitors.

**8** In some patients, there is chronic bronchitis in the large airways and holding the bronchoscope in one position can occasionally lead to abrasion of the bronchial wall over a 10-minute period during which time ultrasound and biopsies are taken. This can lead to some bleeding from the bronchus itself due to this abrasion as opposed to from the lung and it is always important to remain aware of the endobronchial situation even though one's concentration is on the lesion in the periphery of the lung.

**9** Care with transbronchial brushings as mentioned above; over-extension of a bronchial brush can occasionally cause breach of the visceral pleura and pneumothorax. Lesions which are more centrally placed should not pose a problem; however those lesions up against the visceral pleura particularly in the upper lobes may have a risk of pneumothorax if the brush is extended too far.

**10** Once the lesion is found, withdraw the guide sheath to the near end of the lesion so that the ultrasound image is just disappearing. Fix the guide sheath at this point rather than within the lesion as this will facilitate better biopsy positivity as described above.

**11** Interpretation of ultrasound images. This need not hold the procedure up and is often done following the completion of the procedure. The decision to take the biopsy is made before the procedure begins rather than as a result of an interpretation of an image at the time of the procedure. It is easy to record ultrasound images on the hard drive of the ultrasound processor or to record the whole ultrasound procedure on digital video and interrogate still images from that. Such interpretation may be of some assistance in prospective evaluation of one's own performance and demonstrate for audit purposes that the proceduralist is achieving reasonable diagnostic accuracy results by comparing ultrasound image and histology findings.

**12** Where a lesion appears to be a small ground glass opacity and to have an aerated type of appearance,

transbronchial needle aspiration should be added to the biopsy method as described above. This would increase the yield in that such lesions tend not to invade the bronchus and therefore sampling outside the bronchus could improve the results; it can be done without any increased risk of side effects.

**13** Consider a broader range of indications than simply small peripheral nodules. For example, patchy subsegmental pulmonary infiltrates can be very amenable to EBUS biopsy; standard transbronchial lung biopsies can miss infiltrative processes which are quite patchy such as chronic fungal infections or early cases of inflammatory alveololitis. In the author's experience, even in these cases, it is possible to completely miss the pathology in one segmental bronchus, as one retreats and passes the probe into a segmental bronchus only 1 mm away, only to find the probe completely surrounded by pathology.

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# 9 Diagnosis of Peripheral Pulmonary Lesions Using Endobronchial Ultrasonography with a Guide Sheath

## Introduction

Bronchial brushing cytology and transbronchial biopsy (TBB) are used to diagnose peripheral pulmonary lesions (PPLs). Fluoroscopy is required in most cases to direct the operator to site of interest, although it is often difficult to confirm whether the biopsy forceps have reached the lesion. Since 1994, we have been able to delineate PPLs through the introduction of a miniature ultrasonic probe into a peripheral bronchus [1], but this has involved withdrawing the probe after the ultrasound image has been obtained, then introducing a brush or biopsy forceps, and obtaining the tissue or brushing sample. This method has made it difficult to be sure that the tissue or brushing sample has been accurately taken from the site of the lesion, however. To increase the reliability of sample collection from PPLs, we devised a technique using EBUS with a guide sheath (EBUS-GS).

## Equipment

Between 1996 and the commencement of EBUS-GS in 1999, we used a 20 MHz, mechanical-radial type miniature ultrasonic probe (UM-BS20-20R; Olympus Optical Co., Ltd, Tokyo, Japan) with an outer diameter of 1.7 mm. Since 2000, we have used a 20 MHz, mechanical-radial type thin ultrasonic probe (UM-BS20-17R; Olympus) with an outer diameter of 1.4 mm (see Chapter 3, Figure 3.5, Procedure for EBUS-GS). The probe is connected to an Endoscopic Ultrasound System (EU-M30, EU-M2000; Olympus). Guide sheaths are now available commercially under the name of The Guide Sheath Kit (Olympus).

## EBUS-GS Procedure

For preparation of equipment for EBUS-GS, see Chapter 3, p. 28, Video clip 3.3.

For actual EBUS-GS techniques, see Chapter 3, pp. 28–30, Figure 3.6, and Video clip 3.4.

EBUS-GS procedures and images will be described using a representative case.

**Representative Case** (Video Clip 9.1, Figure 9.1)

This 74-year-old man had a 10 × 8 mm nodular lesion in segment B5a of the right lung. Bronchoscopy was performed to establish the diagnosis. A miniature probe covered by a guide sheath was introduced into the B5a bronchus of the right lung, and pulled back to obtain EBUS images. EBUS revealed heterogenous internal echoes in a lesion with an irregular margin that contained almost no vessels or bronchi. These findings were suggestive of a solid tumor with a high cell density. The guide sheath was left at the site of the lesion identified by EBUS, and the probe was withdrawn. A bronchial brush and biopsy forceps were introduced into the bronchus. Cytology of the bronchial brushings revealed adenocarcinoma, and transbronchial biopsy (TBB) confirmed the diagnosis of poorly differentiated adenocarcinoma.

We previously reported the overall yield of EBUS using a thick guide sheath (EBUS-thick GS) to be 77% (116/150), and the diagnostic yield of EBUS-GS in malignant and benign lesions as 81% (82/101)

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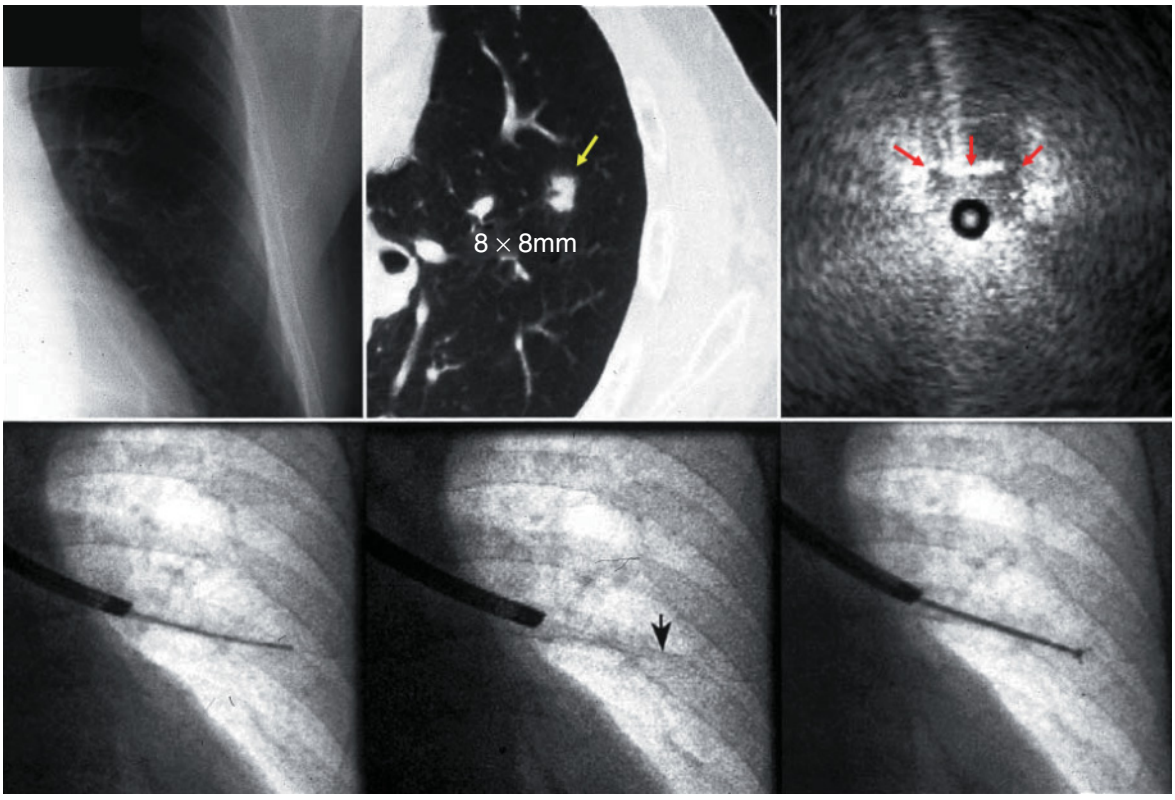


**Figure 9.1** Poorly differentiated adenocarcinoma in the left lingular segment. Top left: the lesion is difficult to identify on this plain chest radiograph. Top center: chest CT revealed a 10 × 8 mm nodular lesion in left segment B5a. Top right: The EBUS image revealed echogenic internal echoes with almost no vessels or bronchi within the lesion. Bottom left: a miniature probe covered by the guide sheath introduced into the left B5a bronchus. Bottom center: guide sheath (arrow) left at the site of the lesion. Bottom right: bronchial biopsy forceps introduced into the lesion.

and 73% (35/49), respectively [2]. Lesions in which the probe was advanced to within the lesion, as determined from the EBUS image, had a significantly higher diagnostic yield (105/121, 87%) than when the probe was adjacent to the lesion on the EBUS image (8/19, 42%). The diagnostic yield using TBB for lesions in which the probe was located within the lesion (85/104, 82%) was significantly higher than when the probe was adjacent to the lesion (1/15, 7%).

The diagnostic yield using EBUS-GS for lesions defined as a mass (>30 mm; 24/26, 92%) was significantly higher than that for lesions defined as nodules (≤30 mm; 92/124, 74%). The diagnostic yields using EBUS-GS for lesions ≤10 mm (16/21, 76%), >10 and ≤15 mm (19/25, 76%), >15 and ≤20 mm (24/35, 69%), and >20 ≤30 mm (33/43, 77%) were similar. In other words, for lesions ≤30 mm, size did not affect the diagnostic yield using EBUS-GS, and the yield was not decreased for lesions ≤10 mm. It was impossible to confirm fluoroscopically that biopsy forceps had reached the lesion in 54 out of 81 lesions ≤20 mm in size. The diagnostic yield in these lesions was 74% (40/54), similar to the yield when it was possible to determine fluoroscopically that the forceps had reached the lesion (18/27, 67%).

The diagnostic yield was affected by the location of the lesion. Positive yield rates were as follows: right upper lobe apical segment (8/13, 64%), right upper lobe posterior segment (8/12, 67%), left upper apical posterior segment (6/15, 40%), upper lobe anterior segment (34/42, 81%), lingula (5/7, 71%), right

middle lobe (14/14, 100%), lower lobe superior segment (12/19, 63%), and lower lobe basal segment (22/27, 81%). The yield from the left upper apical posterior segment (6/15, 40%) was significantly lower than that from other locations.

Moderate bleeding was seen in two (1%) out of 150 patients. Patients required bronchial intubation. There were no deaths, pneumothoraces, or other clinically significant morbidities.

EBUS-GS increases the reliability of specimen collection via bronchoscopy. Reported bronchoscopic diagnostic yields for PPLs ≤2 cm in size vary from 5 to 28% [3–14]. Radlke et al. [6] reported a positive yield of 6/21 (28%), Stringfield et al. [7] reported a positive yield in 4/15 (27%), Fletcher et al. reported a positive yield in 4/32 (12.5%), and Wallance et al. [8] reported a positive yield in 3/65 (5%). The diagnostic yield in this study was far superior to the earlier studies, and similar to the overall yield, even when the lesion was undetectable fluoroscopically. When a fluoroscopically undetectable lesion is in contact with the probe introduced into the bronchus, the lesion can be visualized using EBUS. EBUS-GS is particularly useful for lesions ≤20 mm that are undetectable using fluoroscopy.

EBUS-GS is most successful when the probe can be placed within the lesion. The yield of TBB when the probe was adjacent to the lesion was very low (1/15, 7%). This suggests that lesions visualized as adjacent to the probe may only be in contact with the outer surface of the affected bronchus, and therefore sampling is unlikely to be diagnostic. In this circumstance, the operator should attempt to delineate the lesion via another bronchus.

Chechani [13] reported fluoroscopic localization is most difficult when the lesion is small (<2 cm) and located in the lower lobe basal segment or the upper lobe apical segment. The diagnostic yield for lesions in these two segments (58%) was lower than yields from all other locations (83%). Fletcher et al. [5] reported that the worst diagnostic yields were from the lower lobe basal (2/7, 28%) and superior segments (5/19, 26%). In our EBUS-GS study [2], the worst diagnostic yields were noted for left upper lobe apical posterior segment lesions (6/15, 40%) ($p = 0.003$, $\chi^2$) when compared with yield from all other locations (103/135, 76%). The reason for the lower diagnostic yield in the left upper lobe apical posterior segment is thought to be due to difficulty introducing a probe into the B1+2 bronchi. The yield from the lower lobe basal segments was satisfactory (22/27, 81%). EBUS-GS is therefore superior to fluoroscopy for localising lesions in the lower lobe basal segments.

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 forceps are being inserted into the same bronchial branch for a second biopsy. Further, the bronchial mucosa becomes edematous after several attempts at manipulation, making it difficult to introduce the forceps into the bronchus.

Another advantage of EBUS-GS lies in its ability to protect against bleeding into the bronchus proximal to the biopsy site. Although massive hemorrhage into the bronchus following TBB is infrequent (<2%) [14,15], excessive bleeding may require wedging the tip of the bronchoscope to obtain hemostasis. 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.

The final advantage of EBUS-GS is the ability to obtain short-axis bronchial views of PPLs. Several investigators have reported successful use of miniature probes [1,2].

Yoshikawa [16] evaluated the feasibility and efficacy of TBB and bronchial brushing using EBUS-GS as a guide for diagnosing 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. PPLs located in the middle lobe and the lingular segment had significantly higher diagnostic yields. Multivariate analysis revealed that the diameter and location of the PPL were independent predictors of diagnostic sensitivity by EBUS-GS-guided bronchoscopy.

Further studies are needed to determine the diagnostic yield of transbronchial needle aspiration under EBUS-GS guidance, and the usefulness of using a curette via the guide sheath.

## Changes in EBUS-GS Techniques

When we began EBUS-GS in 1996, we used large bore guide sheaths with an outer diameter of 2.5 mm, but

for almost all PPLs we now insert a narrow bore guide sheaths with an outer diameter of 2.0 mm down the working channel of a bronchoscope with an outer diameter of 4.0 mm. Large bore guide sheaths are used only in cases where relatively large specimens are required. The use of bronchoscopes with an outer diameter of 4.0 mm allows us to select fourth and fifth order bronchi (two or three branchings more peripheral than the standard bronchoscopes around 6 mm in outer diameter).

### How to Identify the Drainage Bronchus Leading to the Target Lesion (Representative Case: Video Clips 9.2–9.8)

#### Identification of the Bronchial Branch Using CT Imaging

On the CT scan we identify the bronchus entering the lesion, and follow the bronchial branches towards the hilum.

From this bronchial route, we identify the bronchial branch, its bronchial segment and subsegment, the branching directions (laterally, mediastinally, etc.), and what are the adjacent subsegments.

We determine the name of the branch from the CT scan, mentally transform this into the bronchoscopic findings in our head, and delineate the bronchial branch that we should approach.

For example, if the candidate bronchus is the right B6c bronchus, and the B6c lesion is next to region of segment B6b on the CT, at bronchoscopy we should introduce the ultrasonic probe, into the bronchus branches of the right B6c bronchus which are closest to the B6b bronchi.

#### Identification of the Bronchial Branch Using Navigation Systems

In recent years, two methods of navigation for PPLs have been developed. The electromagnetic navigation system is a localization device that assists in placing endobronchial equipment 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 [17]. Harms et al. [18] introduced in a technical note a new approach to the treatment of inoperable peripheral lung tumors combining an electromagnetic navigation system and EBUS with 3-D-planned endobronchial brachytherapy. Asano et al. [19–21] 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. This system automatically produced virtual images to fifth order bronchi on average. EBUS visualized 93.8% of cases successfully, providing a tissue diagnosis in 84.4%. Using this bronchoscope insertion guidance system, virtual images can be readily produced, successfully guiding the bronchoscope to the target. This method shows promise as a routine part of PPL biopsy techniques (representative case: Video clips 9.6, 9.7 and 9.8).

## Tips for EBUS-GS

### Use of Signal Attenuation Caused by the Guide Sheath (See Chapter 3, Figure 3.7 and Video Clips 9.9 and 9.10)

This is a method of accurately placing the guide sheath within a PPL. Once a peripheral lesion has been delineated using EBUS, at the point the lesion appears at its largest and clearest, without disturbing the guide sheath the assistant should withdraw the ultrasonic probe 1 mm at a time until the probe transducer enters the guide sheath. When the transducer completely enters the guide sheath, the ultrasonic pulse will be reflected by the guide sheath, and the ultrasound image will suddenly become darker. If the site of this phenomenon is within the lesion, the guide sheath will be placed precisely within the peripheral pulmonary lesion.

### Moving the Probe from Adjacent to the Lesion to within the Lesion on the Ultrasonic Image (See Chapter 3, Figure 3.8 and Video Clip 9.11)

When we use the bronchoscopic image to select the subsegmental bronchus into which to introduce the probe to delineate a lesion using EBUS, the probe is sometimes placed adjacent to the lesion. In that case, the probe should be introduced into another subsegmental bronchus in an attempt to place the probe within the lesion. When the probe has been introduced into the lesion, the guide sheath can be left in the lesion, giving a 90% diagnostic yield.

### When a Lesion Can Be Identified Fluoroscopically, but Cannot Be Delineated Using EBUS (See Chapter 3, Figure 3.9 and Video Clip 9.12)

When a lesion cannot be delineated using EBUS, the ultrasonic probe should be removed without moving the guide sheath, and guide forceps introduced into the guide sheath until their tips protrude. The tip of the guiding device is bent in the direction of the lesion, and the forceps are then withdrawn slowly, looking for a point at which they move slightly towards the lesion. A bronchus leading to the lesion branches off from this point, and the tip of the guiding device have entered this branch, and advancing the guiding device will advance them down the drainage bronchus. As the guiding device is advanced in this direction the guide sheath will follow, allowing accurate placement of the guide sheath within the peripheral pulmonary lesion. The guiding device is then removed, the ultrasonic probe is reintroduced, and the lesion can be delineated.

### When the Bronchus Leading to the Target Lesion Is Stenosed at the Entry to the Lesion (Figure 9.2)

If the ultrasonic probe is introduced as far as the entry to the lesion, sometimes only part of the lesion can be delineated using EBUS, and the probe cannot be

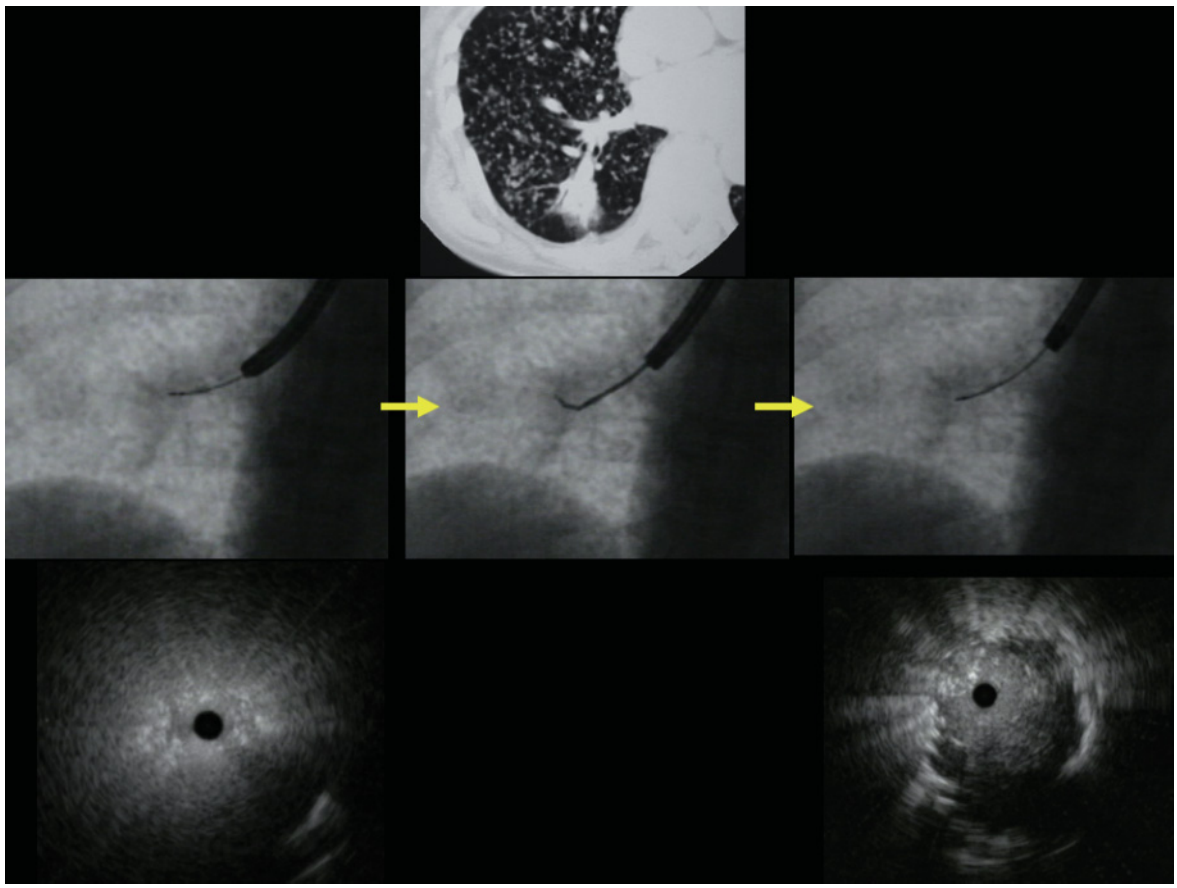

**Figure 9.2** When the bronchus leading to the target lesion is stenosed at the entry to the lesion. If the ultrasonic probe is introduced as far as the entry to the lesion, sometimes only part of the lesion can be delineated using EBUS, and the probe cannot be pushed any further. This is due to stenosis of the bronchus at the tumor entrance. The probe should be withdrawn, and a curette introduced, allowing dilatation of the stenosed bronchus. The probe can now be introduced as far as the interior of the lesion, allowing biopsy and other procedures.

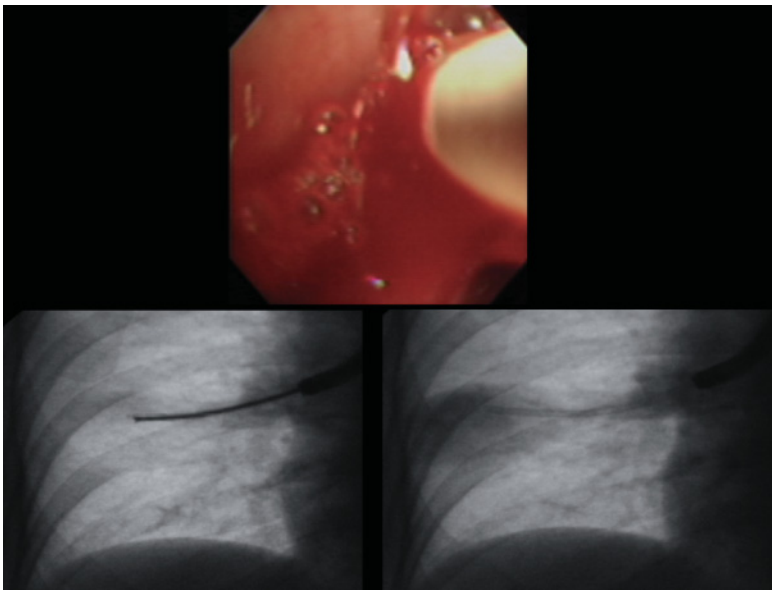

**Figure 9.3** Management of post-biopsy hemorrhage. When hemorrhaging occurs following brushing or biopsy via the guide sheath, the blood usually passes back into the guide sheath rather than into the airway. This is because the outer surface of the guide sheath is snug against the bronchial lumen. If we wait around 2 min before withdrawing the guide sheath, in almost all cases it can be withdrawn without any further hemorrhage. We have experiencing a case of a large intrapulmonary hemorrhage, but thanks to the guide sheath no further treatment was necessary and only a small amount of blood escaped into the airway.

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## Conclusion

EBUS-GS permits more accurate collection of samples from PPLs than other methods. This method facilitates multiple biopsies from the same site, protects against bleeding into the proximal bronchus from the biopsy site, and can delineate the inner structure of PPLs.

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# 10 Endobronchial Ultrasonographic Analysis of Airway Wall Integrity and Tumor Involvement

## Introduction

The clinical application of intralumenal ultrasonography using a miniature ultrasonic probe began with intravascular ultrasonography. A number of reports have been published concerning the use of endoscopic ultrasonography of the gastrointestinal tract for delineation of the structure of the esophageal, stomach and bowel walls, and determination of the depth of tumor invasion. CT scanning has been the mainstay of tracheobronchial diagnostic imaging for invasive disease of the airways. CT scanning can recognize the tracheobronchial wall as the structure between the lumen and the peritracheobronchial tissue, but detailed evaluation of the tracheobronchial wall, only 1 or 2 mm thick, requires an imaging modality with higher resolution such as high frequency ultrasonic tomography. Since 1994, we have performed endobronchial ultrasonography (EBUS) with a thin ultrasonic probe inserted through the working channel of a flexible bronchoscope. When we commenced EBUS, we found that the presence of cartilage gives the tracheobronchial wall a laminar structure [1].

## Laminar Structure of the Tracheobronchial Wall

With EBUS, we can visualize the laminar structure of the tracheobronchial wall. The depth of tumor invasion into the tracheobronchial wall is a most important determinant of the choice of therapy, specifically bronchoscopic laser tumor ablation vs. surgical resection. First, there was a need to analyse the laminar structure of the tracheal and bronchial wall. There are several reports by Hürter et al. [2], Baba et al. [3], Becker [4], and Kurimoto et al. [1] on the bronchial laminar structure as delineated by high-frequency ultrasonography. Hürter [2] stated that the bronchial laminar structure is trilaminar, comprising an inner echodense layer and an intermediate echolucent zone of nearly the same diameter. Baba [3] reported that the intrapulmonary bronchi have six layers: 1st + 2nd layers (epithelium, lamina propria, and submucosa), 3rd + 4th layers (cartilage), and 5th + 6th layers (adventitia). The extrapulmonary bronchi were also seen as having six layers, with cartilaginous and membranous portions similar to the intrapulmonary bronchi: 1st + 2nd layers (epithelium, lamina propria, and submucosa), 3rd + 4th layers (longitudinal muscle layer) and 5th + 6th layers (adventitia or loose connective tissue. Becker [4] stated that the tracheobronchial wall comprises seven layers, and the supporting wall, composed of cartilage and connective tissue which could not be distinguished, provides a triple layer ultrasonographic image of low internal intensity and a strong echo at the internal and external surface of the cartilage and the adjacent structures on both sides – the mucosa and submucosa on the inside and the adventitia on the outside – each showing a ultrasonographic double layer with a strong echo at the surface and an echopoor underlying structure.

Based on the premise that knowledge of the different anatomic layers of the bronchial walls and their ultrasonographic correlations is the basis for interpreting ultrasound images, we performed a needle-puncture experiment [1] (Figure 10.1). We fastened a resected specimen of bronchial wall to a rubber board with two 23 G needles. We inserted a 29 G needle into the cut end and immersed the assembly in water. We

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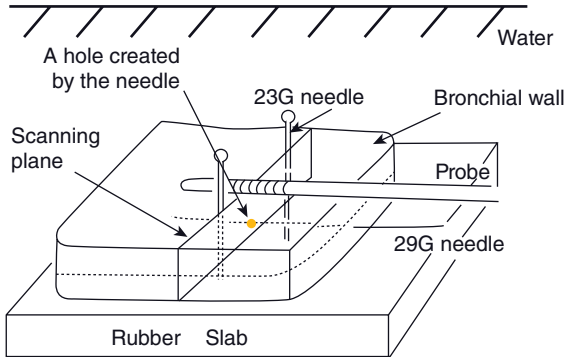


**Figure 10.1** Diagram of the needle-puncture experiment. A resected specimen bronchial wall was fastened to a rubber slab with two 23 G needles. A 29 G needle was inserted into the various layers from the cut end, and advanced so that it passed between the two 23 G needles. We scanned the specimen to obtain an image that included the two 23 G needles with the 29 G needle showing as a dot-like hyperechoic spot. For histopathological evaluation in the ultrasonic scanning plane, a cut was made to include the path of both 23 G needles. The hyperechoic spot of the 29 G needle on the ultrasonogram and the needle hole in the histopathological finding were compared to determine which layers in the tissue specimen corresponded to the ultrasonographic layers.

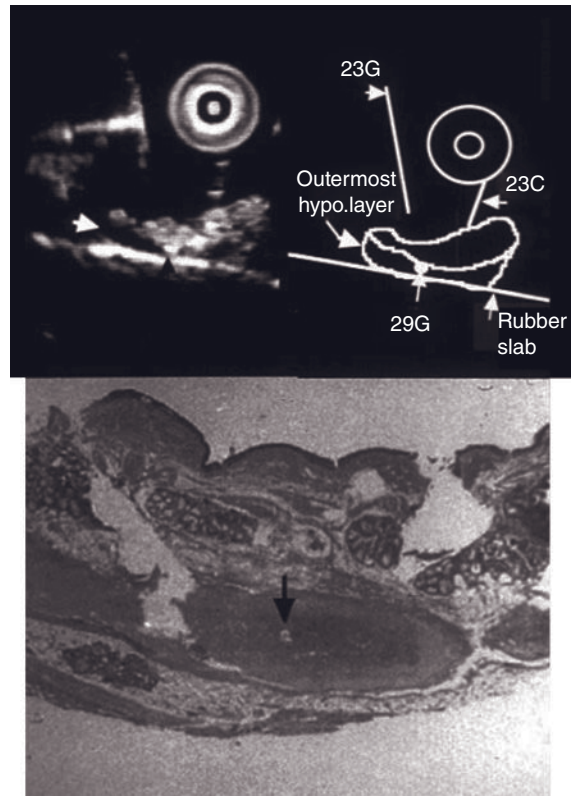


**Figure 10.2** Representative example of the needle-puncture experiment. In this specimen in which the dot-like hyperechoic spot produced by the needle (black arrow) was observed in the center of the outermost hypoechoic layer (white arrow) of a segmental bronchus, the histopathological findings were of a hole in the cartilage (black arrow), indicating that the outermost hypoechoic layer was the cartilage.

scanned the plane, including both 23 G needles, comparing the hyperechoic spot of the 29 G needle with the hole in the pathological sample.

In Figure 10.2, we can see a representative specimen. The dot-like hyperechoic spot from the 29 G needle can be seen in the center of the outermost hypoechoic layer on the ultrasonogram of this segmental bronchus, where the histopathological finding was of a hole in the bronchial cartilage. This confirms that the outermost hypoechoic layer of the segmental bronchus is the cartilage layer.

Conducting this experiment on 45 specimens yielded the following results.

Using a 20 MHz probe, the cartilaginous portion of both extrapulmonary and intrapulmonary bronchi are visualized as five layers. The 1st layer (hyperechoic) is a marginal echo, the 2nd layer (hypoechoic) represents submucosal tissue, the 3rd layer (hyperechoic) is the marginal echo on the inner aspect of the bronchial cartilage, the 4th layer (hypoechoic) represents bronchial cartilage, and the 5th layer (hyperechoic) is the marginal echo on the outer aspect of the bronchial cartilage. In the membranous portion, the 1st layer (hyperechoic) is a marginal echo, the 2nd layer (hypoechoic) represents submucosal tissue, and the 3rd layer (hyperechoic) is the adventitia (Figure 10.3).

A point to be borne in mind when identifying the laminar structure of the wall ultrasonically is that marginal echoes [5] (hyperechoic bands produced by many reverberations) occur wherever there is an interface between tissue types. Aibe [5] reported that marginal echoes include transitional tissue, and that they are high linear echoes that extend distally in the direction of propagation of the ultrasound waves.

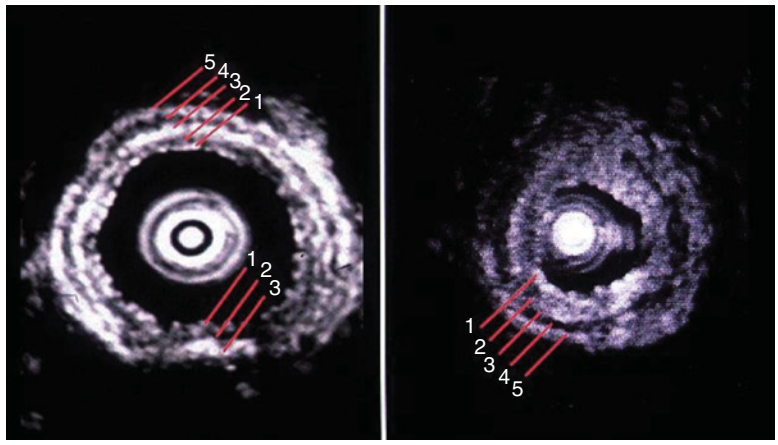


**Figure 10.3** Bronchial wall layers delineated by endobronchial ultrasonography. Extrapulmonary bronchus (left): The cartilaginous portion of the trachea and the extrapulmonary bronchi is visualized as five layers, and the membranous portion as three layers. The 1st layer (hyperechoic) is a marginal echo, the 2nd layer (hypoechoic) represents smooth muscle, the 3rd layer (hyperechoic) is the marginal echo on the inner side of the bronchial cartilage, the 4th layer (hypoechoic) represents bronchial cartilage, and the 5th layer (hyperechoic) is the marginal echo on the outer side of the cartilage. In the membranous portion of the extrapulmonary bronchi, the first layer (hyperechoic) is a marginal echo, the second layer (hypoechoic) represents smooth muscle, and the third layer (hyperechoic) is the adventitia. Intrapulmonary bronchus (right): The intrapulmonary bronchi are visualized as five layers. The 1st layer (hyperechoic) is a marginal echo, the 2nd layer (hypoechoic) represents submucosal tissue, the third layer (hyperechoic) is the marginal echo on the inner side of the bronchial cartilage, the fourth layer (hypoechoic) represents bronchial cartilage, and the fifth layer (hyperechoic) is the marginal echo on the outer side of the cartilage.

Marginal echoes, visualized as hyperechoic, are observed between the lumen and the mucosal epithelium, between the submucosa and cartilage, and between cartilage and the adventitia (Figure 10.4).

We also compared EBUS images of resected lung cancer specimens with the histopathological findings to assess the accuracy of EBUS in determining the depth of tumor invasion [1]. We compared ultrasonographic measurements of the depth of tumor invasion in specimens resected from 24 patients with lung cancer with the histopathological findings. Two representative examples of squamous cell carcinoma arising in the right intermediate trunk are shown in Figure 10.5. The left hand picture shows a tumor in contact with the inner surface of the bronchial cartilage, at the boundary between the membranous and cartilaginous portions. The right hand picture of a tumor adjacent to the inner surface of the smooth muscle of the membranous portion shows a tumor in contact with the second layer on the EBUS image. Comparison of the EBUS images with the histopathological findings in 24 patients with lung cancer showed that measurements of the depth of invasion was the same for 23 cases (95.8%), and different in one case (4.2%). In the case of disagreement between the EBUS and histopathological findings, lymphocytic infiltration protruded between cartilages was mistakenly interpreted as tumor invasion.

Recently, we have encountered some cases with seven layers in the cartilage portion of the trachea and the right and left main bronchi. An adenoid-cystic carcinoma of the trachea was seen to have seven layers using a 20 MHz probe. Compared histopathological findings and the EBUS images, the 5th and 7th hyperechoic layers were the marginal echoes at the outer surface of the bronchial cartilage and collagen fibers outside the loose connective tissue, respectively. The 6th hypoechoic layer corresponded to thick loose connective tissue outside the cartilage (Figure 10.6). If the loose connective tissue outside the cartilage is relatively thin, the 5th hyperechoic layer becomes attached to the 7th hyperechoic layer, so they are visualized as one layer. We believe that in general the cartilaginous portion is visualized as five layers,

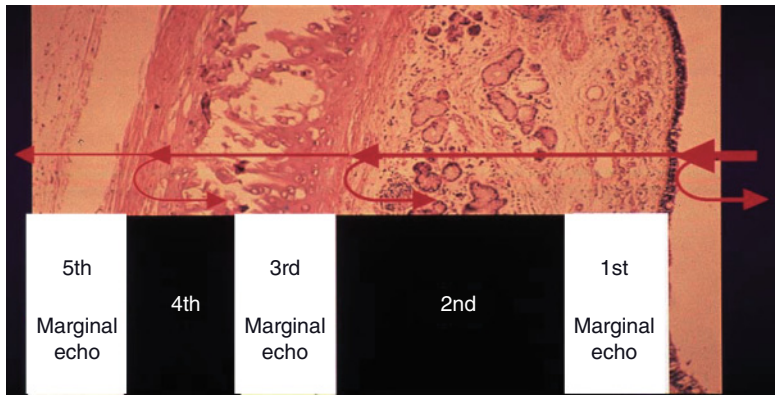


**Figure 10.4** Comparison of ultrasonographic and histopathological layers of the bronchial wall. Marginal echoes include the transitional tissue, and are highly linear echoes that extend distally in the direction of propagation of the ultrasound waves. The marginal echo (1st layer) extends from the inner margin of the mucosal epithelium to the inner part of the submucosa. The marginal echo of the 3rd layer appears to extend from the inner margin of the bronchial cartilage to the middle of the cartilage, and the marginal echo of the 5th hyperechoic layer extends from the outer margin of the bronchial cartilage to the adventitia.

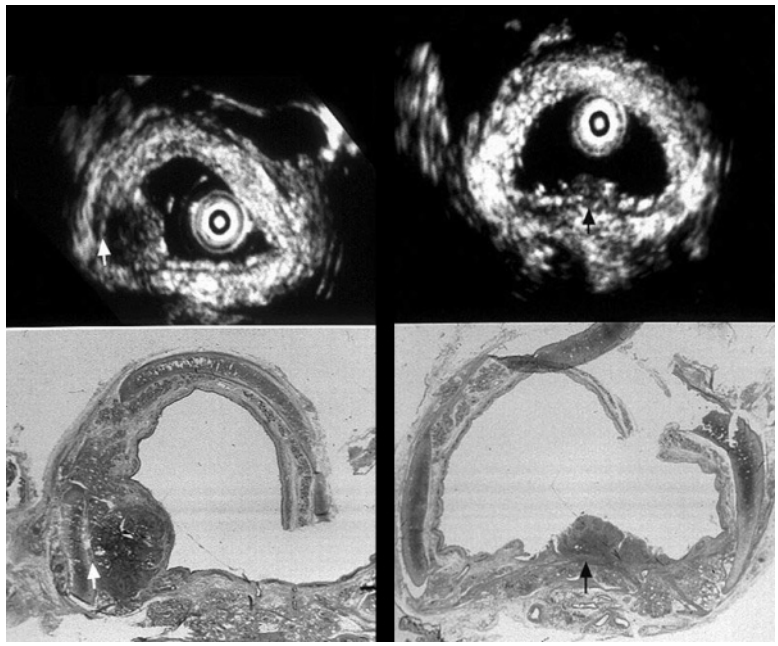

**Figure 10.5** Comparison of ultrasonographic and histopathological findings. Left: representative example of submucosal invasion. This lesion is in contact with the inner side of the hyperechoic third layer (inner marginal echo of cartilage: white arrow), and tumor in contact with the inner surface (white arrow) of the cartilage was observed histopathologically, confirming the ultrasonic determination of the depth of tumor invasion. Right: representative example of invasion as far as smooth muscle of membranous portion. This lesion is in contact with the inner side of the hypoechoic second layer, which corresponds to smooth muscle (black arrow), and this was confirmed on histopathological examination.

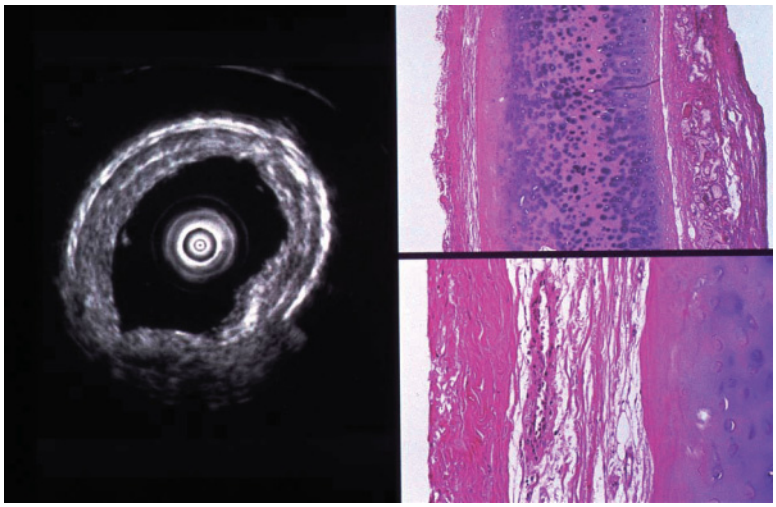

**Figure 10.6** Seven tracheal layers demonstrated using EBUS. Left: This adenoid-cystic carcinoma of the trachea had seven layers visualized using EBUS. Right: Comparison of the histopathological findings and EBUS image showed that the 6th hypoechoic layer corresponds to thick loose connective tissue outside the cartilage, and the 7th hyperechoic layer corresponds to collagen fibers outside the loose connective tissue.

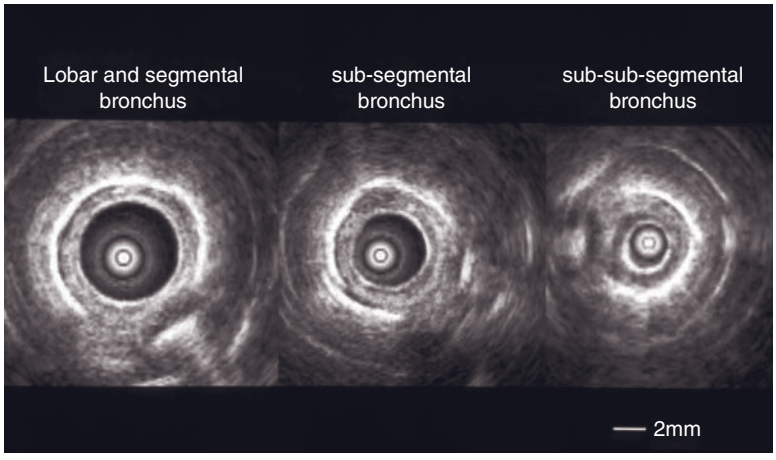


**Figure 10.7** Bronchial cartilage of lobar, segmental, subsegmental, and sub-subsegmental bronchi. Bronchial cartilage is visualized in five layers of the segmental bronchi in these resected specimens. It is rather difficult to point out the bronchial cartilage beyond intact segmental bronchus.

and the cartilaginous portion of the trachea and right and left main bronchi sometimes shows seven layers.

To which bronchial generation can the bronchial cartilage be visualized? The bronchial cartilage is visualized as five layers in a resected specimen of a segmental bronchus. It is rather difficult to detect the bronchial cartilage beyond an intact segmental bronchus (Figure 10.7). However, it is easy to detect the bronchial cartilage if a tumor invades beyond the bronchial cartilage, that is to say bronchial cartilage is present within the tumor (Figure 10.8).

Once again we should make clear that the laminar structures of the bronchial wall as visualized by high frequency ultrasonography include marginal echoes (boundary echoes). Marginal echoes are the artefacts that high frequency ultrasound waves produce at tissue boundaries, such as the cartilage surface. A shallow carcinoma in situ will therefore be hidden behind the 1st hyperechoic layer (marginal echo). Using the laminar structures of the bronchial wall, the depth of tumor invasion of the tracheobronchial wall is classified into five categories: epithelium (superficial subepithelium), subepithelium, cartilage, adventitia, and beyond the adventitia (Figure 10.9, Video clip 10.1).

In the next step, in order to determine the ability of EBUS to delineate the depth of tumor invasion, we

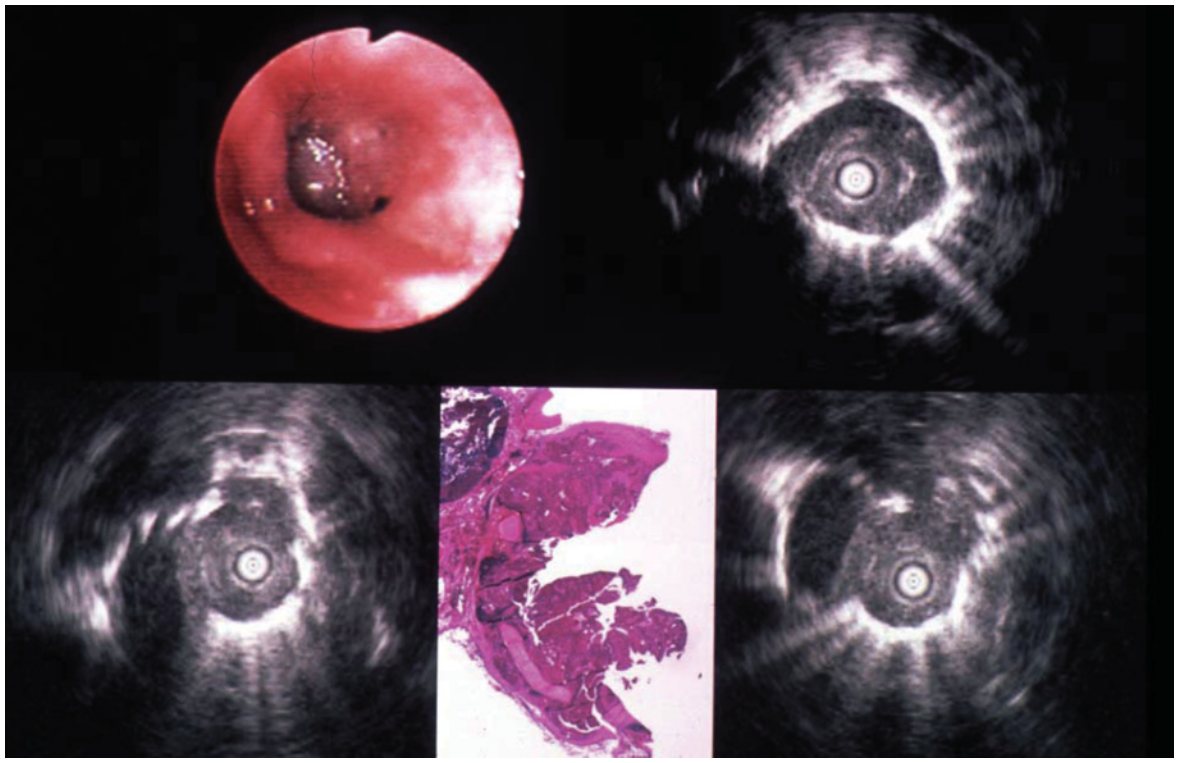

**Figure 10.8** Squamous cell carcinoma (left B3 bronchus). Left: A polypoid lesion obstructing the left B3 bronchus is shown at bronchoscopy. Right upper: Ultrasonography shows this lesion to have invaded beyond the bronchial cartilage to protrude at 12 o'clock beyond the adventitia. Right lower: The histopathological findings also show this lesion to have invaded beyond the bronchial cartilage to protrude at 12 o'clock (arrow), confirming the ultrasonographic determination of the depth of tumor invasion. Hematoxylin and eosin: original magnification ×10.

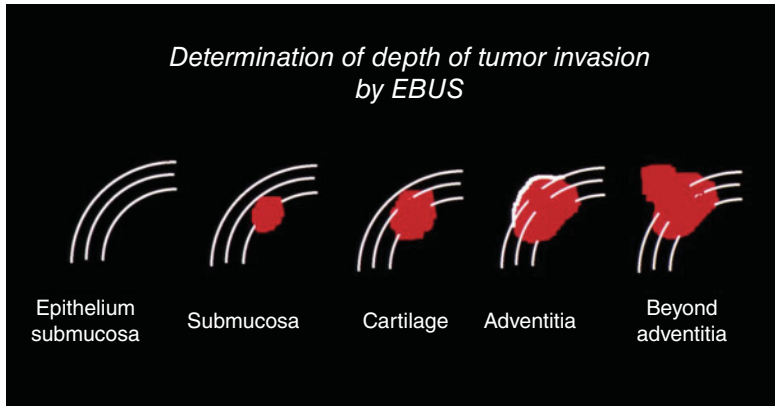


**Figure 10.9** Depth determination using EBUS. Using the laminar structures of the bronchial wall, the depth of tumor invasion of tracheobronchial wall is classified into five categories: epithelium (superficial subepithelium), subepithelium, cartilage, adventitia, and beyond the adventitia.

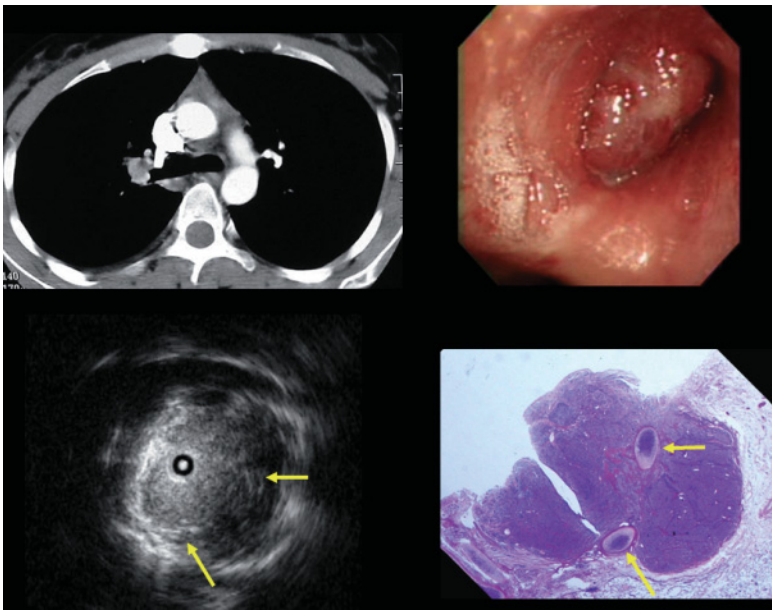

**Figure 10.10** Typical carcinoid in the right upper bronchus. Left upper: Chest CT scanning shows a tumor located in the right upper bronchus. Left lower: Ultrasonography shows that the tumor has invaded beyond the bronchial cartilage (arrow), compressing the fifth layer (adventitia). Right upper: The bronchoscopic findings show this tumor obstructing the right upper bronchus. Right lower: Histopathologically, tumor has invaded beyond the bronchial cartilage (arrow) to compress and invade the adventitia. The histopathological findings confirm the ultrasonographic determination of the depth of tumor invasion. Hematoxylin and eosin: original magnification ×10.

compared preoperative EBUS findings in tracheobronchial tumors with the histopathological findings in surgically resected lungs subjected to complete sectioning. Histopathological examination of 42 specimens showed the depth of tumor invasion as carcinoma in situ (epithelium) in five cases, submucosal (subepithelium) in 7, bronchial cartilage in 1, adventitial in 5, and extramural (beyond the adventitia) in 24. The depth of tumor invasion according to preoperative ultrasonography agreed with the histopathologic findings in 35 out of 42 cases (83%). The accuracy of EBUS according to histological depth was 0% (0/5) for carcinoma in situ, 86% (6/7) for submucosal, 100% (1/1) for cartilage, 80% (4/5) for adventitia, and 100% (24/24) for extramural lesions.

The findings in two representative cases where EBUS determination of the depth of tumor invasion agreed with the histopathologic findings are given below.

A squamous cell carcinoma was located at B3 on the left. Ultrasonography showed this lesion to invade beyond the bronchial cartilage, protruding at 12 o'clock; thus the ultrasonically determined depth of tumor invasion was extramural (Figure 10.8). The histopathological findings confirmed this determination.

In the second case, a typical carcinoid tumor involving the right upper bronchus was ultrasonographically shown to have invaded beyond the bronchial cartilage, compressing the fifth layer (corresponding to the adventitia, Figure 10.10). Histopathologically, the tumor compressed and invaded the adventitia. Again, the histopathological findings confirmed the ultrasonographic determination of the depth of tumor invasion.

On the other hand, one misdiagnosed case was a squamous cell carcinoma that histopathologically compressed and invaded the adventitia, while ultrasonography showed a hypoechoic area extending beyond the adventitia (Figure 10.11). Another misdiagnosed case was a squamous cell carcinoma that histopathologically invaded the submucosa while ultrasonography showed a hypoechoic area extending from the mucosa to the adventitia. While this lesion was diagnosed by EBUS as invading the adventitia, the hypoechoic region extending between the cartilage rings to the adventitia was histopathologically shown to represent lymphocytic infiltration that caused overestimation of the depth of invasion by EBUS (Figure 10.12). The other five misdiagnosed cases were squamous cell carcinomas that histopathologically invaded only the mucosa (carcinoma in situ), in three of which ultrasonography showed five layers with normal appearance (Figure 10.13). The remaining two cases were carcinomas in situ where ultrasonography

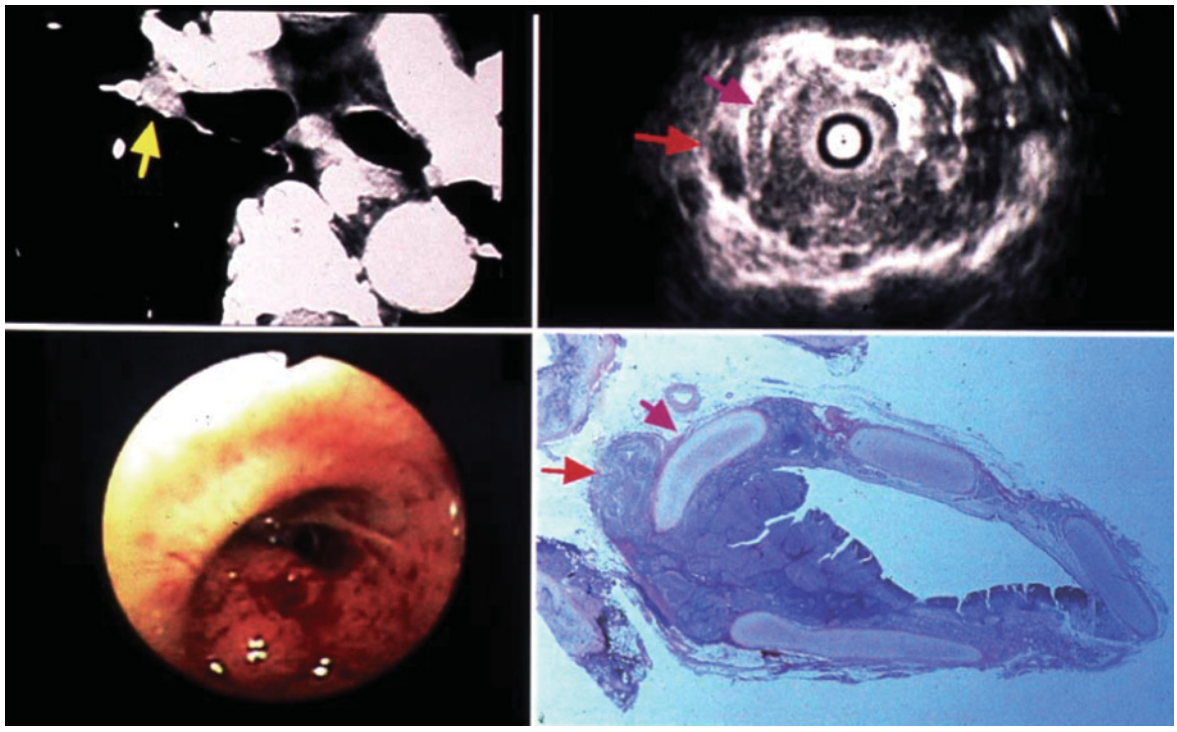

**Figure 10.11** Squamous cell carcinoma in the right upper bronchus. Left upper: Chest CT scanning shows a tumor located in the right upper bronchus. Left lower: The bronchoscopic findings locate this tumor in the right upper bronchus and B3. Right upper: Ultrasonographically, the tumor appears to have invaded beyond the adventitia. Right lower: Histopathologically, the tumor does not extend beyond the adventitia. The depth of tumor invasion has therefore been overestimated. Hematoxylin and eosin: original magnification ×10.

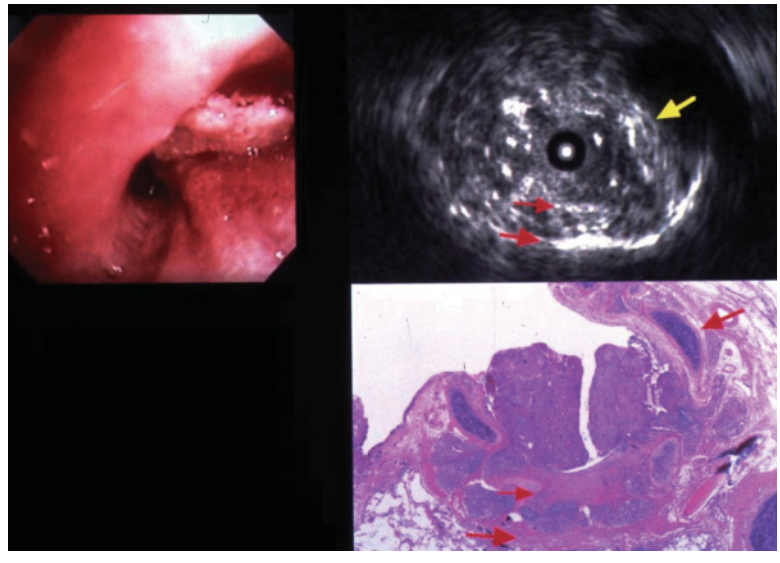

**Figure 10.12** Squamous cell carcinoma in the right B2 bronchus. Left: The bronchoscopic findings locate this tumor in the right upper bronchus and B2. Right upper: Ultrasonography shows a hypoechoic area extending from the epithelium to the adventitia, indicating tumor invasion of the adventitia. Right lower: Histopathologically, this tumor invades the submucosa. The hypoechoic region extending from between the cartilages to the adventitia corresponds to lymphocytic infiltration. The depth of tumor invasion has been overestimated. Hematoxylin and eosin: original magnification ×10.

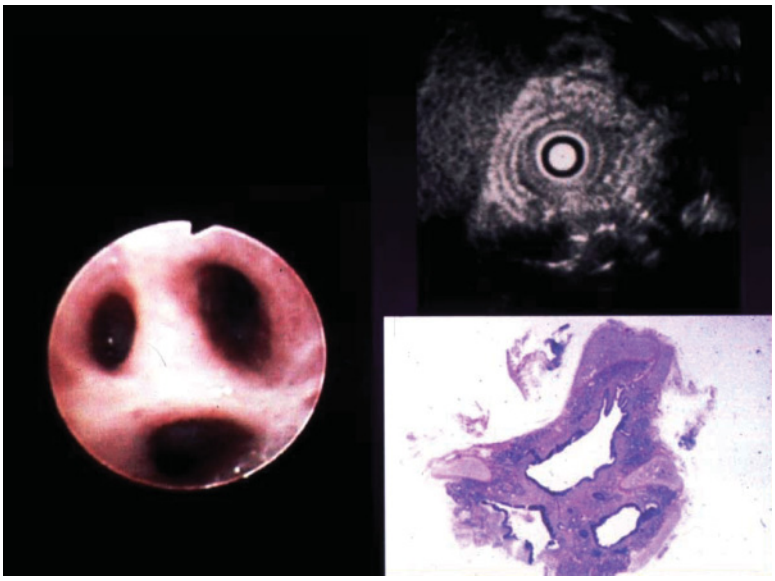

**Figure 10.13** Squamous cell carcinoma (left B6 bronchus). Left: The bronchoscopic findings are of a dull appearance of the surface at the left B6 bifurcation. Right upper: Ultrasonography demonstrates five normal-appearing layers. Right lower: Histopathologically, this tumor was observed to involve the mucosa (carcinoma in situ). The marginal echo (1st layer) extends from the luminal margin of the mucosa to the superficial portion of the submucosa. Carcinoma in situ thus occupies the intact-appearing first layer (hyperechoic, marginal echo) as seen with a 20 MHz probe.

showed a hypoechoic area extending from the epithelium to the adventitia. This was diagnosed by EBUS as tumor invasion of the adventitia, while histopathologically most of the hypoechoic region corresponded to lymphocytic infiltration and prominent bronchial glands, leading to overestimation of the depth of tumor invasion (Figure 10.14).

Unlike other diagnostic imaging methods, EBUS using a 20 MHz probe allows visualization of the depth of tumor invasion of the tracheobronchial wall. When the tumor has invaded beyond the bronchial cartilage, this modality clearly shows the bronchial cartilage within the tumor.

The most important point in determination of the depth of tracheobronchial tumor invasion using EBUS is examination of the third and fourth layers, corresponding to the bronchial cartilage. An important limitation of preoperative EBUS in determination of the depth of tumor invasion is difficulty distinguishing lymphocytic infiltration from tumor invasion (Figure 10.15). As ultrasonography visualizes tissues according to the speed of propagation of ultrasound waves, it would appear that the speed of ultrasound waves from the 20 MHz probe passing through invasive cancer is similar to that through lymphocytic infiltrates and hypertrophied bronchial glands. Arima et al. [6] and Kawano et al. [7] reported that endoscopic ultrasonography (EUS) for oesophageal cancer was not able to distinguish either fibrotic change resulting from esophagitis or lymphoid hyperplasia adjoining a tumor from tumor invasion. Arima et al. [6] similarly noted that changes in the tissues around a tumor such as hyperplasia of lymphoid follicles, cellular infiltration, and fibrosis of tumor invasion, were often misinterpreted as tumor. Kikuchi et al. [8] attributed misdiagnosis of the depth of invasion of colorectal cancers using EUS to attenuation of ultrasound waves related to tumor thickness, as well as difficulty in differentiating between cancer invasion and lymphocytic infiltration, lymphoid follicles, or submucosal fibrosis. Menzel and Domschke [9] also reported that ultrasonographic overstaging of oesophageal cancers might involve misinterpretation of submucosal inflammation. In four lesions (three carcinomas in situ, one submucosally invading carcinoma) we also overestimated the depth of tumor invasion because of lymphocytic infiltration and bronchial glands in the submucosa, and between bronchial cartilage and adventitia. In recent years, we have begun to use a 30 MHz probe to obtain higher resolution images of the superficial layers, and a convex probe to provide longitudinal images of the tracheobronchial wall.

Comparison of the ultrasonographic and histopathologic findings in this study indicated that the depth of

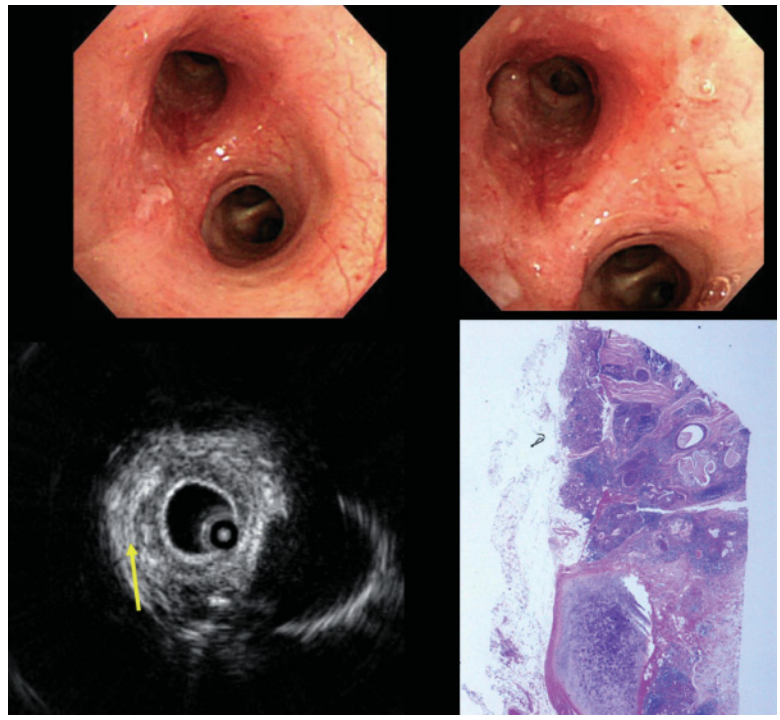

**Figure 10.14** Squamous cell carcinoma (right B2 bronchus). Left upper: Bronchoscopic findings show the right B2 to be near normal. Left lower: Ultrasonographically, the bronchial wall is thickened. A hypoechoic area extending from the epithelium to the adventitia suggests tumor invasion of the adventitia. Right: Histopathologically, this tumor is confined to the mucosa (carcinoma in situ). Most of the hypoechoic region corresponds to lymphocytic infiltration and hypertrophied bronchial glands, causing overestimation of the depth of tumor invasion. Hematoxylin and eosin: original magnification ×10.

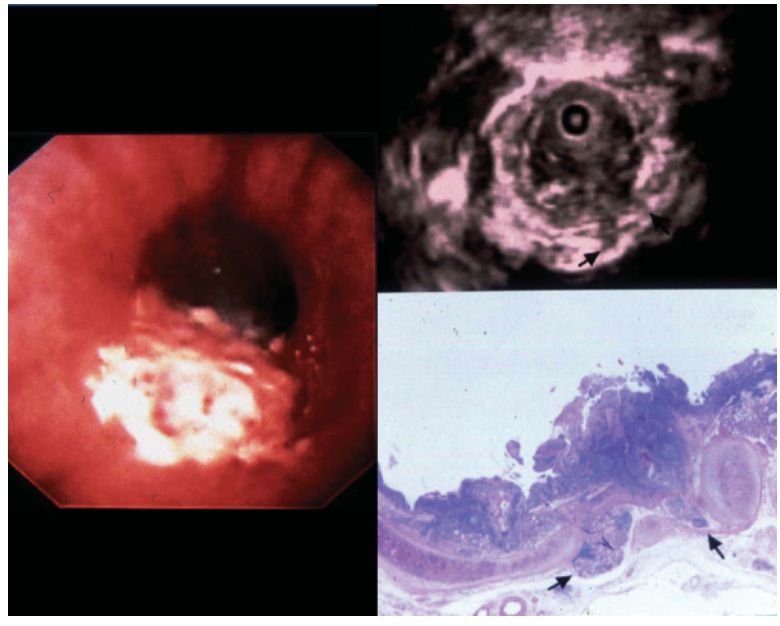

**Figure 10.15** Lymphocytic infiltration of the bronchus. A squamous cell carcinoma located in right B8. EBUS showed a submucosal hypoechoic area connected to the area resembling rabbit ears (arrow). This tumor was assessed as invading the adventitia. Histopathologically the tumor extends to the submucosa. Limitations of preoperative EBUS in determination of the depth of tumor invasion include difficulty in distinguishing lymphocytic infiltration from tumor invasion.

tumor invasion of the bronchial wall can be accurately assigned by EBUS to one of five levels: EP (epithelium, or minimal invasion of subepithelium), SE (subepithelium), C (cartilage), A (adventitia), and Ai (invasion beyond the adventitia). When the bronchus at the site of the lesion still shows five layers, the depth of invasion would be EP. When the lesion extends from the 1st layer (hyperechoic marginal echo) to the 2nd layer (hypoechoic, submucosa), while the third layer (hyperechoic marginal echo from the inner aspect of the cartilage) can be clearly delineated, the depth of invasion is SE. When the lesion extends from the 1st layer to the 4th layer, but the 5th layer (hyperechoic marginal echo at the outer aspect of the cartilage) can be clearly delineated, the depth of invasion is C. When the lesion extends from the 1st layer to the 5th layer, but the 5th layer is intact, the depth of invasion is A. Finally, when wedge-shaped interruptions are seen in layers 3, 4, and 5, the depth of invasion is Ai. An ultrasonographic depth of invasion of EP or SE allows selection of local endobronchial therapy.

## Photodynamic Therapy with EBUS

In bronchoscopic treatment of localized lesions, avoiding tissue destruction beyond the cartilage layer is important for success and safety [10–12]. Miyazu [12] reported that determination of the depth of tumor invasion using EBUS, rather than simply measuring lesion size and height, improves the chances of success of photodynamic therapy (PDT). Eighteen patients with biopsy-proven squamous cell carcinomas, considered to be appropriate candidates for PDT by conventional bronchoscopy under high-resolution computed tomography (HR-CT) control, were enrolled. Nine lesions were diagnosed as intracartilaginous using EBUS (Figure 10.16), and subsequently underwent PDT. Long-term complete remission has been achieved in these patients, with a median follow-up term following PDT of 32 months.

The remaining nine lesions were diagnosed as extracartilaginous using EBUS, and were considered candidates for other therapies such as surgical resection, chemotherapy, and radiotherapy, although two were not detectable using HR-CT, three were superficial, and five were ≤1 cm in diameter at bronchoscopy. The depth of tumor invasion estimated by EBUS was confirmed by histopathological findings in six specimens after surgical resection.

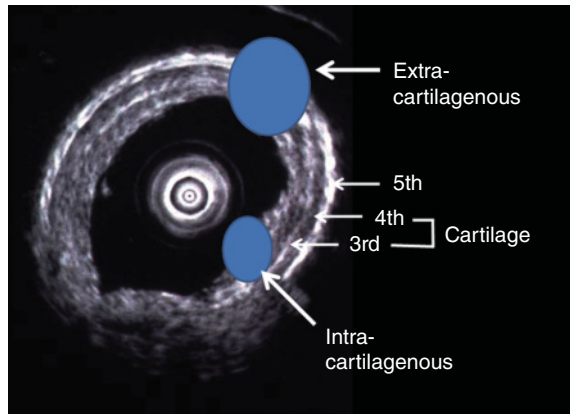


**Figure 10.16** Intracartilaginous or extracartilaginous. Tracheobronchial tumors are diagnosed as intracartilaginous or extracartilaginous using EBUS.

## EBUS for Inflammatory Diseases of the Tracheobronchial Tree

We performed EBUS for the evaluation inflammatory diseases of the tracheobronchial wall, including tuberculosis, relapsing polychondritis, chronic inflammation following tracheotomy, Wegener's granulomatosis, and ulcerative colitis. The greatest benefit of EBUS for inflammatory diseases of the tracheobronchial wall is the ability to visualize and assess the bronchial cartilage.

In Figure 10.17, we can see that in this patient with relapsing polychondritis, EBUS revealed thickening of the tracheobronchial cartilage, containing calcifications, and an intact membranous portion (Figure 10.17). EBUS, with its superior tissue analysis ability, allows us to discern the laminar structure of the membranous portion as well. In chronic inflammatory conditions such as post-tracheotomy inflammation, Wegener's granulomatosis and ulcerative colitis, the inflammatory process involves the entire circumference of the trachea, and thickening of both the cartilaginous and membranous portions of the tracheal and main bronchial walls can be seen on the EBUS images. This allows us to distinguish these conditions from relapsing polychondritis, in which the membranous portion is spared (Figure 10.18).

Another advantage of EBUS in cases of bronchomalacia due to inflammatory diseases of the tracheobronchial wall is that the diameter of the inflated

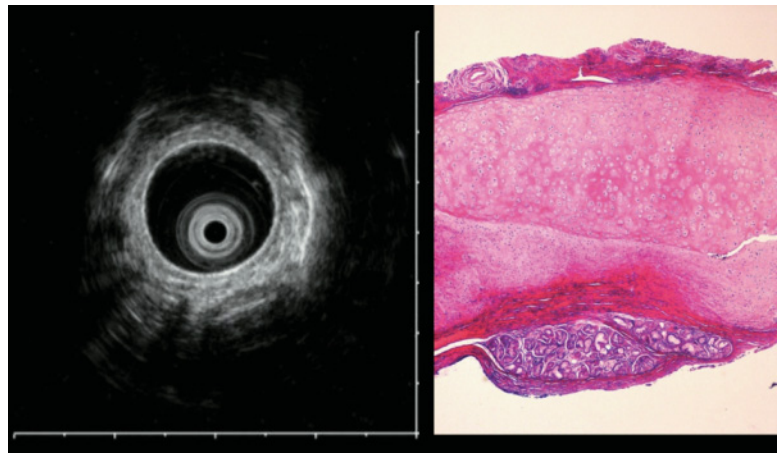

**Figure 10.17** Relapsing polychondritis. In this case of relapsing polychondritis, EBUS revealed thickening of the tracheobronchial cartilage, containing calcifications, and an intact membranous portion.

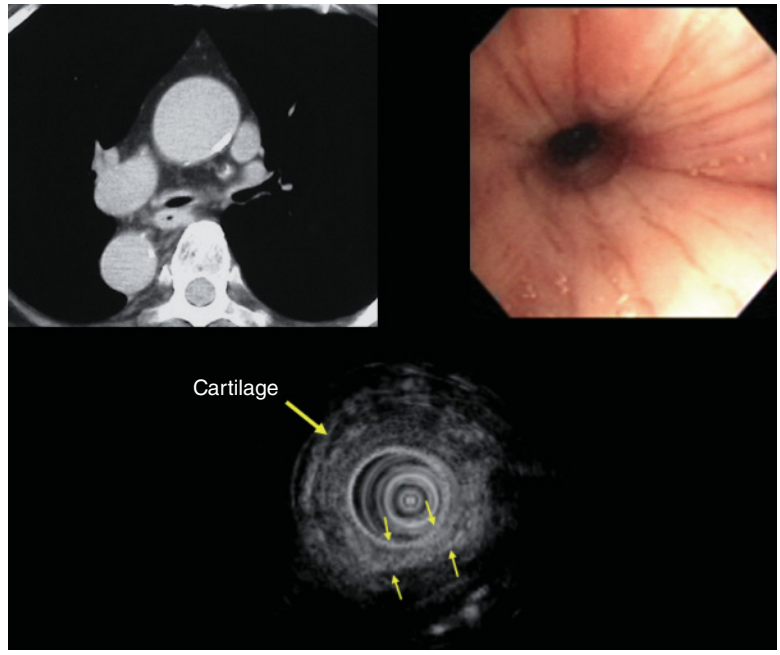


**Figure 10.18** Chronic inflammation. In chronic inflammatory conditions such as post-tracheotomy inflammation, Wegener's granulomatosis and ulcerative colitis, thickening of both the cartilaginous and membranous portions can be seen on the EBUS images, allowing us to distinguish these conditions from relapsing polychondritis.

bronchus can be measured using the inflated balloon probe.

Iwamoto et al. [13] reported the usefulness of EBUS in the management of airway stenosis due to tracheobronchial tuberculosis. Prior to interventions for airway stenosis caused by tracheobronchial tuberculosis, EBUS was performed to evaluate whether the bronchial cartilages were destroyed or intact. When the bronchial cartilage has been destroyed, a stent should be inserted to maintain the patency of the affected bronchus.

## Measurement of Airway Diameters

When performing interventions for airway stenosis, such as stent placement, it is important to accurately measure the internal diameters of the normal bronchus

proximal and distal to the lesion, and of the lesion itself. This will aid in the selection of the optimum diameter stent, and the best size balloon for balloon dilatation. Similarly, when laser ablation is to be performed, Using EBUS we measure the distance between the luminal surface of the lesion to the inner surface of the bronchial cartilage, so the laser depth of penetration can be set.

I conducted an experiment to evaluate the accuracy of measurements using EBUS. I measured the inner diameter of a syringe using EBUS, comparing these findings with the actual diameter. The syringe diameter as measured using EBUS was 0.1 mm greater than the actual diameter. When performing EBUS for central lesions in the clinical setting, a balloon sheath is necessary to exclude air over the target lesion. Shaw et al. [14] evaluated whether inflation of a fluid-filled balloon sheath over the transducer influenced *in vitro* measurements. In vivo comparison of EBUS with high resolution computed tomography scanning (HRCT), statistical analysis of measurements of airway internal diameter and wall thickness with and without the balloon sheath showed agreement between EBUS and HRCT. We believe that the accuracy of measurements using EBUS is acceptable.

CT scanning is also used to measure the internal diameters of the normal bronchus proximal and distal to the lesion, and of the lesion itself. Measurements using EBUS are necessary in the following cases: (1) when tracheobronchomalacia is present; (2) when a build-up of secretions or sputum is present distal to the stenosis; and (3) when CT scanning cannot be performed, e.g. the patient is unable to hold their breath.

In cases of tracheobronchomalacia, as typified by relapsing polychondritis, the tracheobronchial lumen is narrowed during both the inspiratory and expiratory phases. Accurate measurement of the inner diameter with the lumen expanded is necessary, a requirement met by EBUS with the balloon filled with fluid.

## Diagnosis of Invasion of the Bronchial Tree from Outside

The tracheobronchial laminar structure delineated by EBUS using high frequency ultrasonic waves is made up of interface echoes generated at the interfaces between the submucosa and cartilage, and cartilage and serosa. Diagnosis of direct invasion of the tracheobronchial wall from outside can therefore be made when there is a discontinuity of this interface echo. This is particularly useful in determining whether there is tracheal invasion by a thyroid cancer, or direct invasion of the left main bronchus by oesophageal cancer. Herth et al. [15] investigated whether EBUS can reliably differentiate between airway infiltration and compression by tumor. The ability of chest CT and EBUS to distinguish between compression and infiltration was measured against the histological results. They found that EBUS is a highly accurate diagnostic tool, and superior to chest CT in evaluating the question of airway involvement by central intrathoracic tumors.

## 30 MHz Versus 20 MHz

Radial probes operating at 20 MHz have been used since EBUS first began, and now 30 MHz radial probes are available. As the ultrasound frequency increases, the resolution is higher but the depth of penetration decreases (Figure 10.19). Radial probes operating at 30 MHz show more differentiated 2nd and 4th layers than 20 MHz radial probes. At 30 MHz, the submucosal tissue is more echo intense, and the cartilage more hypoechoic. Nakamura et al. [16] compared 20 MHz and 30 MHz probes using a plot profile derived from the image analysis software NIH Image. A normal bronchial wall image consists of five layers, and the plot profile shows a W-shape curve. The differences in mean echo intensity between the 3rd and 4th layers, and the 2nd and 4th layers, were found to be significantly greater with the 30 MHz probe than with the 20 MHz probe. The 30 MHz probe was found to be more useful than the 20 MHz probe in delineating the laminar structures of the bronchial wall.

In the future, higher probe frequencies, electrical scanning, and linear probes will allow higher resolution EBUS images of the tracheobronchial wall. We believe that both cross-sectional and longitudinal images are necessary for accurate diagnosis of the depth of tracheobronchial wall invasion.

## Conclusions

**1** EBUS using a high-frequency ultrasonic probe allows visualization of the depth of invasion of tracheobronchial tumors, not possible with other diagnostic imaging methods.

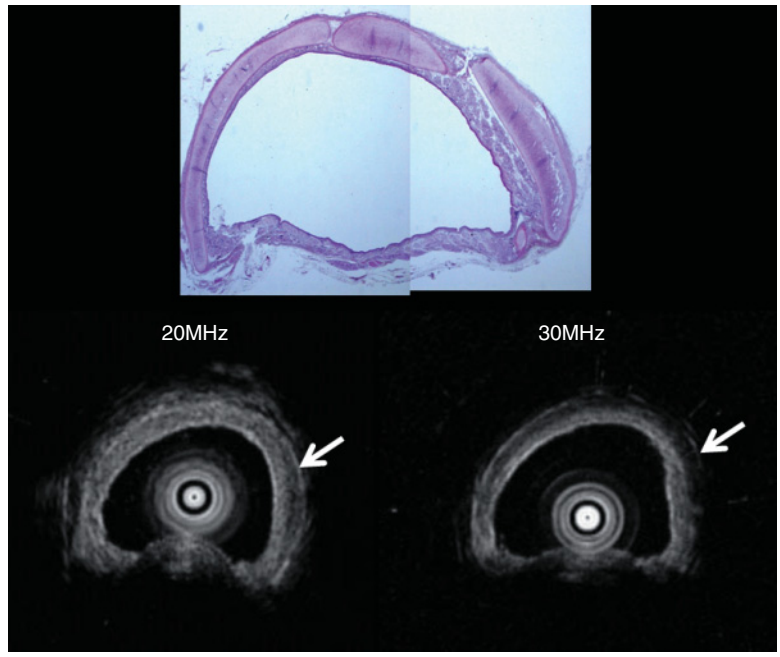


**Figure 10.19** 30 MHz vs. 20 MHz. The differences in the mean echo intensity between the 3rd and 4th layers, and the 2nd and 4th layers were found to be significantly greater with the 30 MHz probe than with the 20 MHz probe.

**2** Preoperative EBUS using a 20 MHz probe clearly visualizes bronchial cartilage within the tumor when the adventitia has been invaded.

**3** Some problems persist with EBUS using a 20 MHz probe for the determination of the depth of tumor invasion, particularly its inability to visualize carcinoma in situ and difficulty in distinguishing tumor invasion from lymphocytic infiltration and hypertrophied bronchial glands.

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# 11 EBUS in Interventional Bronchoscopy

## Introduction

Some of the earliest applications of EBUS were in interventional bronchoscopy techniques [1]. These techniques continue to be used in selected centers, particularly where there is a high throughput of large airway obstructive lesions. The largest series and greatest variety of applications of EBUS has been described by Becker and Herth in Heidelberg [2].To a large extent, this reflects the huge experience of these authors with rigid bronchoscopy and management of obstructing large airway lesions. It also reflects their pioneering role of the use of EBUS in these different clinical situations. The techniques predominantly use the 360° radial probe. In this situation EBUS attempts to carefully scrutinize the layers of the bronchial wall and determine whether these layers are invaded either from the inside by endobronchial tumors or from the outside. Conventional bronchoscopic inspection of the bronchial mucosa can only give a superficial impression of the underlying pathology. EBUS enhances the bronchoscopists' evaluation particularly with reference to tumor staging of both early and advanced tumors. EBUS provides unique information and a number of different studies have been shown greater sensitivity than any other diagnostic modality particularly in comparison with CT or MRI [2].

The early studies as discussed in previous chapters relating to depth diagnosis of small endobronchial lesions are a case in point. In this chapter, large airway assessment for the degree of external compression versus true invasion are described, particularly with reference to surgical decision making in lesions adjacent to the trachea. These techniques have not been evaluated in multicenter studies; however, in the description of these techniques, a better understanding of the benefits of ultrasound can be obtained.

## Technique

In contrast to the miniprobe used for peripheral lesions a saline filled balloon is required to obtain EBUS images in the large airways (Olympus XMAJ-643R). The probe (XUM-BS20-26R) is passed through the biopsy channel (2.8 mm or greater) of a bronchoscope and placed next to the wall at the site for evaluation. The balloon is slowly inflated until by bronchoscopic evaluation, it is seen to fill the bronchus. The EBUS image of the bronchial wall is most detailed where there is approximately 1 cm distance from the probe (inside the balloon) to the wall; however structures at a depth of 4 cm from the bronchus can be visualized [3]. To view the wall over a length it is usual to place the balloon distally first and inflate at that point then gently pull back along the wall of the bronchus as imaging occurs. Becker et al. report that, in terms of the technique of applying the balloon ultrasound probe, the balloon is filled until there is close contact with the bronchial wall. Clearly, this can mean obstruction of one or other of the main bronchi; however, in terms of ventilating the patient, this is rarely a problem. Sometimes there is complete occlusion even of the trachea; however even this can be well-tolerated for short periods under sufficient sedation and with careful preoxygenation. Although it is very uncommon to require it, it is safe

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for the patient to undergo 3 or 4 minutes of apnea for the investigation of mediastinal structures in this way [4].

The method is well-suited for studying compressed airways in that distal access is easily achieved by passing the uninflated balloon probe through the region of bronchial stricture or tumor, then gently inflating until the balloon image on the monitor shows some "molding" by the bronchial wall.

The mucosa on the inner surface immediately adjacent to the balloon shows a very bright echo. Next to this, the submucosa is comparatively hypoechoic. There is a strong echo of the endochondrium and perichondrium (hyperechoic) and this can sometimes reduce the visualization of the outside layers (supporting connective tissue and adventitia). Vessels can be seen by both their pulsations and by their low internal echoes and constant reference to anatomical diagrams assist the proceduralist in becoming familiar with this 360° image. Lymph nodes tend to be more hyperechoic than blood vessels. Adjacent to the left main bronchus, the important structures are the pulmonary trunk and left and right main pulmonary arteries as well as the ascending aorta and aortic arch. Posteriorly, it is easy to see the multilayered structure of the esophagus. In orienting the radial probe, artifacts from bronchial openings can also be helpful, for example, the apical segment bronchus. Important structures on the right main bronchus are the pulmonary trunk and right pulmonary artery, and adjacent the lower trachea the vena cava and aortic root. The azygous vein crosses at the level of the right tracheobronchial angle.

## Studies of Tracheal Compression Versus Tracheal Wall Invasion

In 2003, Herth et al. reported on the ability of EBUS to reliably differentiate between airway infiltration and compression by tumor [5]. These tumors were defined as a mass next to the trachea or within the tracheobronchial angles. From 131 patients referred for evaluation, there were obvious factors which precluded them from subsequent surgery. These included visible tumor growth into the trachea, contralateral endobronchial tumor, N3 node positivity and metastatic disease. This left 105 patients who did undergo surgery. The majority of these were squamous cell carcinomas and adenocarcinomas of the lung. On CT scans in these patients, 81 patients (77%) were reported to have tumor invasion of the airway while 24 patients (23%) were considered to have extrinsic tumor compression of the airway. In contrast, when EBUS was performed, it was considered that 49 patients (47%) had large airway tumor invasion and 56 patients (53%) had tumor compression. On the surgical resected specimens, 55 patients (52%) had tumor invasion and tumor compression was seen in 50 patients (48%). Therefore, all patients that did have tumor invasion as proved by surgical resection had been diagnosed by EBUS. EBUS had six false-negative examinations for tumor invasion within the trachea. Comparing EBUS and chest CT for infiltration by a central tumor of the tracheobronchial tree, accuracies were 94% and 51%, sensitivity 89% and 75%, and specificity 100% and 28% respectively. The correlation between EBUS classification and the surgical classification of airway involvement was very high at 0.89 ($p < 0.01$). Importantly, this was a simple safe technique and only took 3.5 minutes on average to perform. EBUS therefore had been demonstrated as an effective unique means of anatomically staging a patient. Where there were six false-negative results from the EBUS alone, that is, infiltration was present on surgery but not detected by EBUS, it was thought due to poor contact of the probe with the wall because of the large tracheal diameter. It was felt to represent an accurate means of staging; however the clinical relevance in terms of changes in surgical management remains to be determined by long-term studies.

A similar study was reported by Wakamatsu in 2006 [6], however, the subjects had primary tumors of the esophagus and thyroid. The study aimed to compare the utility of EBUS to assess this invasion as compared to the standard diagnostic techniques of CT and MRI. The findings of bronchoscopy with EBUS regarding direct invasion of the airway lumen were used to determine indications for surgical exploration or resection. That is, EBUS was used to change management and where invasion was evident, those with direct invasion underwent chemoradiotherapy. Fifty-four patients were included and from CT, MRI and EBUS, invasion was suspected in 29, 28 and 25 patients respectively. It is important to note that the final diagnosis was an intact trachea or bronchial adventitia in 26 patients and invasion in 28 patients,

but that the invasion was not always proven by surgery. Nonetheless, the sensitivity and specificity of CT, MRI and EBUS for invasion were 59 and 56%; 75 and 73%; and 92 and 83% respectively. With respect to the surgically treated patients, the accuracy of EBUS was significantly different from that of CT and MRI. A total of 37 patients underwent surgery and direct invasion was seen in 11 and intact trachea was seen in 26. EBUS correctly identified direct invasion in 10 of these 11 patients (91%), compared to 5 (45%) and 6 (55%) in CT and MRI respectively. In the intact trachea, EBUS correctly identified this in 22 of 26 patients (85%) compared to 15 (60%) and 17 (68%) in CT and MRI respectively. The success of this study relates to the careful inspection of the adventitial layer seen by radial probe ultrasound. Importantly, the adventitia was too thin to identify on MRI scan whereas the wall of the trachea was approximately 2 mm thick by MRI with two layers, an inner layer corresponding to the mucous membrane and submucosa, and an outer layer of cartilage and adventitia. EBUS, on the other hand, revealed good resolution and imaging of the outer most layer of the trachea and bronchial wall as reported by Shirakawa [7]. It was common for ultrasound depth of diagnosis to go out to 1.5 to 2 cm allowing good visualization of the total bronchial wall thickness as well as lymph nodes and vessels. In this study, a five-layered system for classifying the tracheal wall was used. When the outermost hyperechoic layer of the trachea was indistinguishable, a diagnosis of tracheobronchial invasion by the tumor was made. The membranous portion of the extrapulmonary bronchi has three layers on EBUS. Esophageal cancer is located in the membranous portion of the trachea and the outer hyperechoic layer in this region is the adventitia. At this point, an interruption of the third layer indicates invasion of the membranous portion. In general, where the cartilage layer was infiltrated by the tumor on EBUS, tumor invasion could be seen easily; however, it was considered difficult for those not experienced in the interpretation of the image to be confident of the invasion of the adventitia.

Some authors such as Nakamura [8] have used 30 MHz probe to improve the resolution of images for this indication. In 2004, Nakamura described an image analysis software package to determine the depth of invasion of a tumor through the tracheobronchial wall. The study confirmed the presence of five ultrasound layers roughly corresponding to the mucosa, submucosa, cartilage and adventitia as described in previous chapters. The software determined the differences in the mean echo intensity particularly between the third and fourth layers and second and fourth layers as a means of plotting the extent of involvement. From 10 normal bronchi and 10 patients with lung cancer, the ultrasound images were analysed for the intensity of ultrasound in each of the five layers. There were five peaks and troughs demonstrable. Given the greater resolution of the 30 MHz probe compared to the 20 MHz probe, there were greater differences between the peaks and troughs of the echo intensity comparing the two probes. Importantly, using the package to digitize the ultrasound image, a normal w-shaped curve of the ultrasound intensities was demonstrated; however, when there was a tumor infiltration, this typical w-shaped curve was absent with a flat ultrasound intensity through all of the five layers where previously there had been peaks and troughs. There was a statistically significant superiority of the 30 MHz probe in this type of imaging. Higher frequency ultrasound allows higher resolution of the structures but less in terms of depth of tissue penetration.

## Relapsing Polychondritis with Tracheobronchial Malacia

This condition is well described in Japan and provides a fascinating insight into the potential applications of radial probe endobronchial ultrasound. Miyazawa et al. [9,10] have demonstrated the qualitative aspects of ultrasound interpretation which were important in supporting a diagnosis of this problem. In a case series in 2003, a patient who had presented requiring emergency tracheotomy five years previously presented with breathlessness and at bronchoscopy there was malacia of the tracheobronchial tree with collapse of the trachea on expiration [10]. There was diffuse thickening of the tracheobronchial wall with severely narrowed lumen on CT images. EBUS showed thickening of the bronchial wall due to submucosal edema and the cartilage layer appeared ill-defined and absent in places. This was present in the trachea and in both main bronchi. Biopsy of the tracheal cartilage showed degeneration with fibrous changes and inflammatory cell

infiltrate. In another case, the hyperechoic third and fifth layers of the bronchial wall were indistinct on ultrasound and the hypoechoic fourth layer was markedly swollen indicating cartilage degeneration. In that case, biopsy of the tracheal cartilage confirmed chronic chondritis with inflammatory cell infiltrate. Normally, there would be more clear images of the third and fifth hyperechoic layer if the cartilage was intact. Therefore, there were two patterns of cartilage damage identified by EBUS, namely fragmentation and edema. These could be used to distinguish patients with relapsing polychondritis from other patients who had tracheobronchial malacia and tracheomegaly who would have intact tracheobronchial cartilages by EBUS.

## Endobronchial Stenting

The dynamic changes in airway diameter in patients with either severe tracheobronchial malacia or malignant airway compression can make it difficult to determine what size stent will be required. CT and MRI are limited because of the static nature of images. EBUS gives a real time image and simply by inflating the water-filled balloon and measuring the size of the balloon on the ultrasound monitor when the probe is comfortably inflated, accurate sizing of the stent required can be obtained. In the report of Miyazu with relapsing polychondritis, both patients were stented using prior EBUS measurement which was particularly useful given the complete collapse of the airway and the difficulty of judging diameter [9]. Iwamoto et al. reported in 2004 the utility of the EBUS images to demonstrate tracheobronchial wall changes in evaluating airway stenosis from tracheobronchial tuberculosis [11]. In a series of 30 patients, EBUS was performed in four patients and demonstrated the destruction of the bronchial cartilage or the thickening of the bronchial wall. One of these patients had local interruption of the tracheal cartilages demonstrated by ultrasound and this gave qualitative information supporting the use of an endobronchial stent. In two of the four cases, the demonstration of absence or interruption of tracheal cartilage supported the decision to performed endobronchial stenting.

Similar qualitative information with respect to mural involvement can be obtained for stent evaluation in patients with lung cancer. Miyazawa reported the evaluation of the airway wall proximal to sites of obvious obstruction in patients prior to stenting at the area of the obstruction [9,12]. It was possible to identify areas of cartilaginous malacia by the tumor on EBUS even though this was not obvious by standard bronchoscopic inspection. In these patients, there tended to be a proximal migration of the large airway choke point after the stenting of the original site. Secondary stenting at these subsequent migrated choke points resulted in significant improvement in peak flows over the initial stenting and supported the weakened airway wall. The use of EBUS was therefore able to demonstrate the cause of this choke point migration. In particular, absence of supporting cartilage on EBUS images due to external tumor damage was an important cause of this choke point migration. This type of identification of tracheal or major bronchial wall is not possible by CT scan.

Herth et al. report that the utility of EBUS in stent placement [13]. An important attribute of EBUS is detection of mucosal disease proximal to an area of obvious tumor involvement and hence the placement of longer tracheobronchial stents to include these involved areas and overcome this problem. In 235 cases of stent placement, EBUS assisted in stent placement parameters in 121 cases (51%). In addition to the identification of submucosal disease, extrinsic tumor application to the tracheal wall was a reason to use a longer stent.

## Brachytherapy

EBUS can be used to confirm staging prior to endobronchial brachytherapy. In Herth et al.'s series of 134 patients with endobronchial carcinoma, EBUS revealed 69 (51%) cases which required some form of changed management [13]. In cases where brachytherapy was to be used for curative treatment of early carcinoma, 28% had local disease extension or lymph node metastasis which escaped all other imaging methods. Very small lesions can demonstrate quite significant invasion through the tracheobronchial wall (through the cartilage and adventitia) despite relatively minor mucosal changes and hence require some other form of therapy, namely, surgery or external beam radiotherapy. This was described in detail in the series of photodynamic therapy by Miyazu and Kurimoto [14].

## Thermal Applications

Herth et al. reported the use of EBUS in the performance of thermal applications such as laser and argon plasma coagulation for endobronchial obstructing tumors [13]. This use of EBUS in patients having mechanical tumor destruction changed management in 123 of 346 patients (36%). The significant way that it achieved this was to demonstrate the proximity of the area being treated to the tumor and external large blood vessels. Debridement with laser or APC was stopped when EBUS demonstrated close relationships with blood vessels. No patient undergoing EBUS-guided tumor destruction demonstrated severe bleeding or fistula formation. Images could demonstrate tumors growing through the wall of the bronchus in close proximity to the pulmonary arteries on the anterior wall of the obstructed bronchus. On the left side, it was easy to demonstrate proximity to the descending aorta. In these cases, the ultrasound images obtained by placing the miniprobe in the main bronchus adjacent to the tumor sometimes required only small inflation volumes of the balloon, given the direct application of the tumor to the probe. The authors commented that they used this method in all cases of total airway obstruction before and during thermal tumor destruction.

## Miscellaneous Applications

Nakajima reported the use of EBUS-guided transbronchial needle aspiration to treat central airway stenosis from a mediastinal cyst [15]. Whereas such an application had been reported for non-EBUS guided transbronchial needle aspiration previously, the real time imaging afforded a means of providing great control during this delicate procedure. The cyst was compressing the membranous portion of the trachea with airway narrowing and arose from the upper mediastinum. The dimensions were $65 \times 57 \times 49$ mm. The patient has previously had a left thyroid lobectomy for a goiter and previously had had a diagnostic aspirate performed confirming serous fluid without any malignant cells. There was progressive dyspnea due to the increasing size of this cyst and surgical resection was not possible due to the risk of loss of thyroid and parathyroid function. Also because of a large blood vessel next to the cyst, it was not possible to aspirate via an external CT-guided technique and therefore the EBUS-TBNA was performed. This was done under local anesthetic with mild conscious sedation using 2 mg midazolam. The EBUS image would be of the homogenous low echo mass with multiple septae inside the cyst. 80 mL of fluid was removed after puncture of the cyst by the needle. Repeated punctures were used to allow the overall aspiration to be performed because of septation of the lesion. There was immediate relief of dyspnea.

We have reported the use of convex probe EBUS in the identification of pericardial recesses which mimic paratracheal lymph nodes [16]. Characteristic EBUS images show hypodensity and complete loss of any vascularity adjacent to the trachea in the typical right lower paratracheal node position (4R) in between the azygous vein and the lower part of the superior vena cava. If necessary, cyst fluid can be aspirated for diagnosis, followed by antibiotics.

Shaw et al. reported an interesting application of EBUS, namely the accurate measurement of airway wall thickness with the aim of using this to demonstrate changes in patients receiving treatment for airways diseases such as asthma [17]. In their study of an animal model of 24 cartilaginous airways, the ultrasound and actual airway diameter and wall thickness were calculated. Subsequent to that, 12 controlled subjects underwent both EBUS imaging of the posterior basal bronchus of the right lower lobe and this was compared to the airway wall thickness as demonstrated by high resolution CT scanning. In the animal in vitro studies in 24 airways, there was a mean internal diameter of 4.3 mm and wall thickness of 1.4 mm without balloon inflation and 4.2 and 1.5 mm respectively after inflation. Significant agreement was seen between the two approaches of actual measurement and ultrasound (intra-class coefficient 0.97 ($p < 0.001$) and for wall thickness 0.88 ($p < 0.001$). For the in vitro human airways studies, there was a mean internal diameter of 4.9 mm and wall thickness of 1.3 mm using EBUS and these were measured to be 5.2 mm and 1.2 mm respectively by HRCT. Using gland and Altman plots to compare measurements without balloon inflation on the airway parameters, the mean difference was close to 0 and there was no obvious relationship between the meas-

urement error and the airway parameter. There were no obvious differences when the measurements were made by different observers. The important aspect of this study was the implication that studies done in this way would not require the radiation exposure of high resolution CT scanning. Importantly, the balloon sheath did not cause any increase in the airway diameter or alter the airway wall measurements.

Irani et al. reported the use of quantitative assessment of the bronchial mural structures in lung transplant recipients using EBUS [18]. The objective was to determine whether EBUS analysis could allow the detection of airway anastomosis, infection or rejection. There were 10 lung transplant recipients and EBUS images were obtained from proximal to the anastomosis and distal to the anastomosis. Two hundred images were obtained for qualitative assessment. The important finding was that the relative thickness of the second layer (hyperechoic submucosal tissue) of the transplanted airway was significantly smaller in patients with graft rejection ($p = 0.04$) compared to patients without rejection. Conversely, this was significantly larger in patients with graft infection. An ultrasound miniprobe UMBS 20-26R Olympus was used with a balloon sheath. The Olympus BUM30 processor and MH240 driving unit were used. After digital recording, the film was screened for at least five representative slides from each autologous and allogeneic bronchial portion. The slides which showed the most obvious and well-defined lamina structure were selected by a blinded investigator. These files were saved in tagged image file format and the image was measured using AnalySIS software; soft imaging system; (Munster Germany). The image size was calibrated and then the largest possible sector starting at the center of the bronchus containing cartilage was defined. Then, the absolute values of the thickness of each layer and the relative value of the area of each layer were measured. Because of the anatomic inconsistency of the diameter of the cartilage, the relative values of the other four layers were also calculated after exclusion of the area of the cartilage. As expected, there was a statistically significant correlation found for layer three, that is, the inner hyperechoic marginal echo of the cartilage between the autologous and allogeneic airways, given that there was no change in the cartilage expected due to either infection or rejection. Conversely, the relative area of the second layer of the autologous airways, the relative area of the second layer of the autologous airways was statistically significantly smaller in the rejection group ($p = 0.04$); however there was no difference in the absolute values between the two groups. With respect to infection, there was a statistically significant difference between the groups in the relative area of layer two in the autologous part of the airway ($p = 0.02$). There were some problems in interpreting data, given that full histologic examination of the central airway walls in vivo is not possible and, therefore, comparison between the EBUS and true macroscopic findings could not be done. Overall, it was found to be a safe procedure and the multilayered structure of the allogeneic and autologous wall was well-imaged and was felt to represent a possible future means for surveillance of lung transplant recipients although further study was required.

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# 12 Future Directions for Endobronchial Ultrasonography

## Evaluation of the Depth of Invasion of Tracheobronchial Tumors

Endotracheal 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.

Expectations are also high for evaluation of the depth of invasion of tracheobronchial tumors using bronchial long axial cross-section images obtained with convex probes. At present, due to the low frequency of 7.5 MHz, identification of cartilage is just possible, but delineation of the layer structure is difficult. Once higher frequencies of 20 or 30 MHz are achieved, the bronchial wall will be much more clearly delineated, allowing considerable progress.

## 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 mode, at present only power Doppler, although in the near future the introduction of pulse Doppler is expected to allow Fast Fourier Transform (FFT) analysis of bloodflow.

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.

## 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.

*Endobronchial Ultrasonography,* 1st edition.
By Noriaki Kurimoto, David I. K. Fielding and Ali I. Musani.
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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.

## Training in EBUS

Continuous education in EBUS techniques is essential for bronchoscopists wishing to improve their results. Ongoing education in bronchology is presently available for medical practitioners throughout the world through textbooks such as this one, and through internet sites such as "The Essential Bronchoscopist©" (http://www.essential-bronchoscopy.org/intro_en.asp). Keeping up with the latest developments in EBUS through sources such as these can provide the basis of self-learning activities. Hands-on training in EBUS is also available in Japan and other countries. A number of bronchoscopists have participated in training programs under the aegis of the Japan Society for Respiratory Endoscopy, upgrading their skills in EBUS-TBNA and other EBUS techniques.

# 13 Case Reports

## Introduction

A case of overestimation of the depth of tumor penetration using EBUS – comparison of EBUS images and histopathological findings (Figure 1).

Upper right: In this EBUS image of the resected specimen, an open V-shaped hypoechoic area can be seen continuous with the tumor and extending beyond the cartilage layer (arrows).

Lower right: Histopathological examination (low magnification) revealed that the depth of invasion is from the bronchial lumen only to the submucosal layer, and not as far as the cartilage. The open V-shaped hypoechoic area extending beyond the cartilage layer on EBUS represented lymphocytic infiltration, passing through the cartilage layer and showing exactly the same morphology as seen on EBUS (arrows).

EBUS was unable to differentiate between tumor invasion and lymphocytic infiltration, although very similar looking images are obtained with EBUS as with low magnification light microscopy.

The first patient on whom I ever performed EBUS in 1994 was this case of overestimation of the depth of tumor penetration. I recall how I struggled for 2 hours to obtain the above image from the resected specimen immersed in water. I consider myself lucky to have learned such a useful lesson so early, and I am grateful to the cooperation of the pathologist who sliced up the entire specimen for me.

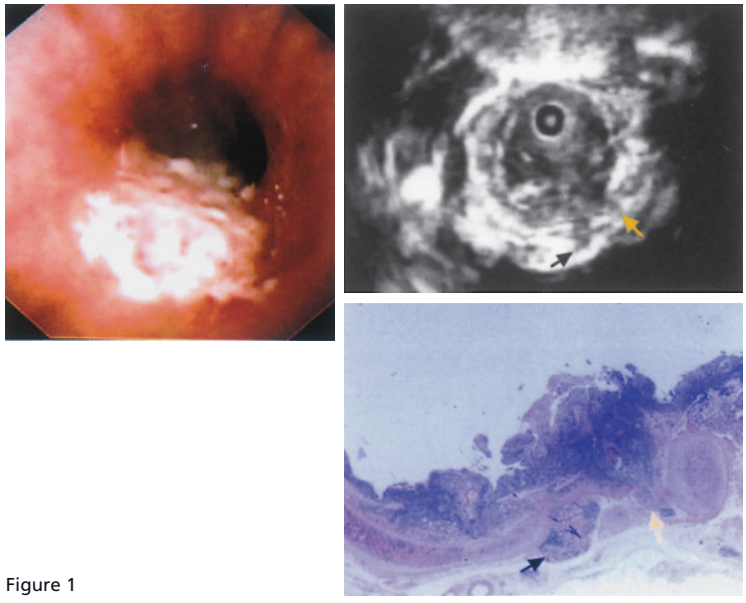

Figure 1

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## Case 1

Squamous cell carcinoma in the right basal bronchus (cartilage islands seen within the tumor).
Moderately differentiated squamous cell carcinoma in the right basal bronchus.

### Presenting Complaint: Hemoptysis

*History:* Presented to previous doctor with hemoptysis, abnormal opacity seen on plain chest radiograph. CT scanning and bronchoscopy revealed a nodular lesion in the right basal bronchus. A class V squamous cell carcinoma was diagnosed from the endobronchial brushing cytology. The patient underwent right lower lobectomy + $R^2$a: t1n0m0, stage IA.

Macroscopic examination of the resected specimen (Figure 1): A nodular invasive squamous cell carcinoma can be seen in the right basal bronchus distal to the $B^6$ bifurcation.

Preoperative EUS findings (Figures 2, 3): We used an UM-3R ultrasonic probe. The target lesion was delineated as a hypoechoic mass extending from 3 o'clock to 9 o'clock, containing triangular and island-shaped areas of cartilage (arrows: high, low, high echo areas). This tumor was thereby shown to have invaded past the bronchial cartilage layer, beyond the adventitia.

Histopathological examination (low magnification, Figures 2, 3): This is a squamous cell carcinoma with a definite tendency towards keratinisation, forming invasive nests if large and small irregular sheets as it proliferates. These specimens, sliced in the same plane as the EBUS images, show cartilage fragments (arrows) of the same shape and in the same position as in the EBUS images (arrows: high, low, high echo areas).

Bronchial cartilage fragments within tumors are delineated as high, low, high echo areas (3rd, 4th and 5th layers in the needle-puncture experiment).

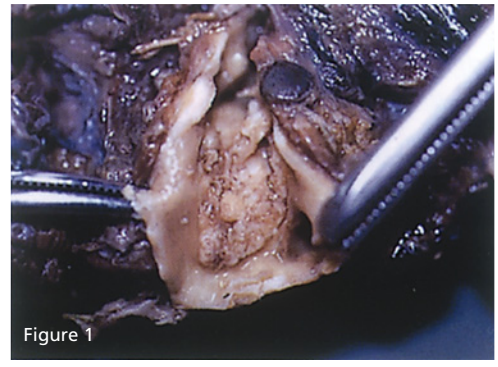


Figure 1

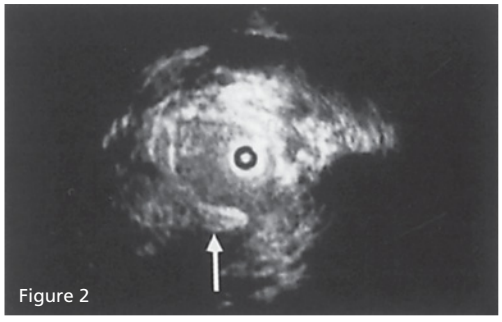


Figure 2

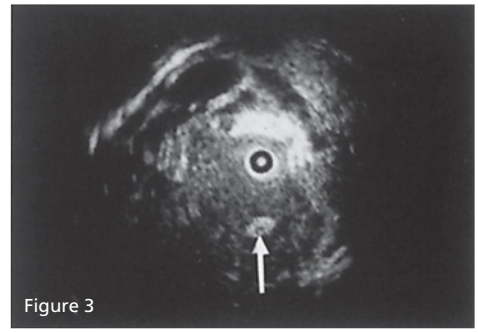


Figure 3

## Case 2

Squamous cell carcinoma in the right $S^6$ region (cartilage detected within the tumor).
Moderately differentiated squamous cell carcinoma in the right $S^6$ region.
35 × 30 × 30 mm.

### Presenting Complaint: Cough

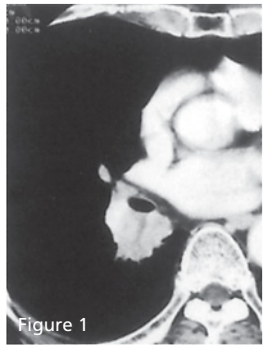
*History:* Presented to previous doctor with cough, abnormal opacity seen on plain chest radiograph. CT scanning and bronchoscopy revealed a nodular lesion in the right $B^6$ directly invading the intermediate bronchus. A class V squamous cell carcinoma was diagnosed from the endobronchial brushing cytology. The patient underwent right lower and middle lobectomy + $R^2$a: t2n0m0, stage IB.

CT scan chest (Figure 1): A nodular mass largest diameter 35 mm arising in the right $B^6$ bronchus is seen to invade the membranous portion of the intermediate bronchus.

Bronchoscopic findings (Figure 2): The target lesion is compressing the right intermediate bronchus from behind, and breaking through the mucosa.

Preoperative EBUS findings (Figure 3): We used an UM-3R ultrasonic probe + balloon. The right pulmonary artery can be seen anterior to the right intermediate bronchus. The target lesion, extending from 3 o'clock to 9 o'clock, has invaded from outside the bronchial wall, past the bronchial cartilage layer (arrow: high, low, high echo area) as far as the submucosa.

Histopathological examination (low magnification, Figure 4): This specimen, sliced in the same plane as the EBUS image, shows a cartilage fragment (arrow) of the same shape and in the same position as in the EBUS image (arrow: high, low, high echo area). Bronchial cartilage fragments within tumors are delineated as high, low, high echo areas (3rd, 4th and 5th layers in the needle-puncture experiment).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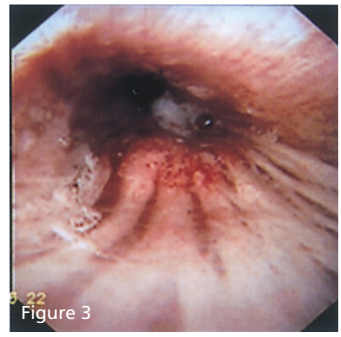
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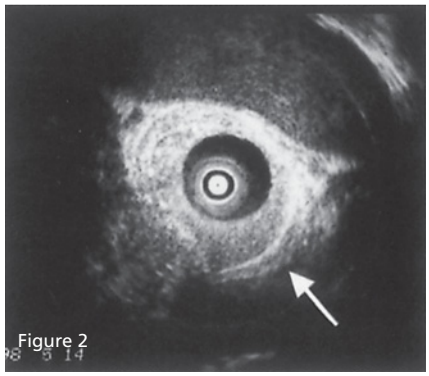


Figure 2

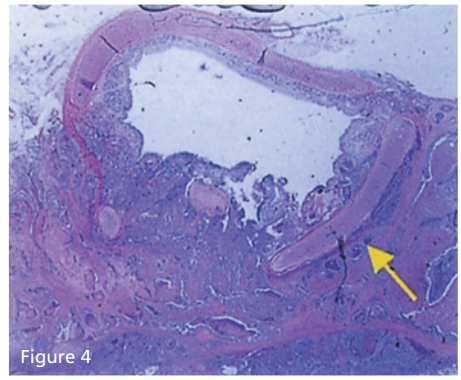


Figure 4

## Case 3

Squamous cell carcinoma in the right $B^8$ bronchus (tumor invading beyond cartilage and adjacent to the pulmonary arteries).

Moderately differentiated squamous cell carcinoma in the right $B^8$ bronchus.

### Presenting Complaint: Class V on Sputum Cytology

*History:* During follow-up for heart disease, sputum cytology in this heavy smoker was class V. Bronchoscopy revealed a polypoid lesion occluding the right $B^8$ bronchus.

CT scan chest (Figure 1): A nodular mass can be seen just distal to the bifurcation of the right $B^8$a and $B^8$b bronchi, intimately associated with the pulmonary artery.

Bronchoscopic findings (Figure 2): A white-coated polypoid lesion is seen occluding the right $B^8$ bronchus.

EBUS findings: We used an UM-3R ultrasonic probe. The probe was passed down what was thought to be the right $B^8$b bronchus, readily passing the target lesion, which was shown to be attached in the direction of the bifurcation (Figure 3). Passing the probe down what was thought to be the right $B^8$a bronchus, it came up against the target lesion, and the hypoechoic tumor was delineated. The target lesion was compressing the adjacent pulmonary artery, and had invaded past the bronchial cartilage layer (arrow: high, low, high echo area) and beyond the bronchial wall (Figure 4).

Bronchial cartilage fragments within tumors are delineated as high, low, high echo areas (3rd, 4th and 5th layers in the needle-puncture experiment).

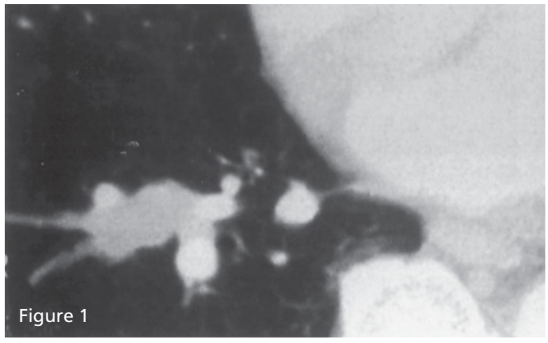
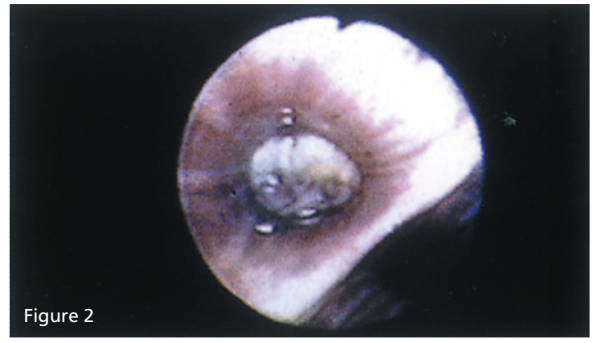


Figure 1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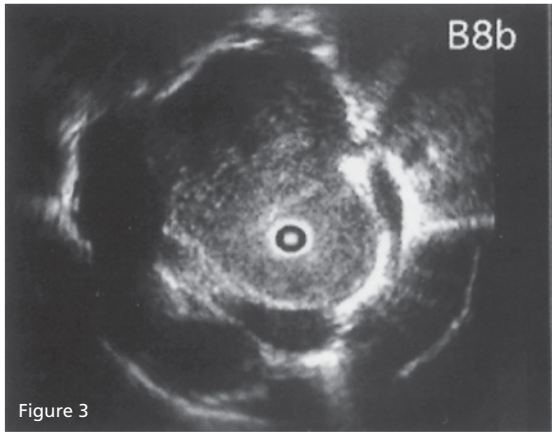


Figure 3

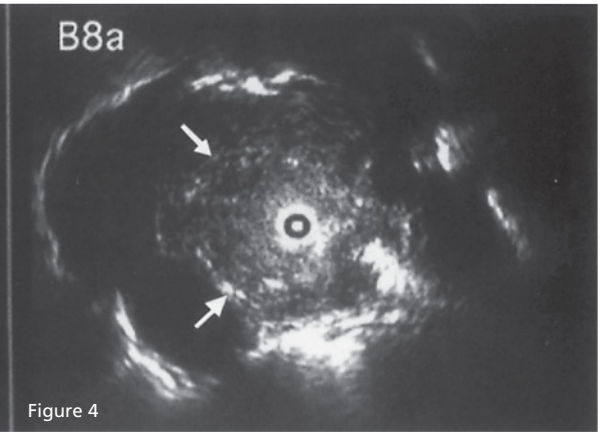


Figure 4

## Case 4

Squamous cell carcinoma in the left main and lower bronchi (irregularly shaped cartilage seen within the tumor).

Squamous cell carcinoma in the left main and lower bronchi.

### Presenting Complaint: Hemoptysis

*History:* Presented to previous doctor with hemoptysis, abnormal opacity seen on plain chest radiograph. CT scanning and bronchoscopy revealed thickening of the left main bronchus. A class V squamous cell carcinoma was diagnosed from the endobronchial brushing cytology.

Bronchoscopic findings (Figure 1): Erosions can be seen extending from the left main bronchus to the left lower bronchus.

CT scan chest (Figure 2): Thickening of the mediastinal aspect of the left main bronchus can be seen.

Preoperative EBUS findings (Figure 3): We used an UM-3R ultrasonic probe + balloon. The target lesion was delineated as a hypoechoic mass extending from 4 o'clock to 9 o'clock, extending from the bronchial lumen through the cartilage layer (arrows: high, low, high echo areas) beyond the adventitia. The cartilage has been deformed, becoming convex to the lumen.

Bronchial cartilage fragments within tumors are delineated as high, low, high echo areas (3rd, 4th and 5th layers in the needle-puncture experiment).

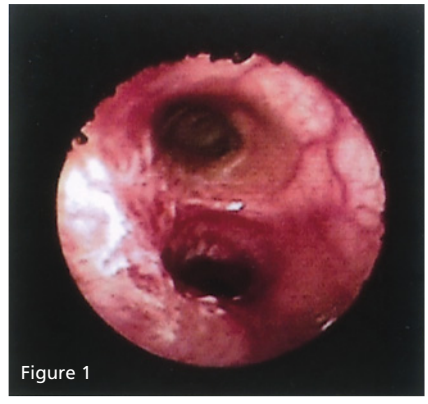
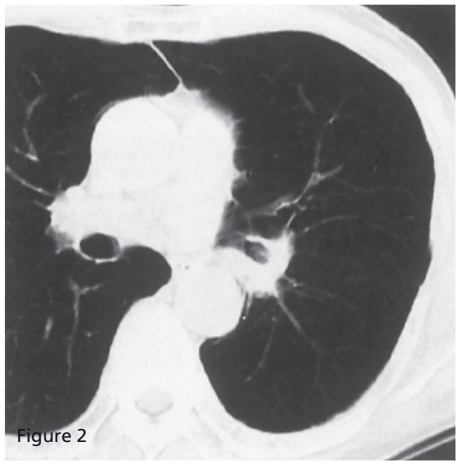


Figure 1



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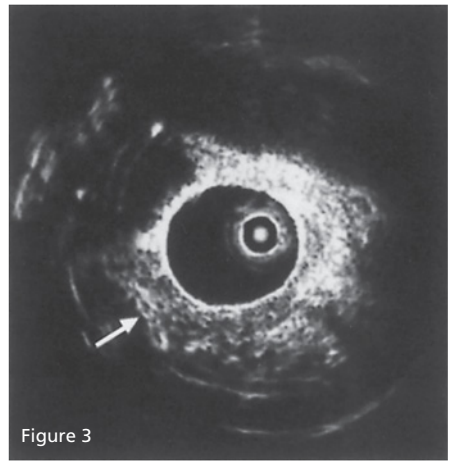


Figure 3

## Case 5

Squamous cell carcinoma in the left $B^3$ bronchus (invasion beyond the bronchial wall, beyond the 5th layer (hyperechoic) can be seen).

Squamous cell carcinoma in the left upper $B^3$ bronchus.

### Presenting Complaint: E Result from Sputum Cytology at Routine Health Check

*History:* Bronchoscopy revealed erythema and thickening of the left upper $B^3$ bronchus. EBUS was performed to assist selection of treatment modality, (photodynamic therapy) PDT or surgery.

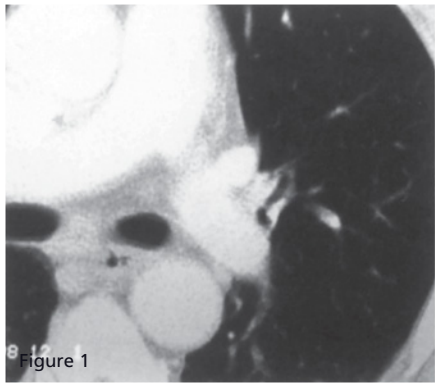
CT scan chest (Figure 1): No abnormality seen on CT scanning, in particular at the bifurcation of the left $B^3$ and $B^{1+2}$ bronchi.

Bronchoscopic findings (Figure 2): Here we can see the origin of the left upper bronchus. The lumen is narrowed from this point until the left $B^3$ bronchus, with erythema and erosions of the mucosa.

EBUS findings (Figure 3): We used an UM-3R ultrasonic probe + balloon. The balloon was inflated at the origin of the left $B^3$ bronchus to allow scanning. The target lesion was delineated as a hypoechoic mass extending from 5 o'clock to 10 o'clock, containing a hyperechoic line (arrow), representing the marginal echo at the outer margin of the cartilage (5th layer). The adventitia cannot be identified outside this hyperechoic line, indicating extramural invasion. (If we follow the hyperechoic line around to the 11 o'clock to 2 o'clock arc, outside it we can see two small blood vessels (bronchial arteries) 2–3 mm in diameter.)

Histopathological examination (low magnification, Figure 4): This squamous cell carcinoma has passed between the bronchial cartilages, invading beyond the bronchial wall.

Bronchial cartilage fragments within tumors are delineated as high, low, high echo areas (3rd, 4th and 5th layers in the needle-puncture experiment).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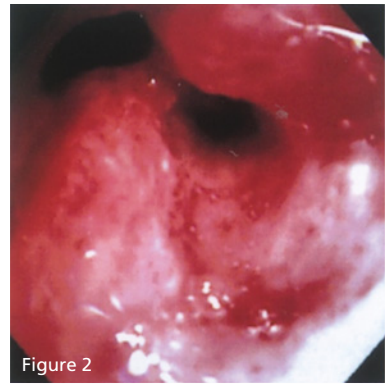
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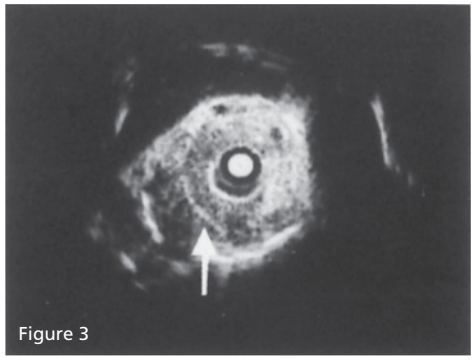
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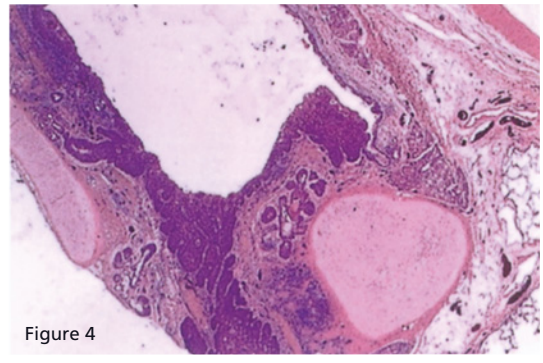


Figure 4

## Case 6

Squamous cell carcinoma in the right middle bronchus (irregularly shaped cartilage seen within the tumor).

Moderately differentiated squamous cell carcinoma in the right middle bronchus.

### Presenting Complaint: Abnormal Opacity Seen on Plain Chest Radiograph

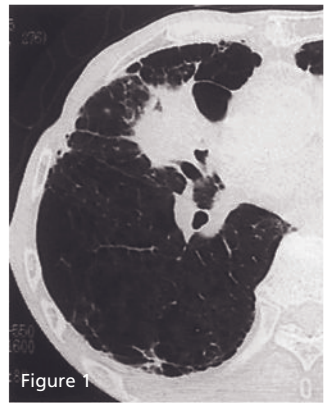
*History:* Abnormal opacity seen on plain chest radiograph by previous doctor. CT scanning and bronchoscopy revealed nodular lesion in the right middle bronchus. A class V squamous cell carcinoma was diagnosed from the endobronchial brushing cytology.

CT scan chest (Figure 1): A mass can be seen in the right middle bronchus at the bifurcation of the right $B^4$ and $B^5$ bronchi.

EBUS findings (Figures 2, 3): We used an UM-4R ultrasonic probe, introducing it into the right $B^5$ bronchus, which was completely occluded by the target lesion. The tumor extended from the bronchial lumen through the hyperechoic cartilage layer and invaded beyond the adventitia (arrow).

### Points of Advice

When evaluating the depth of tumor invasion, the following points need to be elucidated: (1) At what angle is the tumor to be found? (2) What is the length of the lesion? (3) Where is its deepest extent? (4) Where is the bronchial cartilage, the outermost hypoechoic layer? (5) Can the adventitia be delineated around the entire circumference? and (6) What has happened to the peribronchial vasculature?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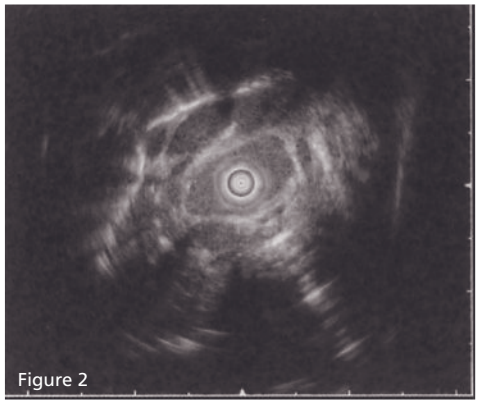
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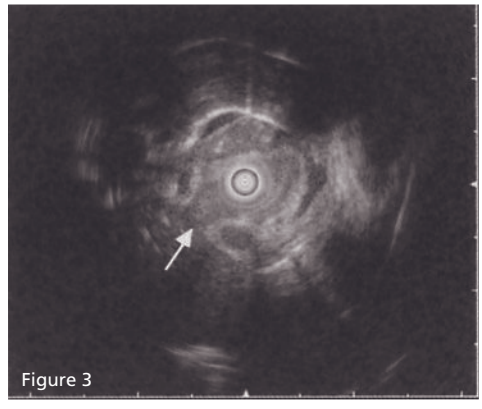


Figure 3

## Case 7

Squamous cell carcinoma in the left $B^3$ bronchus (observation of the 5th layer shows invasion beyond the bronchial wall in one area).

Squamous cell carcinoma in the left $B^3$ bronchus.

### Presenting Complaint: Class III Sputum Cytology During Follow-Up for Pulmonary Emphysema

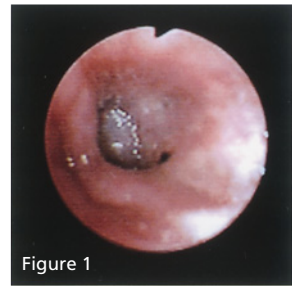
*History:* During follow-up for pulmonary emphysema, sputum cytology yielded a class III result. Bronchoscopy revealed an intraepithelial cancer involving the bifurcation of the left upper and lingual bronchi and the origin of the left upper bronchus. PDT was performed for this tumor. Follow-up bronchoscopy 4 weeks later revealed a polypoid lesion at the origin of the left $B^3$ bronchus. Biopsy showed this to be a moderately differentiated squamous cell carcinoma, for which the patient underwent surgery. We compared the preoperative EBUS images and the histopathological findings for this polypoid lesion arising from the origin of the left $B^3$ bronchus.

Bronchoscopic findings (Figure 1): A polypoid lesion obstructs the left $B^3$ bronchus.

Preoperative EBUS findings (Figure 2): We used an UM-3R ultrasonic probe + balloon. Cartilage can be clearly seen within the polypoid lesion (black arrow). This hypoechoic mass extends from the bronchial lumen to beyond the cartilage. The 5th layer can be discerned almost around the entire circumference, although the hypoechoic mass does protrude beyond the bronchial wall in one area (red arrow), indicating extramural invasion.

Histopathological examination (low magnification, Figures 3, 4): In this slice that corresponds to the plane of the EBUS image, we see a cartilage fragment (black arrow) of the same shape and in the same position as in the EBUS images (arrows: high, low, high echo areas), with hypoechoic cancer cells beyond it. In one area tumor invades beyond the adventitia into the lung parenchyma (red arrow), corresponding to the hypoechoic area on the EBUS image.

When the hypoechoic area continues beyond the bronchial cartilage, observation of the 5th hyperechoic layer (including the adventitia) will help distinguish between intramural disease and extramural invasion.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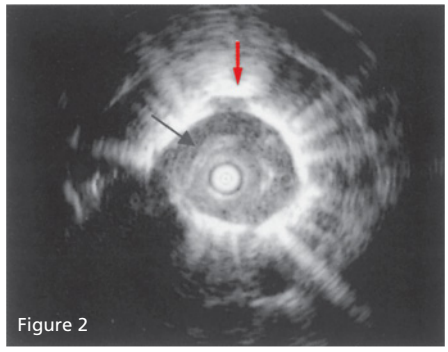
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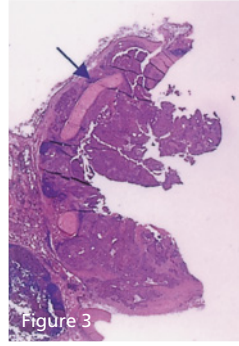
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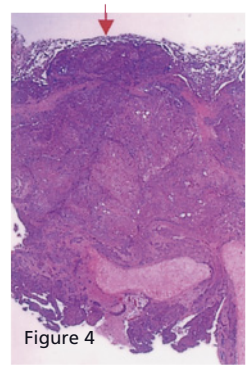


Figure 4

## Case 8

Squamous cell carcinoma in the right upper bronchus (observation of the 5th layer the key to determination of the depth of tumor invasion = adventitia).
Moderately differentiated squamous cell carcinoma in the right upper lobe $B^3$ bronchus.

### Presenting Complaint: "Positive" Result from Sputum Cytology at Routine Health Check

*History:* At routine health check, sputum cytology yielded an E result. CT scanning and bronchoscopy revealed a polypoid lesion in the right upper lobe $B^3$ bronchus. A class V squamous cell carcinoma was diagnosed from the endobronchial brushing cytology. The patient underwent right upper lobectomy + $R^2$a.

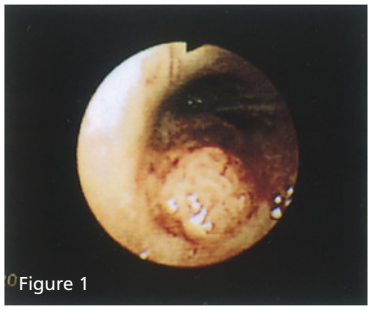
Bronchoscopic findings (Figures 1, 2): A polypoid mass, lacking a mucosal surface, extends from the right upper lobe bronchus to the right $B^3$ bronchus. Squamous cell carcinoma was strongly suspected.

CT scan chest (Figure 3): A nodular mass is present in the bronchial wall, extending from the right upper lobe bronchus to the right $B^3$ bronchus.

Preoperative EBUS findings (Figure 4): We used an UM-3R ultrasonic probe + balloon. Cartilage can be clearly seen within the polypoid lesion (arrow), and a hypoechoic area extends from the bronchial lumen to beyond the cartilage. The hyperechoic 5th layer (including the adventitia) is continuous with the outer edge of the hypoechoic area inferiorly (arrow). This was interpreted as the tumor compressing the adventitia, and the depth of tumor invasion was assessed as "to the adventitia".

Histopathological examination (low magnification, Figure 5): This specimen of the origin of the right upper lobe bronchus, sliced in the same plane as the EBUS image, shows a cartilage fragment (arrow) of the same shape and in the same position as in the EBUS image (arrow: high, low, high echo area). Tumor has invaded beyond the cartilage, corresponding to the hypoechoic area, pressing up against the adventitia, but not extending beyond it.

When the hypoechoic area continues beyond the bronchial cartilage, observation of the 5th hyperechoic layer (including the adventitia) will help distinguish between intramural disease and extramural invasion.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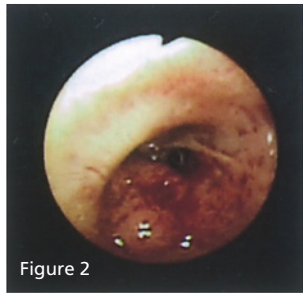
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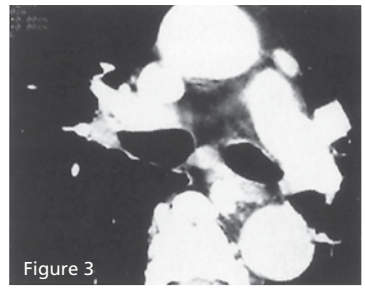
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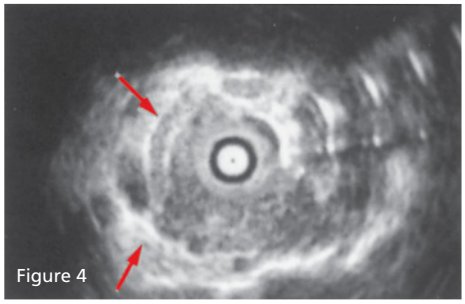
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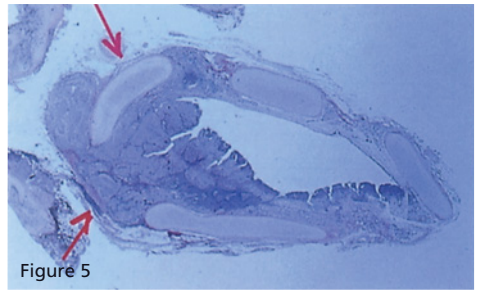


Figure 5

## Case 9

Squamous cell carcinoma in the right intermediate bronchus (hyperechoic line corresponds to submucosal collagen fibers, depth of tumor invasion = cartilage layer).

Moderately differentiated squamous cell carcinoma in the right intermediate bronchus

### Presenting Complaint: Cough

*History:* Presented to previous doctor with cough, abnormal opacity seen on plain chest radiograph and CT scan. CT scanning and bronchoscopy revealed a nodular lesion in the right B6 bronchus, continuous with thickening of the membranous portion of the right intermediate bronchus. A class V squamous cell carcinoma was diagnosed from the endobronchial brushing cytology. The patient underwent right lower and middle lobectomy + $R^2$a: t2n0m0, stage IB. We compared the preoperative EBUS images and the histopathological findings for this tumor.

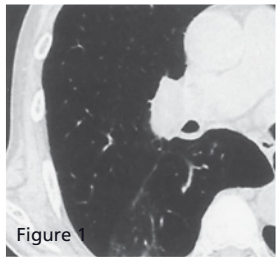
CT scan chest (Figure 1): We can see thickening of the membranous portion of the right intermediate bronchus, but cannot discern the bronchial wall structure.

Bronchoscopic findings (Figure 2): A flat polypoid mass extends from the origin of the right $B^6$ bronchus to the right lower lobe and intermediate bronchi. A superficial spreading squamous cell carcinoma with no mucosal cover was strongly suspected.

Preoperative EBUS findings (Figure 3): We used an UM-3R ultrasonic probe + balloon. Thickening of the bronchial wall extends from 1 o'clock to 11 o'clock, nearly circumferential. The tumor has invaded deep enough to contain cartilage between 2 o'clock and 3 o'clock (arrow: high, low, high echo area), but does not compress the adventitia, and the depth of tumor invasion was assessed as "to the cartilage layer".

Histopathological examination (low magnification, Figure 4): This lesion is a squamous cell carcinoma forming villous projections into the lumen. This specimen, sliced in the same plane as the EBUS image, show a cartilage fragment (arrow) of the same shape and in the same position as in the EBUS image (arrow: high, low, high echo area). Tumor infiltrates between cartilages, giving a depth of tumor invasion to the cartilage layer.

Hyperechoic lines can be seen in the thickened bronchial wall (arrow at 5 o'clock), corresponding to hyperplastic collagen fibers (arrow) within the squamous cell carcinoma forming villous projections.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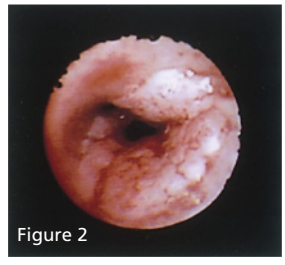
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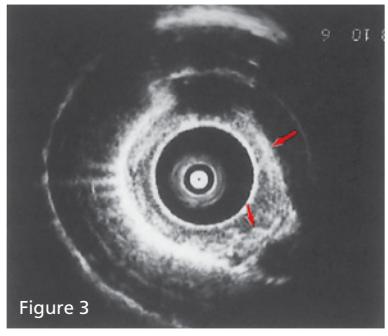
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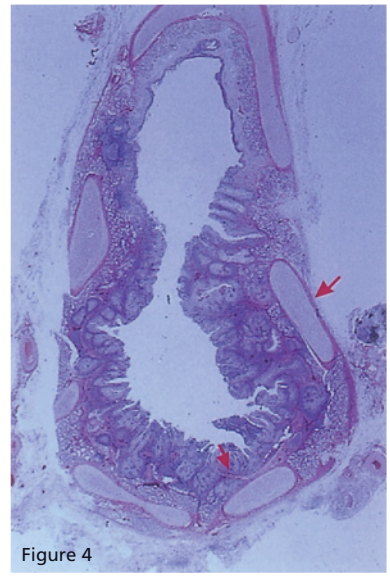


Figure 4

## Case 10

Squamous cell carcinoma in the left upper segmental bronchus (cartilage compressed by tumor, depth of tumor invasion = submucosa).

Poorly differentiated squamous cell carcinoma at the bifurcation of the left $B^{1+2}$ and $B^3$ bronchi.

### Presenting Complaint: Polypoid Lesion Detected at Bronchoscopy

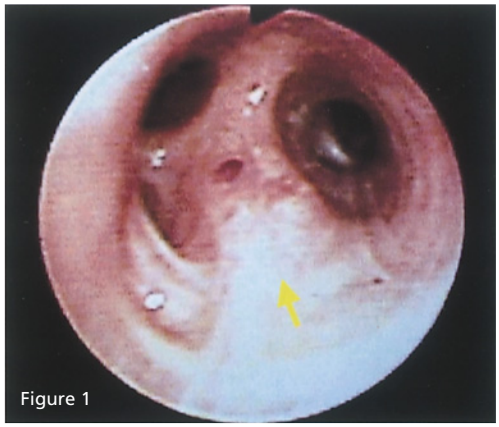
*History:* Polypoid lesion at the bronchial spur between the left $B^{1+2}$ and $B^3$ bronchi detected at bronchoscopy by previous doctor for assessment of interstitial pneumonitis. Biopsy confirmed squamous cell carcinoma.

Bronchoscopic findings (Figure 1): A polypoid lesion can be seen at the bronchial spur between the left $B^{1+2}$ and $B^3$ bronchi (arrow). Biopsy showed poorly differentiated squamous cell carcinoma.

CT scan chest (Figure 2): No abnormality can be seen at the bifurcation of the left $B^{1+2}$ and $B^3$ bronchi.

EBUS findings (Figures 3, 4): We used an UM-3R ultrasonic probe + balloon. The tumor is delineated as a polypoid lesion at 6 o'clock. The leading edge of the tumor compresses the cartilage (high, low, high echo area), making it convex to the outside. The depth of tumor invasion was assessed as "to the submucosa". Complete remission was achieved with PDT.

In this case of a lesion near a bronchial spur, we had difficulty obtaining a usable images due to the tendency of the balloon to slip past. We blew up the balloon so that it completely occluded the bifurcation, and achieved a good image by moving the probe back and forth.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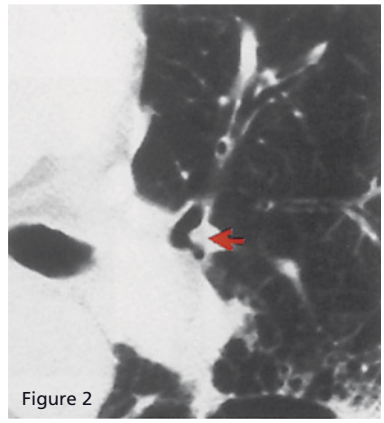
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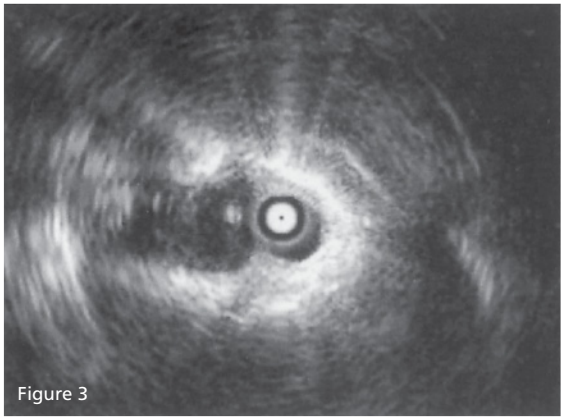
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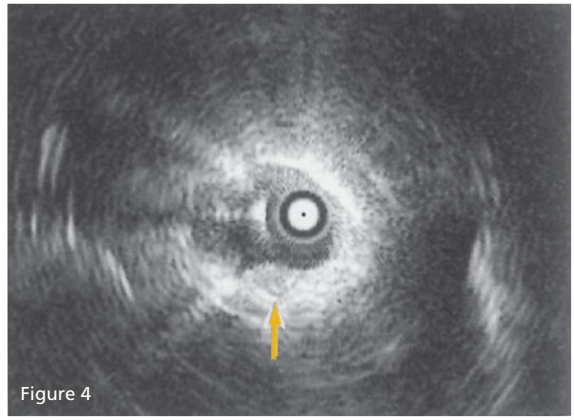


Figure 4

## Case 11

Squamous cell carcinoma at the origin of the left $B^6$ bronchus (cartilage loss detected using EBUS, depth of tumor invasion = adventitia).

Squamous cell carcinoma at the origin of the left $B^6$ bronchus.

### Presenting Complaint: E Result from Sputum Cytology At Routine Health Check

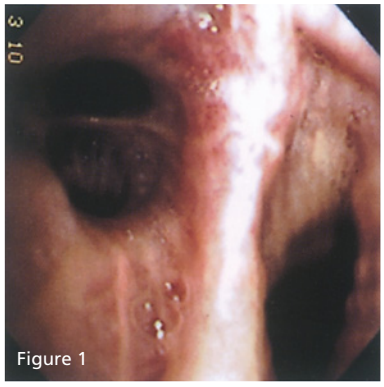
*History:* This patient underwent left partial upper lobectomy 3 years previously for squamous cell carcinoma. At follow-up the previous year, an area of erythema on the upper wall of the origin of the left $B^6$ bronchus was diagnosed as early squamous cell carcinoma. Although complete remission was achieved with PDT, a biopsy of the same site (arrow) approximately 1 year later yielded squamous cell carcinoma. EBUS was performed to evaluate the depth of tumor invasion.

Bronchoscopic findings (Figures 1, 2): An erythematous polypoid lesion can be seen at the origin of the left $B^6$ bronchus (arrow, at 1 o'clock near the spur with the basal bronchus).

CT scan chest (Figure 3): No abnormality can be seen at the origin of the left $B^6$ bronchus.

EBUS findings (Figure 4): We used an UM-3R ultrasonic probe + balloon. The tumor is delineated as a hypoechoic lesion between 10 o'clock and 2 o'clock. Cartilage (red arrow, high, low, high echo area) can be clearly seen at the periphery of the polypoid lesion. The submucosal layer of the lesion is thickened (the tumor itself). The cartilage tapers and disappears at 12 o'clock, with only the adventitia preserved (yellow arrow). The depth of tumor invasion was assessed as "to the adventitia".

When cartilage visible at the periphery of a lesion trappers and disappears within the lesion, the tumor is assessed as invading beyond the cartilage layer.



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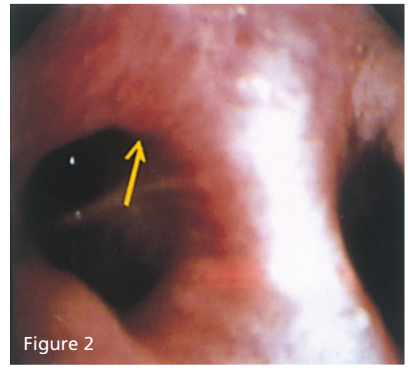
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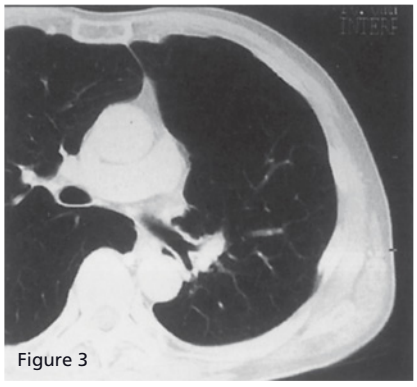
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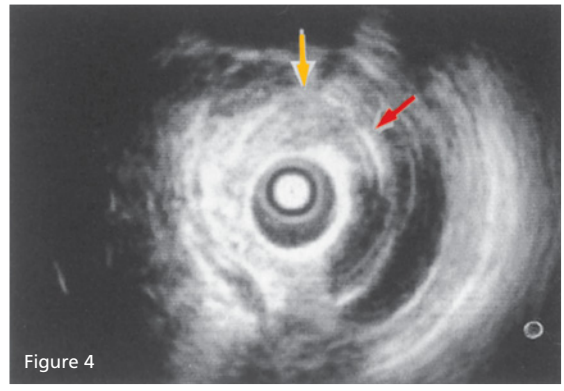


Figure 4

## Case 12

Adenoid cystic carcinoma of the trachea (important finding of tumor invasion between cartilage rings, depth of tumor invasion = adventitia).
Adenoid cystic carcinoma of the trachea.

### Presenting Complaint: Cough

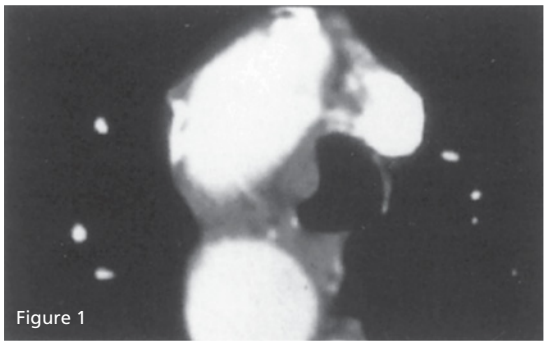
*History:* Presented with cough, polypoid lesion of the trachea on CT scan chest.

Reversed CT scan chest (Figure 1): For comparison with the EBUS images, we reversed the image so it appears that we are looking down from above. Endoscopic examinations and treatments are, of course, conducted looking down from above. A polypoid lesion can be seen arising form the left tracheal wall.

Bronchoscopic findings (Figure 3): A polypoid lesion can be seen on the left tracheal wall, protruding through the mucosa with a white stripe on its apex. It appeared to be submucosal in origin, and biopsy yielded a diagnosis of adenoid cystic carcinoma.

Preoperative EBUS findings (Figures 2, 4): We used an UM-3R ultrasonic probe. The target lesion is delineated as a hypoechoic lesion between 7 o'clock and 11 o'clock. At the cartilaginous portion (Figure 2), the hypoechoic layer corresponding to the tracheal ring (arrow, 4th layer) is preserved, and the lesion can be seen in contact with the marginal echo on the inner side of the tracheal cartilage (3rd layer). Tumor can be seen protruding between tracheal rings, adjacent to the hyperechoic layer corresponding to the adventitia (arrow). From the above, the target lesion has invaded past the line between neighboring tracheal rings, up to but not beyond the adventitia, so the depth of tumor invasion was assessed as "to the adventitia".

In the extrapulmonary tracheobronchial tree with cartilage rings, the depth of tumor invasion must be assessed in both the cartilaginous portion and in the membranous portion between cartilage rings.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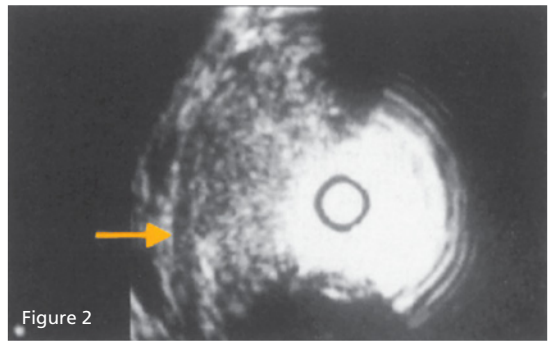
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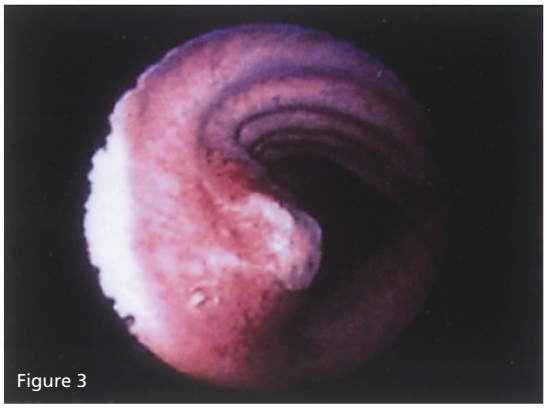
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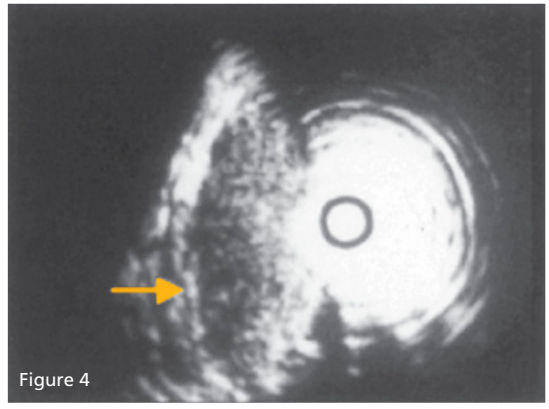


Figure 4

## Case 13

Squamous cell carcinoma of the right lower lobe (thickening of the right intermediate bronchial submucosa (2nd layer) due to tumor invasion).

Squamous cell carcinoma at the origin of the right lower lobe bronchus.

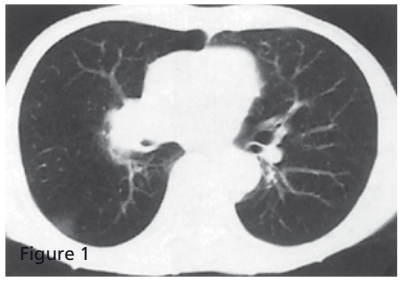
### Presenting Complaint: Exertional Dyspnea

*History:* Presented to previous doctor with exertional dyspnea, abnormal opacity seen on plain chest radiograph.

CT scan chest (Figures 1, 2): A cavity-containing tumor was seen at the origin of the right lower lobe bronchus. Stenosis of the right intermediate bronchus was seen on 1 cm slice CT scanning, although it could not be determined whether the right middle lobe bronchial wall was thickened.

Bronchoscopic findings (Figures 3, 4): Erythema of the bronchial mucosa and narrowing of the lumen extended from the right intermediate bronchus as far as could be seen down the lower lobe bronchus. A polypoid lesion was seen at the origin of the right lower lobe bronchus.

EBUS findings: Although the right main bronchial wall was normal, thickening of the right intermediate bronchus is seen from the bifurcation with right upper lobe bronchus distally, strongly suggestive of tumor invasion (Figure 5). Having passed the probe as far as the $B^8$ bronchus, we see destruction of cartilage within the tumor (arrow), representing extramural invasion from the right lower lobe tumor (Figure 6).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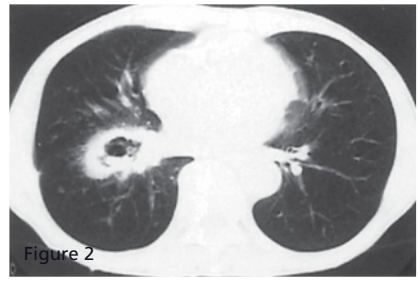
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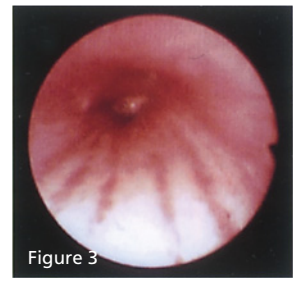
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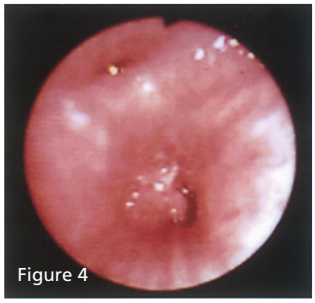
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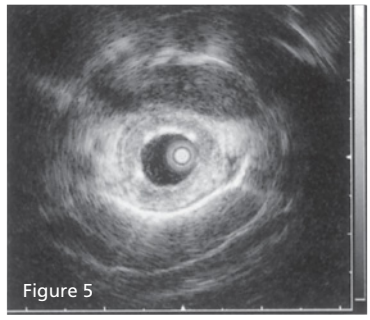
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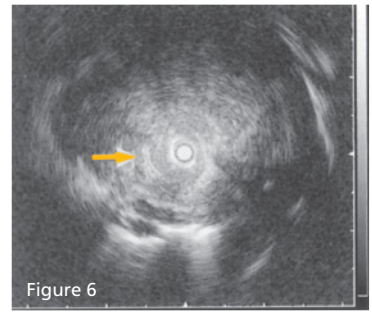


Figure 6

## Case 14

Esophageal carcinoma (EBUS to determine if the tumor had invaded the membranous portion of the left main bronchus).
Squamous cell carcinoma of the esophagus.

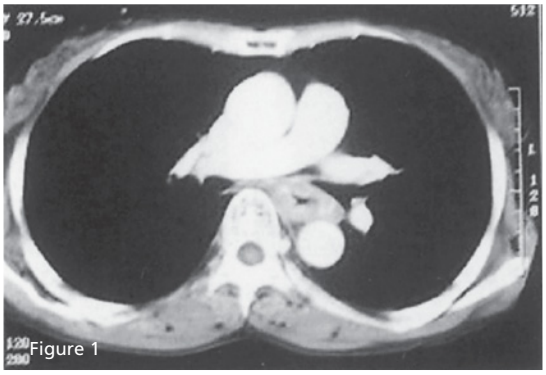
### Presenting Complaint: Difficulty Swallowing

*History:* Presented to previous doctor with difficulty swallowing, esophageal stricture at 25 cm from the incisors. Biopsy yielded the diagnosis of squamous cell carcinoma. EBUS was performed to determine if the tumor had invaded the membranous portion of the left main bronchus.

CT scan chest (Figure 1): In the slice showing the bifurcation of the left upper and lower lobe bronchi, the thickened wall of the esophagus was seen to compress the left main bronchus from behind.

Bronchoscopic findings (Figure 2): External compression of the dorsal aspect of the membranous portion is seen from the left main bronchus to the left lower lobe bronchus. No abnormality of the mucosa of the membranous portion is seen.

Preoperative EBUS findings (Figures 3, 4): We used an UM-3R ultrasonic probe + balloon. The esophageal carcinoma is delineated as a hypoechoic lesion from 4 o'clock to 8 o'clock. No abnormality is seen in the laminar structure of the membranous portion of the left main bronchus, so we concluded that there was no tumor invasion. At operation, it was confirmed that the esophageal carcinoma had not invaded the membranous portion.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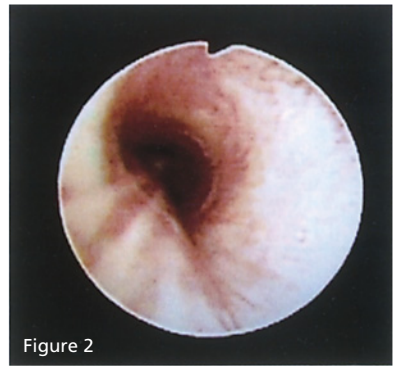
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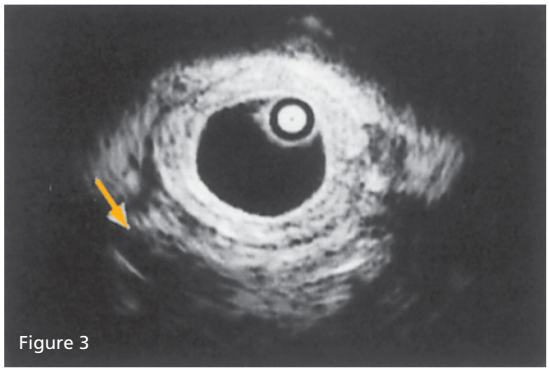
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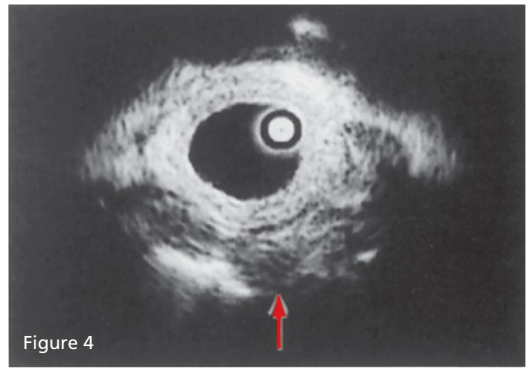


Figure 4

## Case 15

A metastatic peribronchial lymph node that directly invaded the right intermediate bronchial wall.

Invasion of the right intermediate bronchial wall by #10 metastatic lymph node (squamous cell carcinoma).

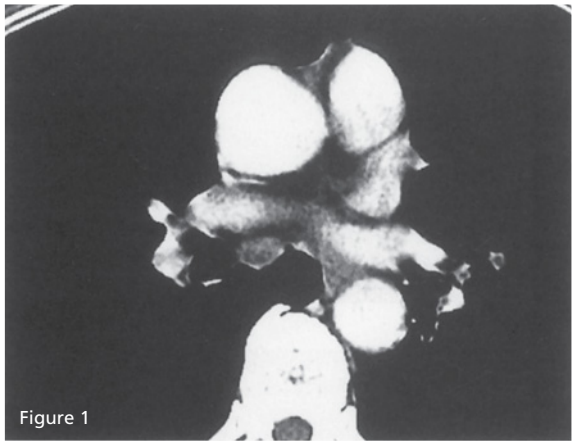
### Presenting Complaint: Feeling of Things Getting Stuck in the Throat

*History:* Abnormal opacity seen in the left upper lobe on plain chest radiograph. Bronchoscopy revealed squamous cell carcinomas in two positions, in the left $B^3$ bronchus and the origin of the right intermediate bronchus. EBUS was performed to determine if the latter lesion was the result of invasion by the #10 metastatic lymph node.

CT scan chest (Figure 1): We could see enlargement of the #10 lymph node is seen, and suspected metastatic squamous cell carcinoma. We could not determine whether the #10 lymph node invaded the right intermediate bronchus.

Bronchoscopic findings (Figure 2): External compression of the dorsal aspect of the membranous portion is seen from the left main bronchus to the left lower lobe bronchus. No abnormality of the mucosa of the membranous portion is seen.

Preoperative EBUS findings (Figures 3, 4): We used an UM-3R ultrasonic probe + balloon. The target lesion is delineated as a hypoechoic lesion from 8 o'clock to 10 o'clock. Looking at the site of the polypoid lesion, we see the #10 lymph node invades past the cartilage (arrow, high, low, high echo area) as far as the submucosa.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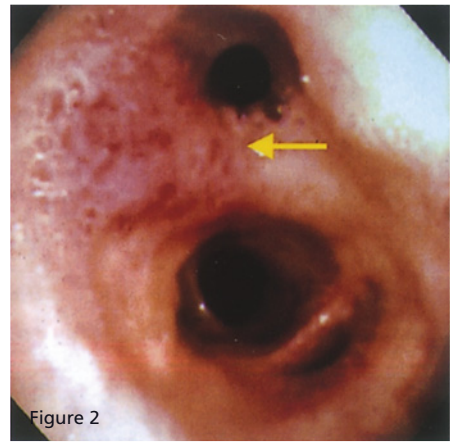
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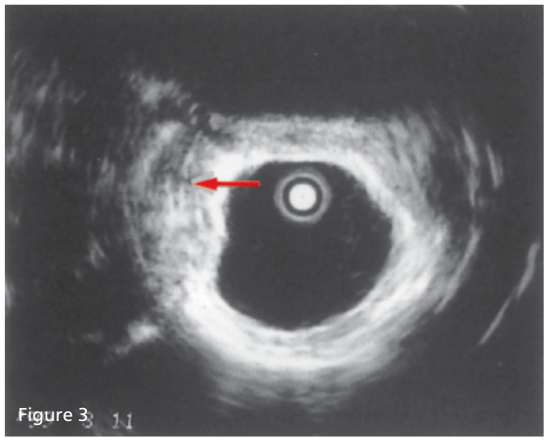
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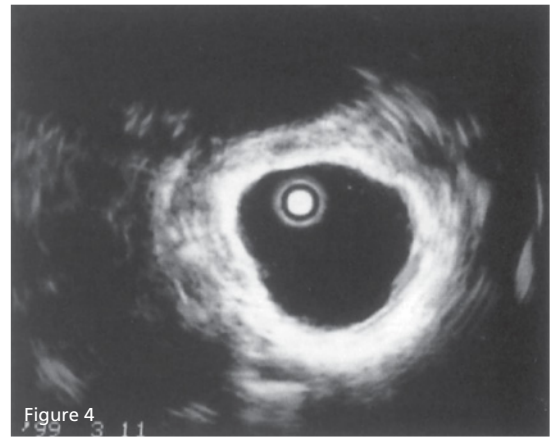


Figure 4

## Case 16

Small cell carcinoma (metastatic right #11i lymph node directly invaded the right middle lobe bronchus).

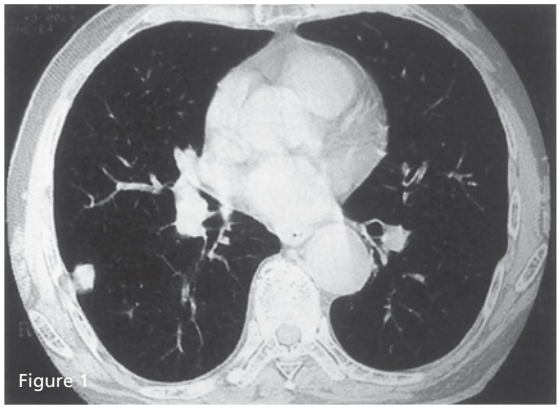
### Presenting Complaint: Abnormal Opacity Seen on Plain Chest Radiograph at Routine Health Check

*History:* Referred in May 1997 after an abnormal opacity was seen on plain chest radiography at a routine health check.

CT scan chest (Figure 1): A subpleural 1.8 × 1.7 cm primary tumor is located at the right S8a region. Enlargement of the #12l, #11i, #7 and #3 lymph nodes led to staging as cT1N2M0, stage IIIA.

Bronchoscopic findings: A submucosal (breaking through the mucosa) polypoid lesion was seen protruding in to the dorsal aspect of the membranous portion of the right middle lobe bronchus (Figure 2).

EBUS findings: We positioned an UM-3R ultrasonic probe directly against the polypoid lesion in the membranous portion of the right middle lobe bronchus. The intramural submucosal polypoid lesion was heterogenous but relatively highly echogenic, with loss of cartilage within (Figure 3). The relatively highly echogenic submucosal polypoid lesion was continuous with the extramural enlarged lymph node (Figure 4). This was considered to be small cell carcinoma that had metastasised to the right #11i lymph node, and then invaded the right middle lobe bronchus directly.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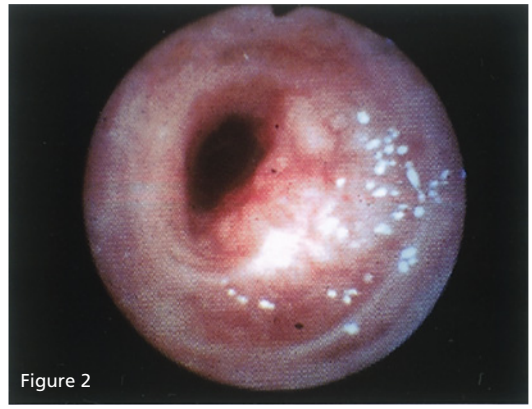
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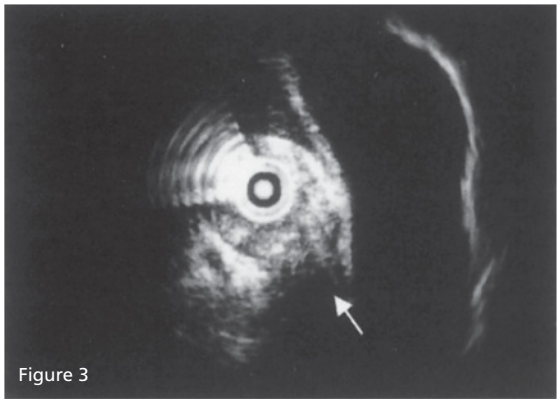
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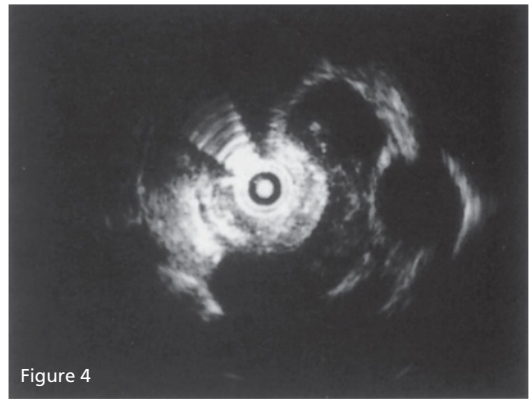


Figure 4

## Case 17

Breast cancer (V-shaped bronchial cartilage fragment caused by metastatic left #11 lymph node compressing the bronchial wall from outside).
Left #11 metastatic lymph node (breast cancer).

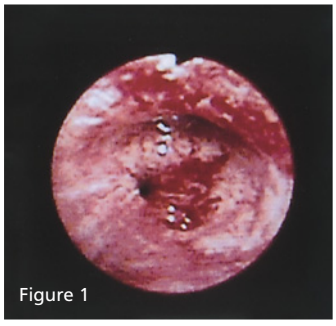
### Presenting Complaint: Abnormal Opacity on CT Scan Chest at Follow-Up after Surgery for Breast Cancer

*History:* Referred after abnormal opacity seen on follow-up CT scan chest 2 years after surgery for breast cancer.

Bronchoscopic findings (Figure 1): Erythema and erosions were seen extending from the left main bronchus to the bifurcation of the left upper and lower lobe bronchi. Metastatic breast cancer was diagnosed from the endobronchial brushing cytology.

CT scan chest (Figure 2): An enlarged left #11 lymph node was seen to compress the bifurcation of the left upper and lower lobe bronchi.

EBUS findings (Figure 3): We introduced an UM-3R ultrasonic probe + balloon into the left B6 bronchus. The target lesion is delineated as a circumferential hypoechoic lesion. The left #11 lymph node is enlarged, and directly invades bronchial wall submucosal layer. Observation of a deformed section of bronchial cartilage allows us to determine whether it is compressed by proliferating extramural tumor or compressed by proliferating tumor on the mucosal side.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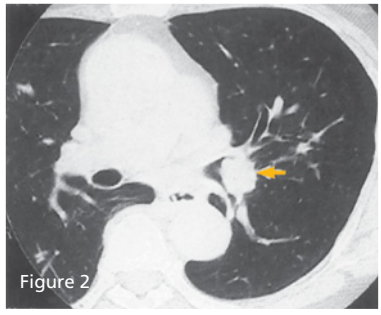
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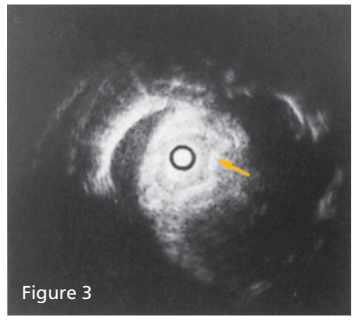


Figure 3

## Case 18

Mucoepidermoid carcinoma arising from the origin of the right lower lobe bronchus (difficult evaluation of the depth of tumor invasion).

Mucoepidermoid carcinoma at the origin of the right lower lobe bronchus.

### Presenting Complaint: Abnormal Opacity Seen on Plain Chest Radiograph During Hospital Admission

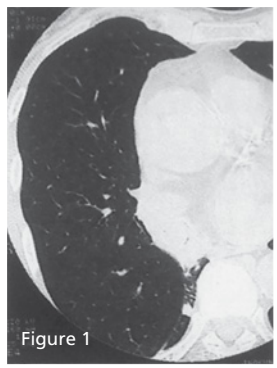
*History:* Transferred after right lower lobe atelectasis seen by previous doctor in plain chest radiograph during hospital admission.

CT scan chest (Figure 1): A tumor can be seen almost completely obstructing the lumen at the origin of the right intermediate bronchus.

Bronchoscopic findings (Figure 2): A pale tumor can be seen obstructing the right intermediate bronchus. Biopsy showed mucoepidermoid carcinoma.

EBUS findings: We used an UM-3R ultrasonic probe. The laminar structure of the bronchial wall was difficult to visualize in this case because the tumor was located in the right intermediate bronchus obstructing the right lower lobe bronchus, thereby attenuating the ultrasound pulse before it reached the bronchial wall (Figures 3, 4, 5). This tumor in fact arose from the bronchial spur between $B^7$ and $B^{10}$ bronchi, invading the right intermediate bronchus from outside. An anechoic region within the tumor was thought to represent an area of necrosis (red arrow, Figure 3). An extramural area of different echodensity to the intrabronchial tumor (red arrow, Figure 4) was though to correspond to the atelectasis.

In cases such as this where a tumor obstructs a large bronchus, attenuation of the ultrasound waves makes it difficult to visualize the laminar structure of the bronchial wall, or evaluate the depth of tumor invasion.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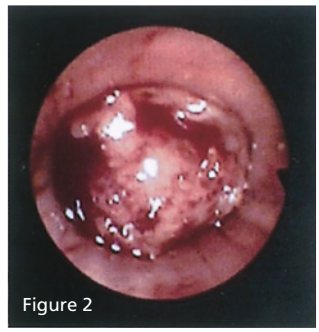
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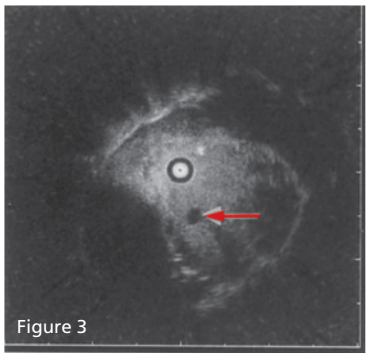
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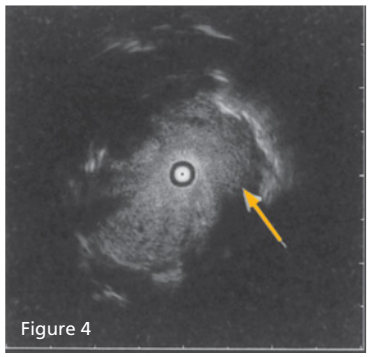
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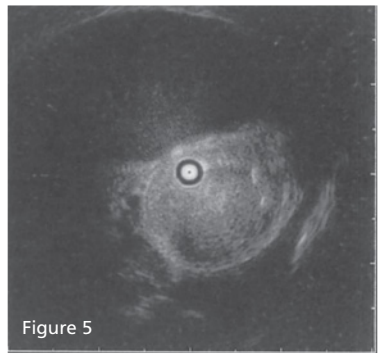


Figure 5

## Case 19

Comparison of EBUS findings of right #11i lymph node with intraperative findings.

Poorly differentiated squamous cell carcinoma of the right lower lobe.

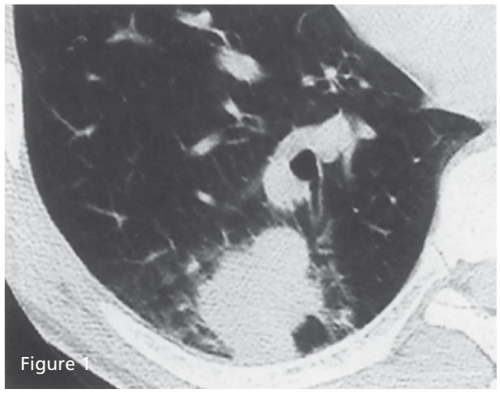
### Presenting Complaint: Abnormal Opacity Seen on Plain Chest Radiography at a Routine Health Check

*History:* Abnormal opacity seen on plain chest radiography at a routine health check. CT scanning and bronchoscopy revealed a poorly differentiated squamous cell carcinoma in the right lower lobe $S^{10}$ region. A class V squamous cell carcinoma was diagnosed from the endobronchial brushing cytology. The patient underwent right lower lobectomy + $R^2$a: t2n0m0, stage IB.

CT scan chest: A mass can be seen in the right lower lobe $S^{10}$ region (Figure 1). Although it measures less than 1 cm on its minor axis, the right #11i lymph node can be identified (Figure 2).

Preoperative EBUS findings (Figure 3): We used an UM-3R ultrasonic probe + balloon, inflating the balloon in the right lower lobe bronchus. The pulmonary artery (PA) 7-10 can be seen between 12 o'clock and 3 o'clock, and to its left the right #11i lymph node (arrow), measuring 11.9 × 10.4 mm.

Intraoperative findings (Figure 4): The lower part of this photograph is the caudal direction. Somewhat distally placed outside the right middle lobe bronchus, we can see the #11i lymph node, next to PA 7-10, in agreement with the EBUS findings. The #11i lymph node was negative for metastasis.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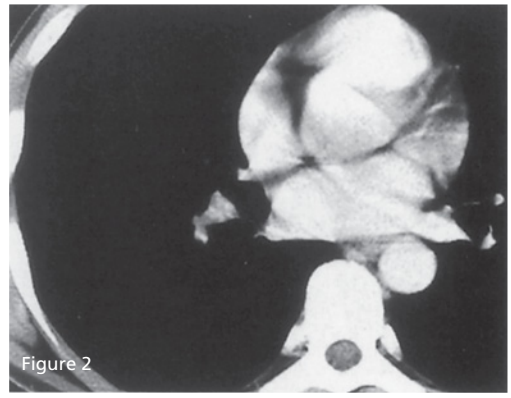
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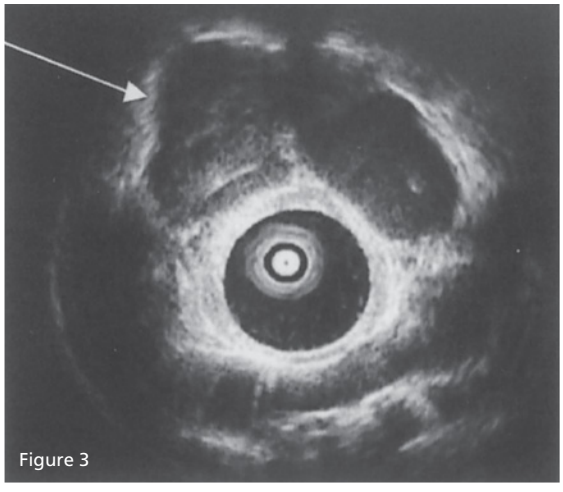
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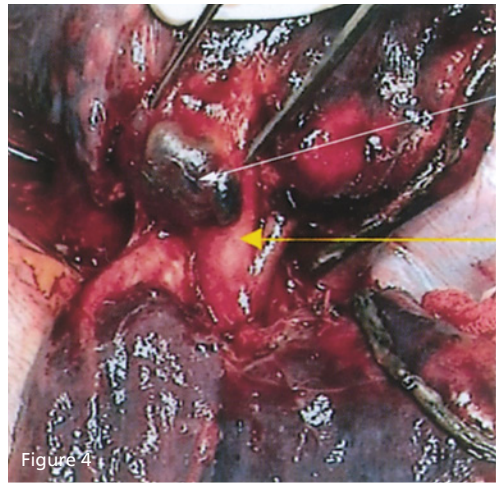


Figure 4

## Case 20

Right #10 lymph node and bronchial artery identified using EBUS.

Poorly differentiated squamous cell carcinoma of the right lower lobe.

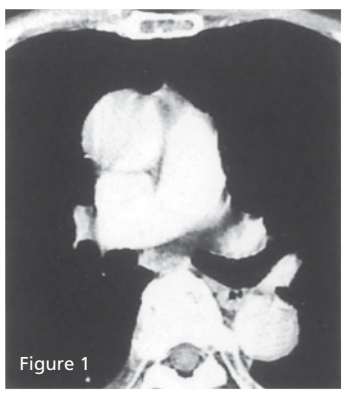
### Presenting Complaint: Abnormal Opacity on CT Scan Chest Following Surgery for Colorectal Cancer

*History:* Abnormal opacity seen on follow-up CT scan chest 4 years after surgery for rectal cancer. CT scanning and bronchoscopy revealed a poorly differentiated squamous cell carcinoma in the right lower lobe $S^6$ region. A class V squamous cell carcinoma was diagnosed from the endobronchial brushing cytology. The patient underwent right lower lobectomy + $R^2$a: t1n0m0, stage IA.

CT scan chest: Although it measures less than 1 cm on its minor axis, the right #10 lymph node can be identified (Figure 1).

Preoperative EBUS findings (Figures 2, 3): We used an UM-3R ultrasonic probe + balloon, inflating the balloon in the right intermediate bronchus. The pulmonary artery can be seen at 12 o'clock. The right #10 lymph node can be seen at 9 o'clock, measuring 8.4 × 6.4 mm, triangular in shape. Two blood vessels are delineated running anterior to this lymph node (arrow), and a blood vessel running parallel to the bronchus can be seen in the vicinity.

Intraoperative findings (Figure 4): The lower part of this photograph is the caudal direction. The #10 lymph node can be seen attached to the right intermediate bronchus. This bronchial artery (arrow) seen intraperatively corresponds to the vessel seen using EBUS. The #10 lymph node was negative for metastasis.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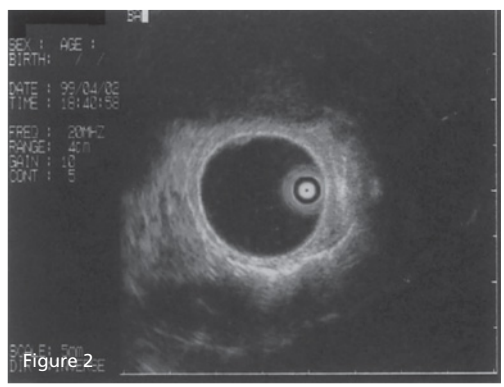
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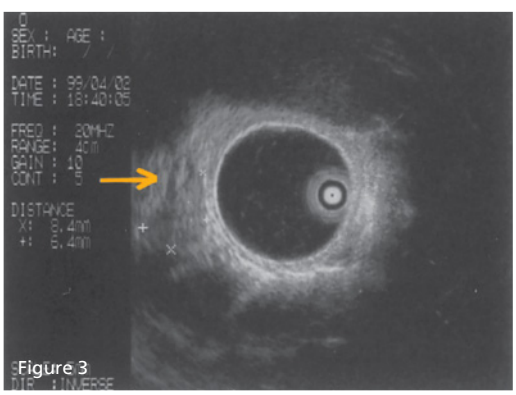
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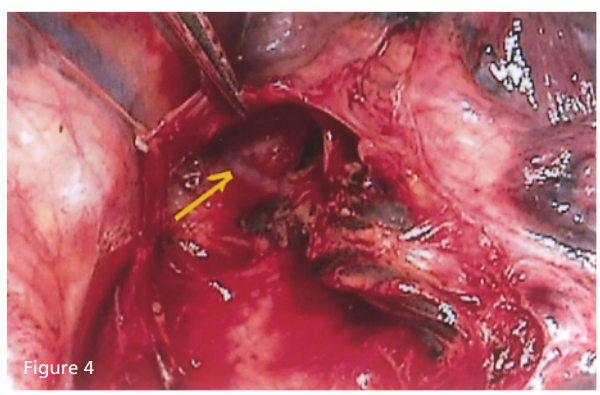


Figure 4

## Case 21

Subpleural organizing pneumonia (blood vessels delineated within the lesion).
Organizing pneumonia in the right $S^9$b region.

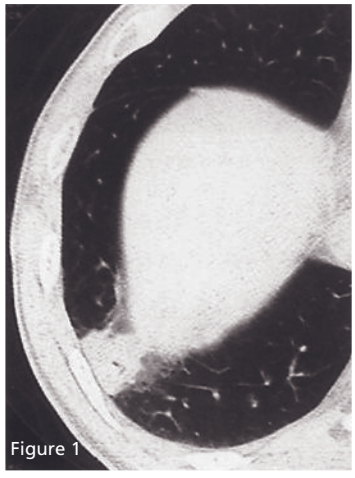
### Presenting Complaint: Cough

*History:* Presented to previous doctor with cough, abnormal opacity seen on plain chest radiograph. CT scanning and bronchoscopy confirmed an opacity in the right $S^9$b region. Transbronchial lung biopsy (TBLB) yielded the diagnosis of organizing pneumonia. Patient responded to oral antimicrobial therapy, with no abnormality on follow-up radiography 2 months later.

CT scan chest (Figure 1): A nodular opacity 18 mm in greatest diameter, containing an air bronchogram, can be seen at the right $S^9$b region.

EBUS findings (Figure 2): This lesion has a clearly delineated border, and patent blood vessels can be seen in several places. Hyperechoic points running alongside blood vessels represent patent bronchioles (arrow).

Findings of patent blood vessels distributed regularly throughout the lesion are characteristic of soft lesions such as pneumonia or organizing pneumonia.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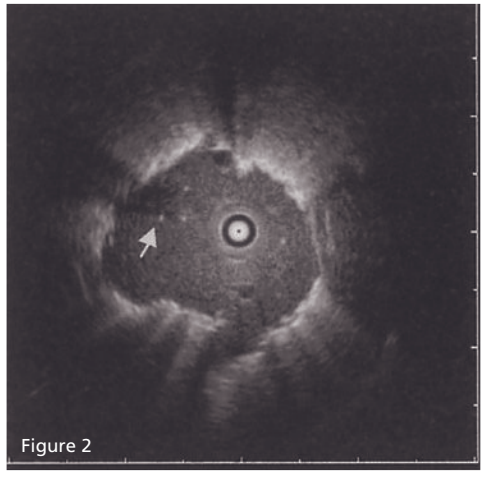


Figure 2

## Case 22

Organizing pneumonia (regularly distributed patent blood vessels).
Left $S^{10}$ organizing pneumonia.

### Presenting Complaint: Fever, Cough

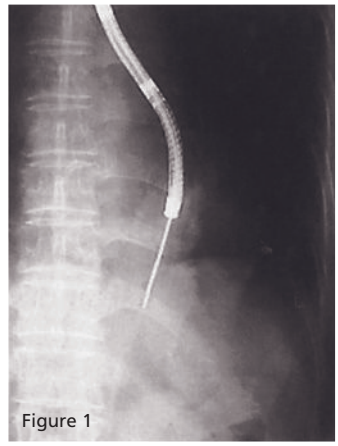
*History:* Presented to previous doctor with fever and cough, abnormal opacity seen on plain chest radiograph. CT scanning and bronchoscopy confirmed an opacity in the left $S^{10}$c region. TBLB yielded the diagnosis of organizing pneumonia.

Fluoroscopy at the time of EBUS (Figure 1): The UM-3R probe has passed down the bronchoscope instrument channel into the left B10c bronchus.

CT scan chest (Figure 2): A round nodular opacity 50 mm in greatest diameter can be seen in the left $S^{10}$c region.

EBUS findings (Figure 3): Although we were unable to define the boundaries of this lesion due to its size, blood vessels remained patent (arrow) throughout the lesion. No hyperechoic air-containing dots are seen, differentiating this lesion from a highly differentiated adenocarcinoma.

Findings of patent blood vessels distributed regularly throughout the lesion, and no hyperechoic air-containing dots, are characteristic of pneumonia or organizing pneumonia.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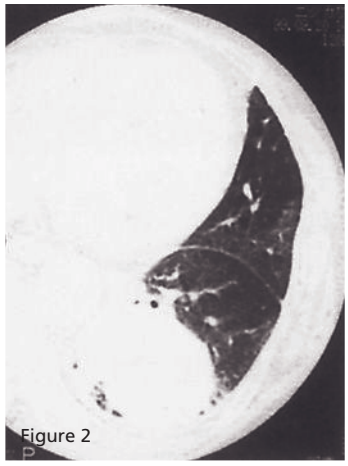
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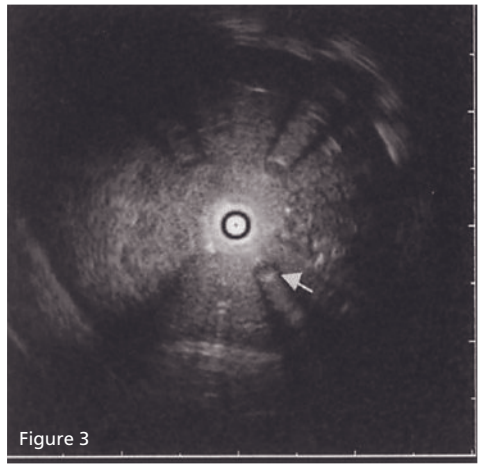


Figure 3

## Case 23

Tuberculoma (homogenous echo pattern with no patent vessels or bronchioles).
Tuberculoma in the left $S^{1+2}a$ region.

### Presenting Complaint: Abnormal Opacity Seen on Plain Chest Radiograph at Routine Health Check

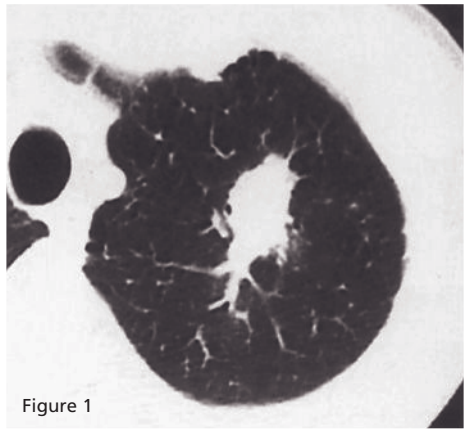
*History:* Abnormal opacity seen on plain chest radiograph at company health check 3 months earlier. Tuberculosis was diagnosed on the basis of a Gaffky rating 1 from bronchial washings obtained at bronchoscopy. Near resolution of the radiographic changes was achieved with antituberculosis therapy.

CT scan chest (Figure 1): A thin elongated nodular opacity 30 mm in greatest diameter can be seen in the left $S^{1+2}a$ region.

EBUS findings (Figure 2): This thin elongated lesion has a clearly delineated border. No blood vessels can be seen within the lesion, and the internal echoes are homogeneous with no hyperechoic points.

### Points of Advice

The EBUS findings for tuberculomas are varied, including the following possibilities: (1) no patent blood vessels, no hyperechoic points and homogeneous internal echoes; (2) microcalcifications; and (3) patent blood vessels and bronchioles as with pneumonia.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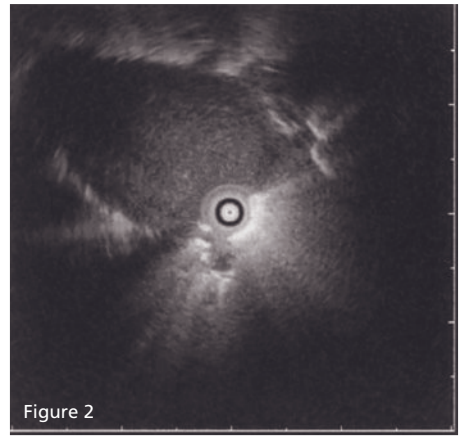


Figure 2

## Case 24

Cryptococcosis (regular distribution of blood vessels and bronchioles throughout the lesion).
Cryptococcosis in the right $S^6$ region.

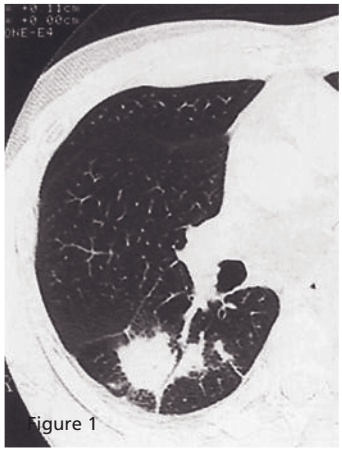
### Presenting Complaint: Abnormal Opacity Seen on Plain Chest Radiograph at Routine Health Check

*History:* Abnormal opacity seen on plain chest radiograph at company health check 1 month earlier. Cryptococcosis was diagnosed on the basis of TBLB obtained at bronchoscopy. Near resolution of the radiographic changes was achieved with 2 months antimicrobial therapy.

CT scan chest (Figure 1): A nodular opacity 30 mm in greatest diameter can be seen at the right $S^6$ region, with associated pleural indentation and air bronchogram.

EBUS findings (Figure 2): This lesion has a clearly delineated border, linear in places. Patent blood vessels can be seen throughout the lesion, accompanied by hyperechoic points corresponding to patent bronchioles. The internal echoes are homogenous.

Findings of patent blood vessels distributed regularly throughout the lesion, hyperechoic corresponding to patent bronchioles, and homogeneous internal echoes, are characteristic of inflammatory conditions.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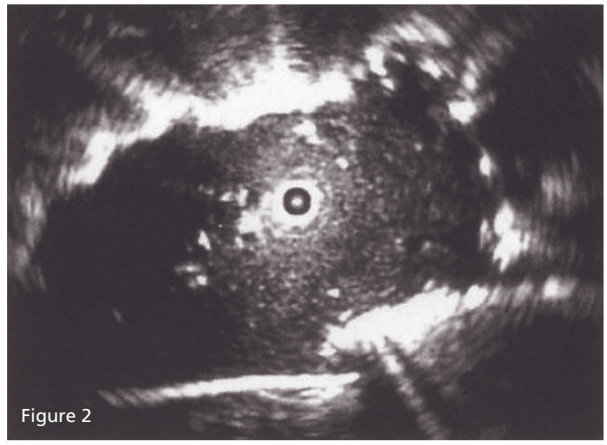


Figure 2

## Case 25

Organizing pneumonia (lesion with star-shaped border).

Organizing pneumonia in the right $S^4a$ region.

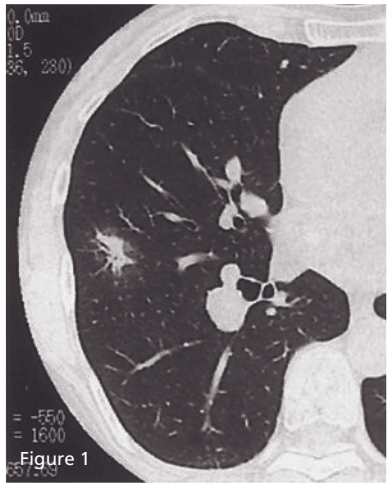
### Presenting Complaint: Abnormal Opacity Seen on Plain Chest Radiograph at Routine Health Check

*History:* Abnormal opacity seen on plain chest radiograph at municipal health check 1 month earlier. TBLB yielded the diagnosis of organizing pneumonia. Near resolution of the radiographic changes was confirmed 1 month later without treatment.

CT scan chest (Figure 1): A nodular opacity 15 mm in greatest diameter can be seen at the right $S^4a$ region.

EBUS findings (Figure 2): This lesion has a clearly delineated border, linear in places, forming a star-shape centred on the bronchus.

An irregular star-shaped pattern centred on a bronchus is characteristic of a peribronchial inflammatory condition such as organizing pneumonia.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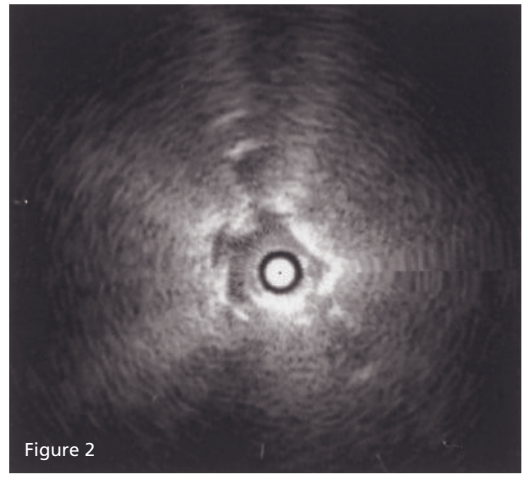


Figure 2

## Case 26

Organizing pneumonia (lesion with star-shaped border).
Inflammatory pseudotumor in the right $S^4$ region.

### Presenting Complaint: Fever

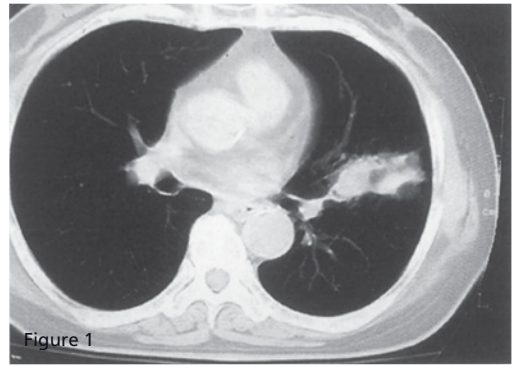
*History:* Presented to previous doctor with fever of 1 month's duration, referred with abnormal opacity seen on plain chest radiograph. Investigations including bronchoscopy TBLB failed to yield a definitive diagnosis. Due to persistent pyrexia and enlargement of the lesion, the patient underwent left lingulectomy.

CT scan chest (Figure 1): A nodular opacity 25 mm in greatest diameter can be seen at the left $S^4$ region, with an infiltrative pattern distally.

EBUS findings (Figure 2): This round lesion has a clearly delineated border, and contains a star-shaped anechoic area.

Histopathological examination (Figure 3): A fluid collection within the lesion, corresponding to the star-shaped anechoic area seen using EBUS, is the dilated bronchial lumen itself.

An irregular star-shaped anechoic area seen on EBUS sometimes corresponds to dilatation of a bronchus. We have also experienced some cases where an anechoic area corresponded to a necrotic area within a squamous cell carcinoma.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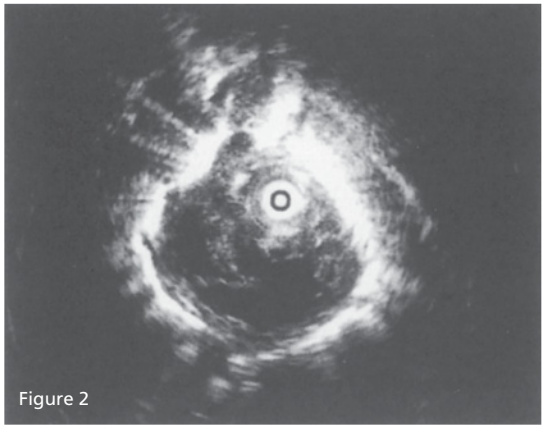
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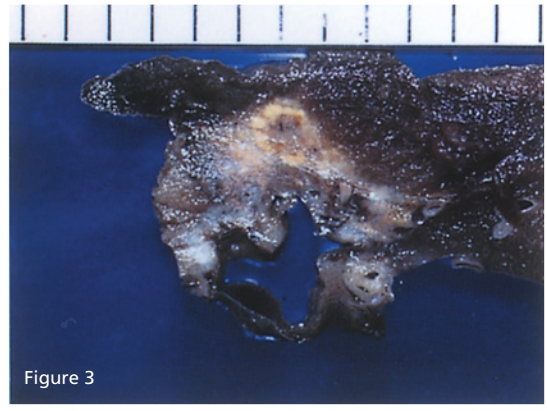


Figure 3

## Case 27

Well-differentiated adenocarcinoma containing air and blood vessels.

Well-differentiated adenocarcinoma (papillary type, Noguchi C 17 mm) of the left $S^9$ region.

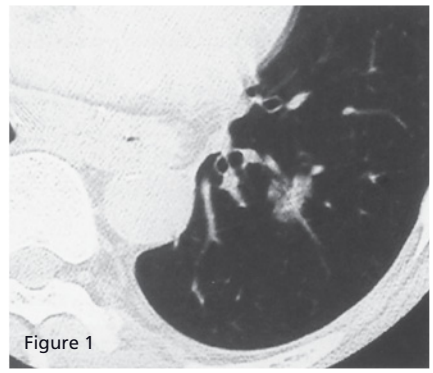
### Presenting Complaint: Abnormal Opacity Seen on Chest CT Scan

*History:* Ground-glass opacity detected in the left lower lobe on CT scan chest at the time of surgery for esophageal cancer. Priority was given to the surgery, as the esophageal cancer was advanced, and the abnormal opacity was observed with CT scanning. The left lower lobe ground-glass opacity had increased in size from 15 mm to 17 mm after 1 year, so the patient then underwent left lower lobectomy + $R^1$: sT1N0M0, P0, D0, E0, PM0: c-stage IA.

CT scan chest (Figure 1): A localized ground-glass opacity of largest diameter 17 mm, with increased density centrally, can be seen in the left $S^9$a region.

Preoperative EBUS findings (Figure 2): The target lesion was rounded with well-defined margins. It contains a ribbon-like hypoechoic structure, thought to be a blood vessel (arrow). Multiple hyperechoic points are scattered irregularly throughout the lesion.

Histopathological examination (low magnification, Figure 3): The target lesion is a well-differentiated adenocarcinoma (papillary type, Noguchi C) of the left $S^9$ bronchus, with central fibrosis, and growing out replacing the alveolar mucosa. In this specimen, sliced in the same plane as the EBUS image, we can see a bronchial artery, 0.7 mm in diameter, passing through the lesion corresponding to the ribbon-like hypoechoic structure in the EBUS image (arrow). The hyperechoic points in the EBUS image correspond to alveolar air, trapped within the tumor as it invades the alveoli.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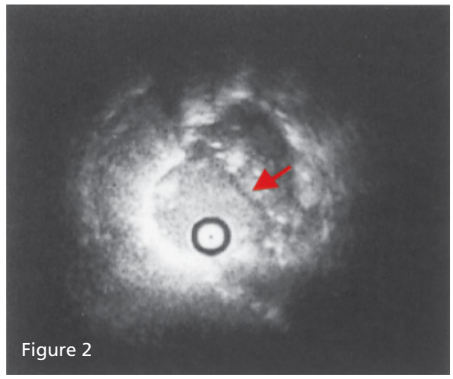
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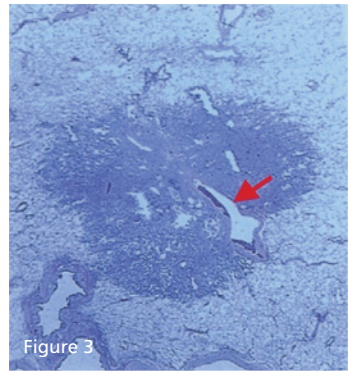


Figure 3

## Case 28

Well-differentiated adenocarcinoma (blood vessels and hyperechoic points distributed irregularly through the lesion).

Well-differentiated adenocarcinoma (papillary type) of the right $S^1$ region.

### Presenting Complaint: Abnormal Opacity Seen on Plain Chest Radiograph

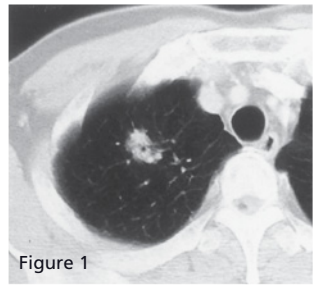
*History:* Nodular opacity detected in the right upper lobe on plain chest radiograph at company health check. The patient underwent right upper lobectomy + $R^2$a: sT1N0M0, P0, D0, E0, PM0: c-stage IA. We compared the preoperative EBUS images and the histopathological findings.

CT scan chest (Figure 1): A nodular opacity of largest diameter 20 mm, with a central air bronchogram, can be seen in the right S1 region.

Preoperative EBUS findings (Figures 2, 3): The margins of the target lesion are well-defined but irregular. It contains a ribbon-like hypoechoic structure, thought to be a blood vessel passing through the lesion (arrow). Multiple hyperechoic points are scattered irregularly throughout the lesion.

Histopathological examination (low magnification): The target lesion is a well-differentiated adenocarcinoma (papillary type). In this specimen, sliced in the same plane as the EBUS image, we can see a bronchial artery, 0.65 mm in diameter, corresponding to the ribbon-like hypoechoic structure in the EBUS image (Figure 2, arrow). The hyperechoic points in the EBUS image correspond to alveolar air, trapped within the tumor as it invades the alveoli (Figure 3, arrow).

Hyperechoic lines and points are also seen in EBUS images of inflammatory conditions, but they are regularly distributed in inflammatory conditions, and tend to be irregularly distributed in neoplastic lesions. When a patent blood vessel is seen passing through a tumor in the EBUS image, this indicates that the tumor is relatively soft, and suggests it is likely to be well-differentiated.



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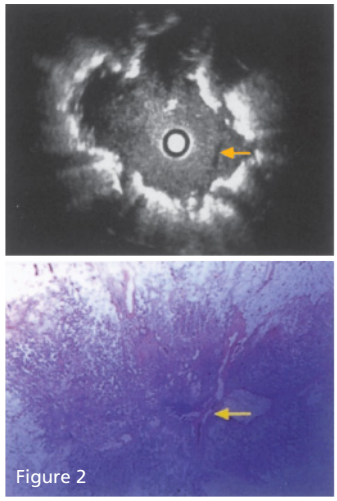

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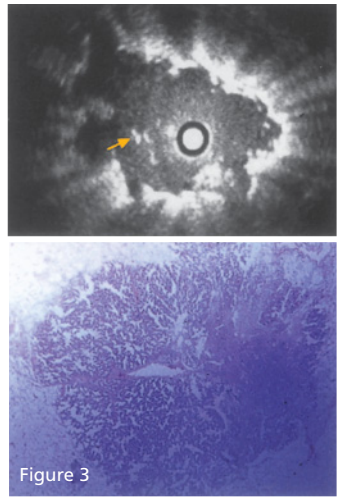


Figure 3

## Case 29

Well-differentiated adenocarcinoma with indistinct margins.
Well-differentiated adenocarcinoma (papillary type) of the left $S^5$ region.
19 × 18 × 18 mm.

### Presenting Complaint: Abnormal Opacity Seen on Plain Chest Radiograph

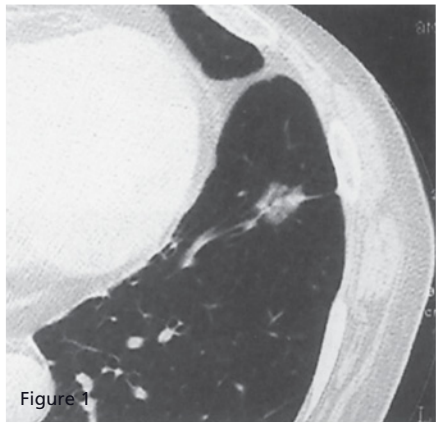
*History:* Nodular opacity detected in the left middle lungfield on plain chest radiograph at company health check. The patient underwent left upper lobectomy + $R^2$a: sT1N0M0, P0, D0, E0, PM0: s-stage IA. We compared the preoperative EBUS images and the histopathological findings.

CT scan chest (Figure 1): A nodular opacity of largest diameter 18 mm can be seen in the left $S^5$ region, associated with pleural indentation.

Preoperative EBUS findings (Figure 2): The margins of the target lesion are indistinct. Multiple hyperechoic points are scattered irregularly throughout the lesion.

Histopathological examination (low magnification, Figure 3): The target lesion is a well-differentiated adenocarcinoma (papillary type) with central fibrosis. The hyperechoic points in the EBUS image correspond to alveolar air, trapped within the tumor as it invades the alveoli.

The reason the margins of this tumor were indistinct is because it invades by replacing alveolar mucosa, trapping alveolar air as it spreads peripherally.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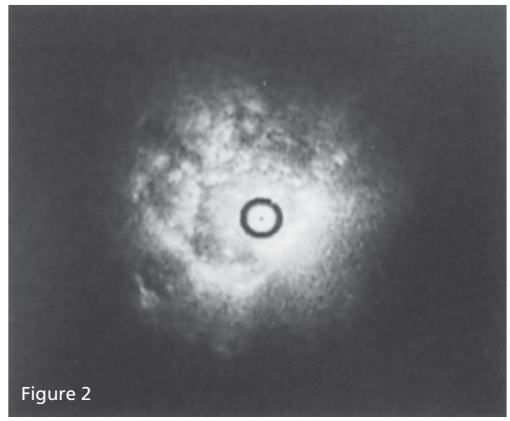
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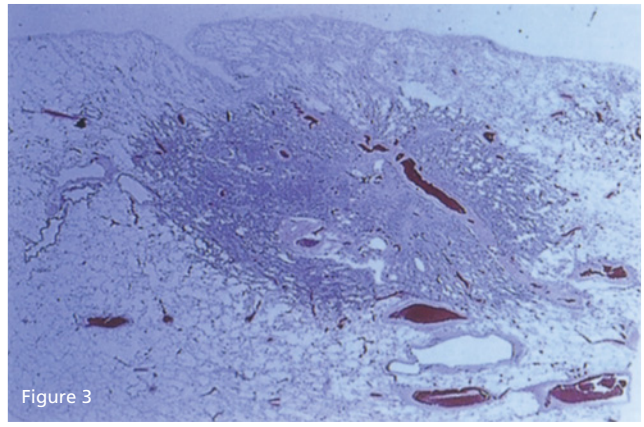


Figure 3

## Case 30

Moderately differentiated adenocarcinoma (with indistinct margins and hyperechoic points distributed irregularly through the lesion).
Moderately differentiated adenocarcinoma of the left $S^3$a region.
1.5 × 1.5 × 1.0 cm.

### Presenting Complaint: Abnormal Opacity Seen on Plain Chest Radiograph at Municipal Health Check

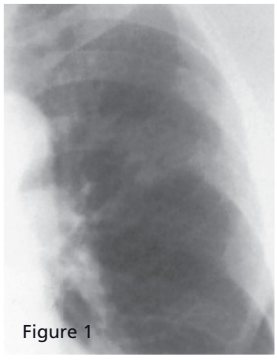
*History:* Abnormal opacity seen on plain chest radiograph at company health check. TBLB yielded the diagnosis of adenocarcinoma, and the patient underwent left upper lobectomy + $R^2$a: sT1N0M0, P0, D0, E0, PM0: s-stage IA. We compared the preoperative EBUS images and the histopathological findings.

Plain chest radiograph, CT scan chest (Figures 1, 2): A nodular opacity of largest diameter 15 mm can be seen at the boundary of the left $S^3$a and b regions, some areas containing air.

Preoperative EBUS findings (Figures 3, 4): The margins of the target lesion are well-defined but irregular. Multiple hyperechoic lines and points are scattered irregularly throughout the lesion.

Histopathological examination (low magnification, Figure 5): The target lesion is a moderately differentiated adenocarcinoma (papillary type) with central fibrosis, invades by replacing alveolar mucosa as it spreads peripherally.

The hyperechoic lines and points in the EBUS image correspond to air trapped inside bronchioles and alveoli within the tumor.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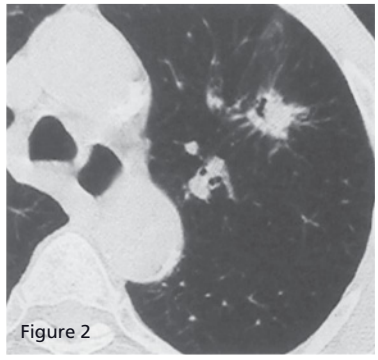
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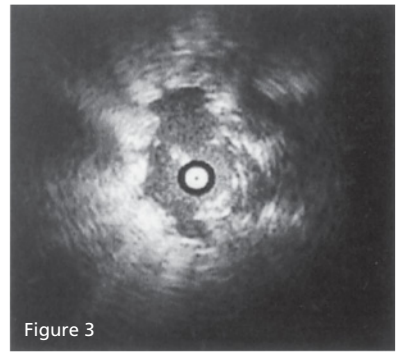
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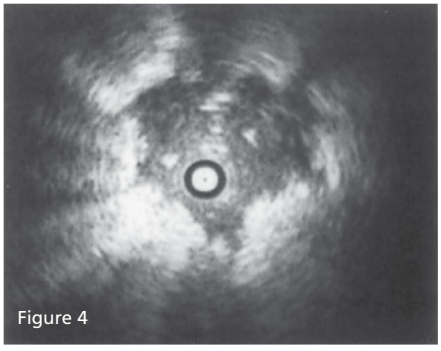
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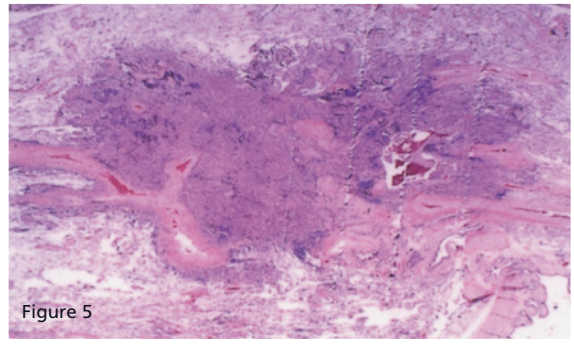


Figure 5

## Case 31

Moderately differentiated adenocarcinoma (two blood vessels entering the lesion detected).
Moderately differentiated adenocarcinoma of the right $S^5$b region.

### Presenting Complaint: E Result from Sputum Cytology at Municipal Health Check

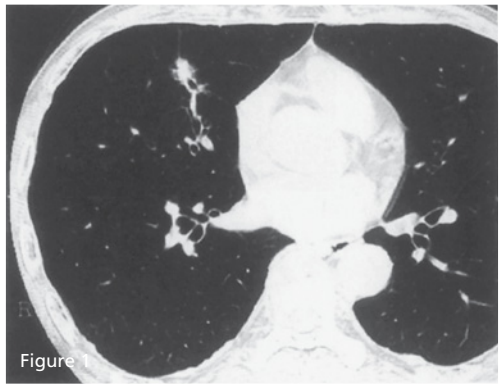
*History:* Adenocarcinoma cells detected on sputum cytology at municipal health check. The patient underwent right middle lobectomy + $R^2$a: sT1N0M0, P0, D0, E0, PM0: s-stage IA. We compared the preoperative EBUS images and the histopathological findings.

CT scan chest (Figure 1): A nodular opacity of largest diameter 15 mm can be seen in the right $S^5$b region.

Preoperative EBUS findings (Figure 2): At the first bronchoscopy, the endobronchial cytology brush passed through the lesion, and a definitive diagnosis could not be obtained. At the second attempt, we were able to vizualize the lesion using a UM-3R probe with a guide sheath. The margins of the target lesion are well-defined but irregular. At the edge of the lesion, we can see two round hypoechoic structures, thought to be blood vessel passing through the lesion (yellow arrows). Leaving the guide sheath in position, we removed the ultrasonic probe, introduced an endobronchial cytology brush into the guide sheath, and we were able to identify adenocarcinoma cells from the brushings.

Histopathological examination (low magnification, Figure 3): The target lesion is a moderately differentiated adenocarcinoma. In this specimen, sliced in the same plane as the EBUS image, we can see two bronchial arteries in the periphery of the tumor, corresponding to the two round hypoechoic structures in the EBUS image (yellow arrows).

One of the merits of EBUS for periphery pulmonary lesions is that it can be used in the place of fluoroscopy to identify the location of a lesion.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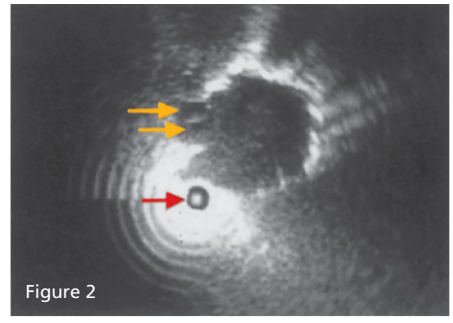


Figure 2

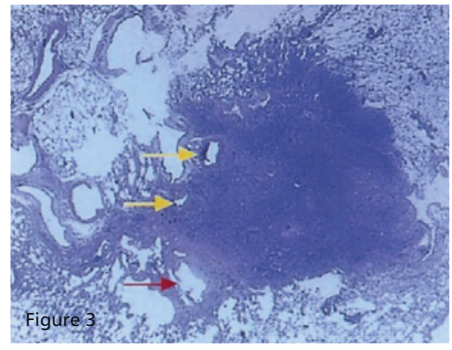


Figure 3

## Case 32

Moderately differentiated adenocarcinoma (detectable using EBUS, but not fluoroscopy).

Moderately differentiated adenocarcinoma of the left $S^3$a region.

### Presenting Complaint: Abnormal Opacity Seen on Plain Chest Radiograph at Municipal Health Check

*History:* A nodular opacity was seen in the left $S^3$a region on plain chest radiograph at municipal health check. A class V adenocarcinoma was diagnosed from the endobronchial brushing cytology. The patient underwent left upper lobectomy + $R^2$a: sT1N0M0, P0, D0, E0, PM0: s-stage IA. We compared the preoperative EBUS images and the histopathological findings.

CT scan chest (Figure 1): A nodular opacity of largest diameter 20 mm can be seen in the left $S^3$a region. The tumor was surrounded by hemorrhage from the tumor that had been taken up by the nearby alveoli.

Fluoroscopy at the time of EBUS (Figure 2): Although the nodular opacity could not be seen under fluoroscopy, the probe introduced into the left $B^3$a bronchus was successful in delineating the target lesion.

Preoperative EBUS findings (Figure 3): The margins of the target lesion are well-defined but irregular. A plaque-shaped hyperechoic area can be seen in one part of the lesion, but the majority of the target lesion shows an irregular heterogeneous internal echo pattern, with no blood vessels or hyperechoic areas.

Histopathological examination (low magnification, Figure 4): The target lesion is a moderately differentiated adenocarcinoma. It is a highly cellular tumor, with only one air-containing area. The plaque-shaped hyperechoic area corresponded to compressed blood vessels and bronchioles.

One of the merits of EBUS for periphery pulmonary lesions is that it can be used in the place of fluoroscopy to identify the location of a lesion.

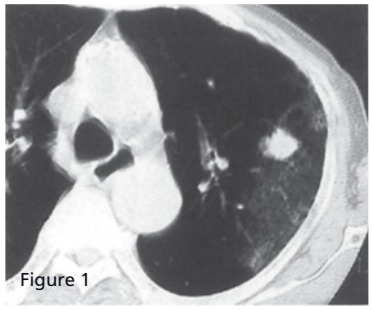
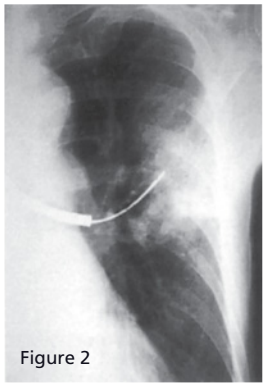


Figure 1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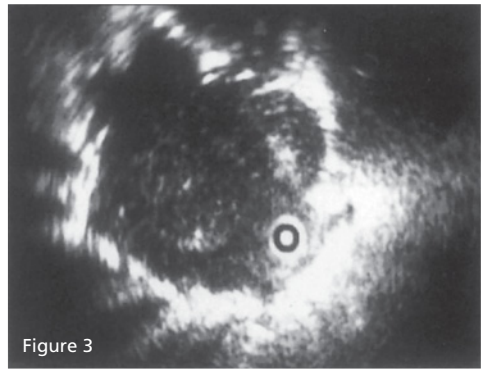
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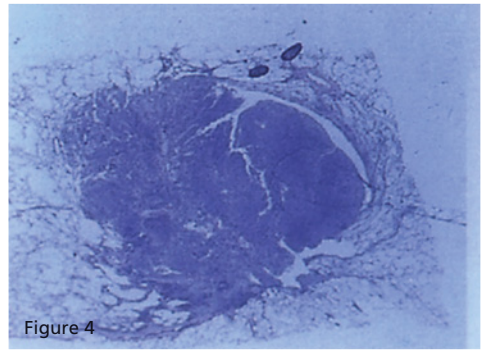


Figure 4

## Case 33

Poorly differentiated adenocarcinoma (no blood vessels or bronchioles detectable within the lesion).

Poorly differentiated adenocarcinoma of the right $S^5b$ region.

### Presenting Complaint: Abnormal Opacity on CT Scan Chest During Follow-Up after Surgery for Left Lower Lobe Moderately Differentiated Adenocarcinoma

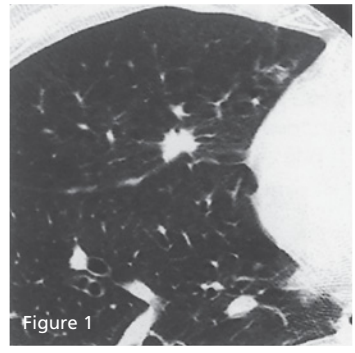
*History:* The patient underwent left lower lobectomy (t2n0m0, stage IB) for left lower lobe moderately differentiated adenocarcinoma. An 8 mm opacity was seen in the right $S^5b$ region on follow-up CT scan chest 3 years 6 months after surgery. The patient underwent right middle lobectomy + $R^2a$: t1n2m0, stage IIIA. We compared the preoperative EBUS images and the histopathological findings.

CT scan chest (Figure 1): A nodular opacity of largest diameter 8 mm can be seen in the right $S^5b$ region, drawing in the adjacent pleura.

Preoperative EBUS findings (Figure 2): We introduced an UM-3R ultrasonic probe into the right $S^5b$ bronchus, and visualized the target lesion. The margins of the target lesion are well-defined but irregular. Collapse of the pleural surface has been delineated (arrow). No blood vessels, hyperechoic spots or lines can be seen.

Histopathological examination (low magnification, Figure 3): The target lesion is a poorly differentiated adenocarcinoma. It is a solid tumor, with no air-containing areas.

EBUS findings of no blood vessels or hyperechoic spots within a lesion are characteristic of poorly differentiated adenocarcinoma.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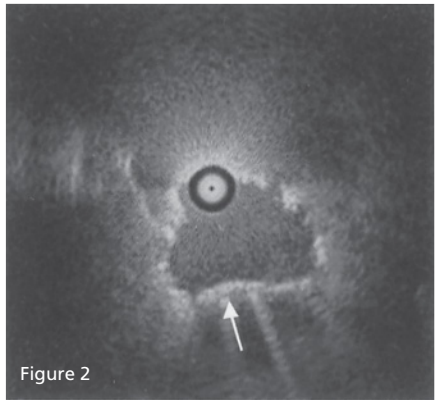
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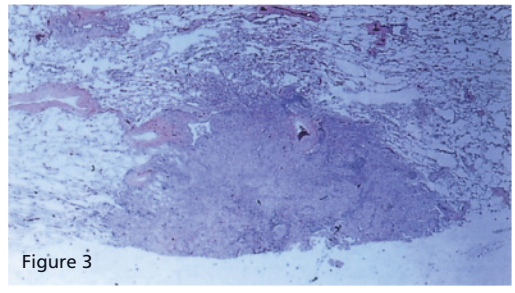


Figure 3

## Case 34

Poorly differentiated adenocarcinoma (no blood vessels or bronchioles detectable within the lesion).
Poorly differentiated adenocarcinoma of the right $S^3b$ region.

### Presenting Complaint: Abnormal Opacity on CT Scan Chest

CT scan chest (Figure 1): A nodular opacity of largest diameter 30 mm can be seen in the right $S^3b$ region.

EBUS findings (Figure 2): We introduced an UM-3R ultrasonic probe into the right $S^3b$ bronchus, and vizualized the target lesion. The margins of the target lesion are well-defined. No blood vessels, hyperechoic spots or lines can be seen.

EBUS findings of no blood vessels or hyperechoic spots within a lesion are characteristic of poorly differentiated adenocarcinoma.

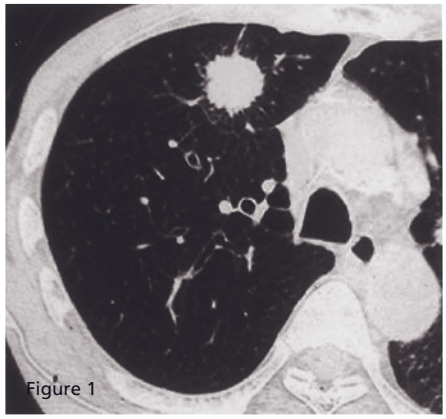


Figure 1

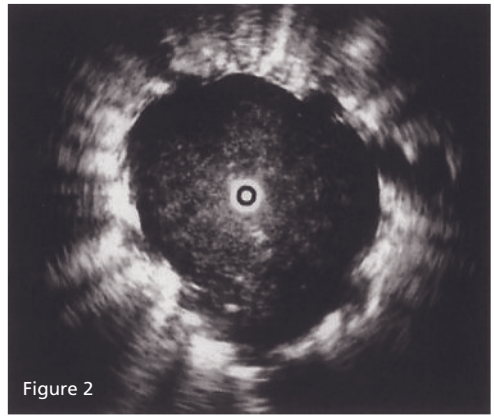


Figure 2

## Case 35

Moderately differentiated squamous cell carcinoma (hyperechoic spots caused by tumor invasion of emphysematous area).

Moderately differentiated squamous cell carcinoma in the left $S^9$ region.

$25 \times 22 \times 20$ mm.

### Presenting Complaint: Abnormal Opacity Seen on Plain Chest Radiograph at Municipal Health Check

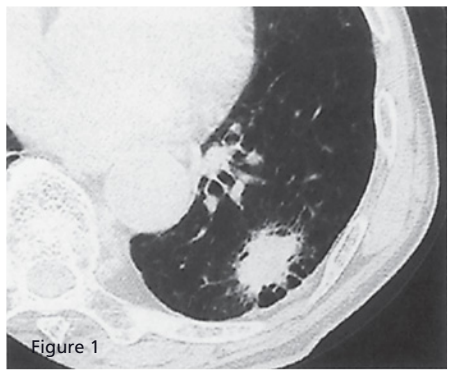
*History:* Abnormal opacity seen on plain chest radiograph at municipal health check. CT scanning and bronchoscopy revealed a nodular lesion in the left $S^9$ region. A class V squamous cell carcinoma was diagnosed from the endobronchial brushing cytology. The patient underwent left lower lobectomy + $R^2$a: sT1N1M0, P0, D0, E0, PxM0: c-stage IIA. We compared the preoperative EBUS images and the histopathological findings.

CT scan chest (Figures 1, 2): A nodular opacity of largest diameter 25 mm can be seen in the left $S^9$a region, invading the adjacent emphysematous lung.

Preoperative EBUS findings (Figure 3): The margins of the target lesion are indistinct, with no identifiable border. A few hyperechoic points, reflecting the presence of air, can be seen in the central part of the lesion, and some hyperechoic points are scattered irregularly around the tumor margins.

Histopathological examination (low magnification, Figure 4): This is a squamous cell carcinoma with a tendency in one area towards keratinisation, forming invasive nests if large and small irregular sheets as it proliferates. At its periphery, it invades the adjacent emphysematous lung.

The hyperechoic points in the EBUS image correspond to air contained in emphysematous lung that has been invaded at the periphery of the tumor.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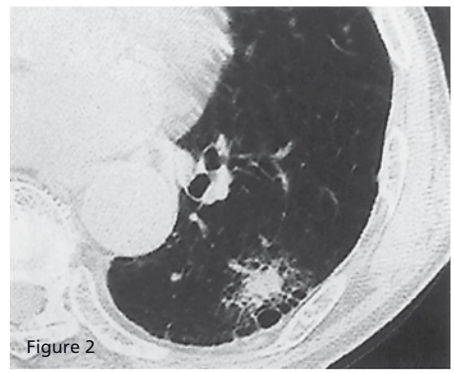
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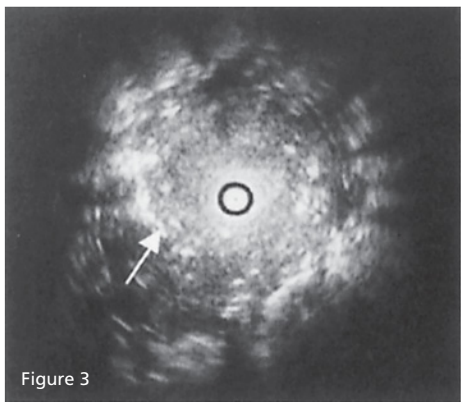
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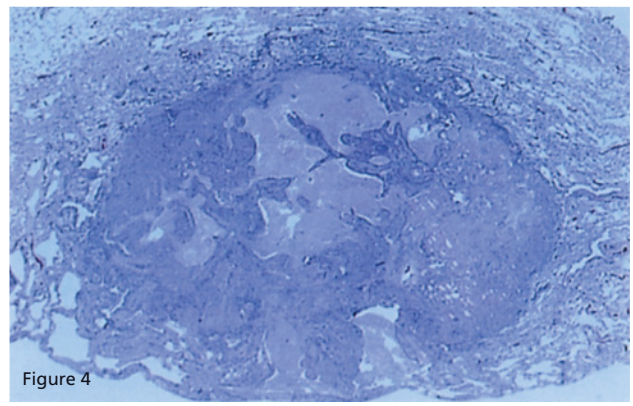


Figure 4

## Case 36

Metastatic squamous cell carcinoma (areas of cystic change within the tumor).

Metastatic squamous cell carcinoma in the left lower lobe.

### Presenting Complaint: Abnormal Opacity Seen on Plain Chest Radiograph after Surgery for Cancer of the Floor of the Mouth

*History:* Abnormal opacity seen on plain chest radiograph during follow-up after surgery for cancer of the floor of the mouth. Bronchoscopy revealed a nodular lesion in the left $S^9$ region. Class V squamous cell carcinoma, thought to be metastatic oral cancer, was diagnosed from the endobronchial brushing cytology. The patient underwent left lower lobectomy + $R^2$.

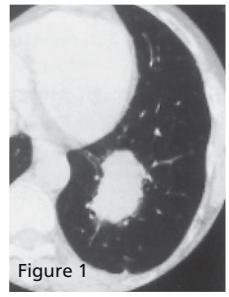
We compared the preoperative EBUS images and the histopathological findings.

CT scan chest (Figure 1): A nodular opacity of largest diameter 45 mm can be seen in the left lower lobe, compressing the pulmonary artery at its edge.

Preoperative EBUS findings (Figures 2, 3): The margins of the target lesion are well-defined but irregular. Multiple round anechoic areas are seen within the lesion.

Histopathological examination (low magnification, Figure 4): This is a squamous cell carcinoma with a tendency in one area towards keratinization, forming invasive nests if large and small irregular sheets as it proliferates, consistent with metastatic oral cancer. Multiple necrotic fluid filled cysts are seen within this tumor.

The multiple round anechoic areas in the EBUS image correspond to the histopathological finding of necrotic fluid-filled cysts.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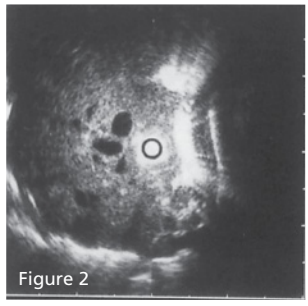
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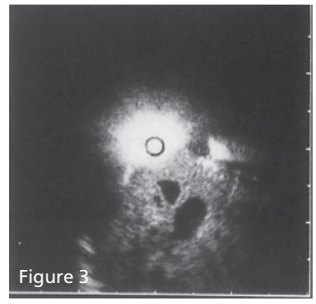
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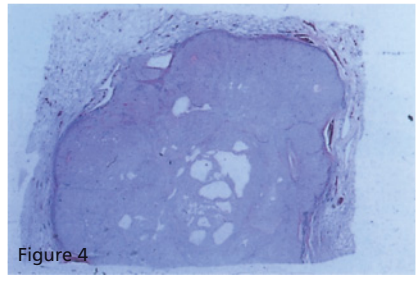


Figure 4

## Case 37

Small cell carcinoma in a peripheral bronchus (direct invasion of adjacent pulmonary artery).
Small cell carcinoma (intermediate type) in the left $S^8$a region.
15 × 10 × 5 mm

### Presenting Complaint: Abnormal Opacity Seen on Plain Chest Radiograph At Municipal Health Check

*History:* Abnormal opacity seen on plain chest radiograph at municipal health check. The patient then underwent left lower lobectomy + $R^2$a: s-T1N0M0, s-stage IA.

CT scan chest (Figure 1): An elongated nodular opacity of largest diameter 15 mm can be seen in the left $S^8$a region.

Preoperative EBUS findings (Figure 2): The target lesion was rounded with well-defined margins. At its periphery it contains a ribbon-like hypoechoic structure, thought to be a blood vessel passing through the lesion (arrow).

Histopathological examination (low magnification, Figure 3): The target lesion is a small cell carcinoma, intermediate type. In this specimen, sliced in the same plane as the EBUS image, we can see a pulmonary artery corresponding to the ribbon-like hypoechoic structure in the EBUS image (arrow).

The findings in this case were of a small cell carcinoma, arising in the bronchial wall, directly invading a pulmonary artery running beside the bronchus.

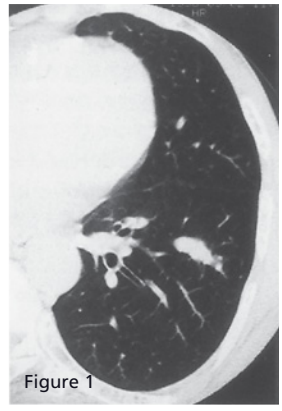
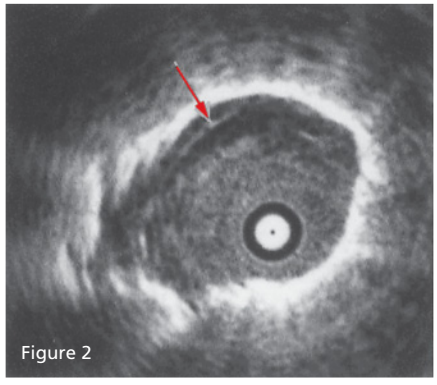


Figure 1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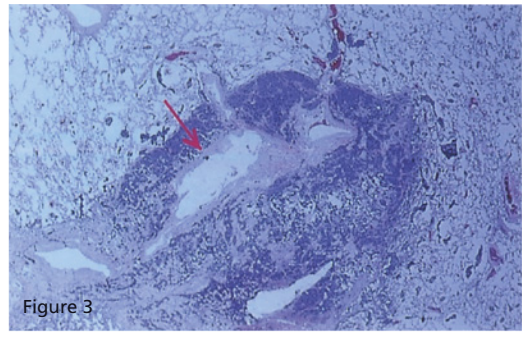


Figure 3

## Case 38

A snowman-shaped carcinoid tumor.
Typical carcinoid in the left $S^{1+2}c$ region.

### Presenting Complaint: Enlargement of Abnormal Opacity Seen on Plain Chest Radiograph During Follow-Up for Diabetes Mellitus

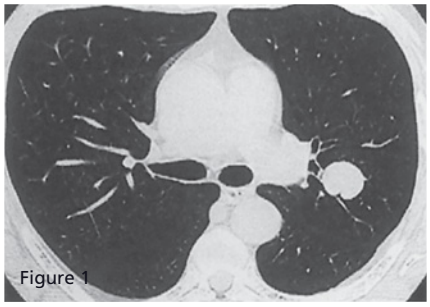
*History:* Abnormal opacity seen on plain chest radiograph during follow-up for diabetes mellitus with previous doctor 2 years earlier. Referred this year with enlargement of the opacity. Bronchoscopy and biopsy yielded the diagnosis of typical carcinoid in the left $S^{1+2}c$ region. The patient then underwent left upper lobectomy + $R^2a$: t1n0m0, stage IB.

CT scan chest (Figure 1): A snowman-shaped nodular opacity can be seen in the left $S^{1+2}c$ region.

Bronchoscopic findings (Figure 2): A polypoid lesion is seen obstructing the right $B^{1+2}c$ bronchus.

Preoperative EBUS findings (Figures 3, 4): We introduced an UM-3R ultrasonic probe into the left B1 + 2c bronchus between the polypoid lesion and the bronchial wall. The tumor is snowman-shaped (Figure 4), with a hyperechoic line at the snowman's neck corresponding to the bronchial cartilage (Figure 3). Hyperechoic plaques are seen within the lesion (arrow).

Histopathological examination (Figure 5): The target lesion is snowman-shaped. Bronchial cartilage corresponds to the hyperechoic line at the snowman's neck, indicating that the tumor has invaded the bronchial wall from the lumen. The hyperechoic plaques correspond to hemorrhagic foci.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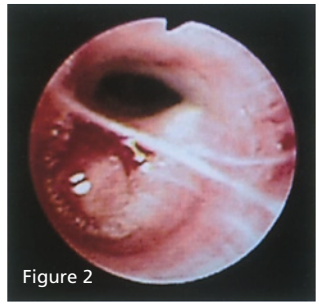
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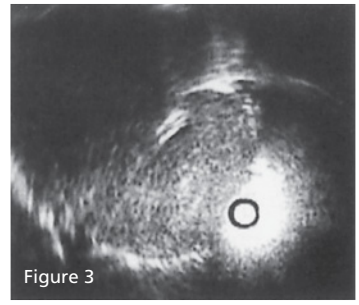
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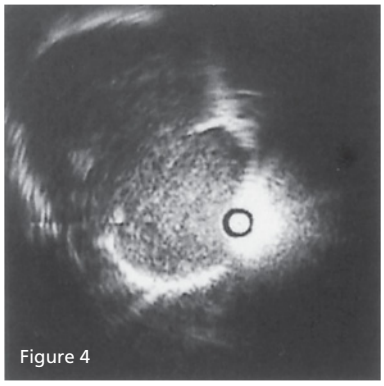
Figure 4

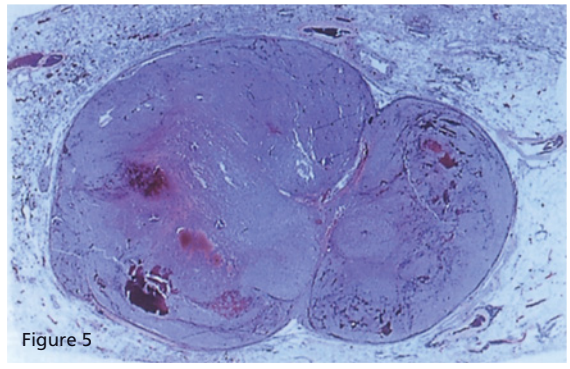
Figure 5

## Conclusion

### Analysis of internal structures in peripheral pulmonary lesions using EBUS

Our experience with a large number of cases has shown us that with EBUS we can visualize the internal structures in peripheral pulmonary lesions. Analysis of the cases where we were able to compare EBUS images with the histopathological findings showed that EBUS can delineate the following structures (Figure 1):

**1** Blood vessels (with diameters greater than 0.65 mm as measured histopathologically).
**2** Normal bronchioles.
**3** Intratumor hemorrhage (carcinoid tumors).
**4** Calcification (moderately differentiated adenocarcinoma, papillary thyroid carcinoma metastases).
**5** Dilated bronchi (inflammatory pseudotumor).
**6** Multiple necrotic cysts (squamous cell carcinoma).
**7** Alveolar air (well-differentiated adenocarcinoma).

The following characteristics were seen in EBUS images related to the histological type and degree of differentiation of lung cancers:

**1** Well-differentiated adenocarcinoma: Hyperechoic dots and lines (usually less than 1 mm in size), representing alveolar air, are irregularly distributed though these lesions. Patent blood vessels may or may not be present.
**2** Moderately differentiated adenocarcinoma: Hyperechoic dots and lines (greater than 1 mm in size), representing compressed blood vessels and bronchioles, are see within these lesions. The internal echoes are heterogeneous. Patent blood vessels are rarely seen.
**3** Poorly differentiated adenocarcinoma: No hyperechoic dots or lines are seen within lesions, nor patent blood vessels. The internal echoes are heterogenous.
**4** Squamous cell carcinoma: Multiple necrotic cysts are seen. When a tumor is located between the hilum and pleura, the probe can be passed through the middle of the lesion (bronchial lumen) and the tumor can be seen to compress the bronchial cartilage and adventitia as it proliferates.
**5** Small cell carcinoma: Thickening of the submucosal tissue is seen due to tumor infiltration. Tumor sometimes involves a bronchial artery running alongside the affected bronchus.

With its superior tissue resolution, EBUS can delineate structures that cannot be visualized using CT or other imaging modalities. EBUS is a tool that can provide new information to the field of diagnostic imaging.

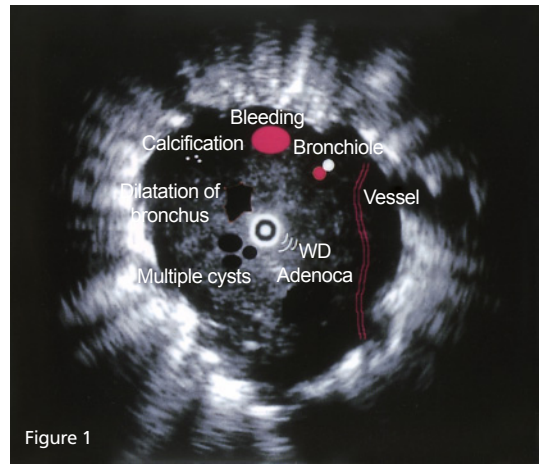

Figure 1

# Appendix: Videos

**Video clip A1:** *EBUS-TBNA for No.4L lymph node.*
0–0:6 seconds
A lymph node of No.4L was enlarged.
0:6–0:19 seconds
A lymph node of about 2cm in diameter was observed at A-P window between aortic arch and left pulmonary artery.
0:19–0:28 seconds
Power Doppler mode revealed vessels in the lymph node.
0:28–0:42 seconds
The TBNA needle was advanced into the tracheal wall.
0:42–0:53 seconds
We could see the real-time movement of the needle in the lymph node.
0:53–1:20 seconds
Seven or eight strokes of the movement of needle were performed.

**Video clip A2:** *EBUS-TBNA for No.12m lymph node.*
0–0:7 seconds
A lymph node of No.12m was enlarged.
0:7–0:13 seconds
The lymph node was located just beside the middle lobe bronchus.
0:13–0:28 seconds
The tip of the bronchoscope was introduced into the middle lobe bronchus.
0:28–0:51 seconds
The EBUS image revealed the enlarged lymph node beside the vessel.
0:51–1:07 seconds
Power Doppler mode revealed vessels in the lymph node.
1:07–1:17 seconds
After puncturing, the stylet was advanced into the end of the needle to prevent plugging of the bronchial wall.
1:17–1:31 seconds
The needle was moved back and forth in the lesion.

**Video clip A3:** *EBUS-TBNA for left No.10 lymph node with the Navigation System.*
0–0:6 seconds
A lymph node of left No.10 was enlarged.
0:6–0:35 seconds
The Navigation System (Olympus) showed the location of the target lymph node beside the left main bronchus.
0:35–0:55 seconds
The probe of the bronchoscope was attached at the inner surface beside the lymph node.
0:55–1:09 seconds
The lymph node was located between left main pulmonary artery and descending aorta.
1:09–1:20 seconds
The bronchoscopist decided the angle of the scope providing the largest area of the lymph node.
1:20–1:55 seconds
Using power Doppler mode, we should not puncture the bronchial artery outside the lymph node.

**Video clip A4:** *Lesion "peripheral" to EBUS miniprobe.*
70-year-old man with lesion in RS10. The EBUS-GS appearance is of a lesion "peripheral" to the probe. This would be expected to some extent based on the CT appearance. Biopsies showed adenocarcinoma.

**Video clip A5:** *Large white points on EBUS due to air spaces within consolidated lung.*
65-year-old man. EBUS GS biopsy showed bronchiolitis obliterans organizing pneumonia. Resolved with steroid treatment. Note the

*Endobronchial Ultrasonography,* 1st edition.
By Noriaki Kurimoto, David I. K. Fielding and Ali I. Musani.
Published 2011 by Blackwell Publishing Ltd.

large white areas around the probe at 1–2 o'clock, corresponding to the air spaces seen on CT.

**Video clip A6:** *Changing placement of miniprobe.*
Lesion in LUL. Notice first entry of EBUS miniprobe shows only the probe next to a pulmonary vessel (at 3 o'clock in relation to probe.) Probe then removed and placed in 1 subsegment laterally and clear difference in EBUS appearance is apparent with probe well-centered in 2 cm lesion.

**Video clip A7:** *Respiratory movement of EBUS probe in RB10a.*
(see enclosed JPEG)
55-year-old man with rounded lesion in S10. note on video there is a lot of respiratory movement, moving the EBUS probe (in RB10) in and out of the lesion. The lesion is homogenous and at the bottom of the lesion open vessels can be seen. Biopsies showed benign atelectasis; no change on CT with 4 years follow-up.
See accompanying CT.

# Index

Note: The following abbreviations are used in the index: EBUS: endobronchial ultrasonography; EUS-FNA: endoscopic ultrasound-guided fine needle aspiration; GS: guide sheath; PPL: peripheral pulmonary lesion; TBNA: transbronchial needle aspiration