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Does Addition of Endobronchial Ultra-Sonography (EBUS) to Bronchoscopy and Computer Tomography improve Diagnosis in Bronchial Cancer?

- A Prospective Study -

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List of abbreviations

BAL	Bronchoalveolar lavage
BB	Bronchial biopsy
BL	Bronchial lesion
BW	Bronchial wash
C	Central lesion
CA	Carcinoma
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DR	Detection rate
EBL	Extrabronchial lesions
EBUS	Endobronchial ultrasonography
EUS	Endoscopic ultrasonography
FFB	Flexible fiberoptic bronchoscopy
Hz	Hertz
Lt	Left
LN	Lymph node
LNs	Lymph nodes
MHz	Megahertz
MRI	Magnetic resonance imaging
N	Number
NSCLC	Non small cell lung cancer
NRS	Non-representative sample
PL	Peripheral lesion
PBL	Peribronchial lesion
PDT	Photodynamic therapy
RPM	Round per minute
Rt	Right
SCLC	Small cell lung cancer
TBLB	Transbronchial lung biopsy
TBNA	Transbronchial needle aspiration
TUS	Transtracheobronchial ultrasound
US	Ultrasound
USTBNA	Ultrasound-directed TBNA

1. Introduction

1.1 Background

The view of the bronchoscopist is limited to the lumen and the internal surface of the airways. Intramural or extraluminary pathological changes can only be suspected from indirect signs of tumor, such as discoloration and swelling of the mucosa, hyper-vascularization, leveling of the superficial cartilagenous relief, or impression, displacement, or disruption of airway wall architecture. As especially in malignancies, assessment beyond the endoscopically visible may be crucial for the fate of the patient, thus there is a definite need to extend the bronchoscopist's view beyond the confinement of the tracheobronchial wall (32).

Radiological diagnostic procedures such as computed tomography scan and magnetic resonance imaging have certain shortcomings in mediastinal staging of lung cancer (12, 44, 45). An example is the exact detailed structure of the tracheobronchial wall; subsequently the depth of tumor invasion is often difficult or impossible to define precisely. Hence there is need to improve diagnostic procedures in this setting (82).

Ultrasound has gained wide acceptance as a standard diagnostic imaging technique (73). The introduction of real–time systems and improved resolution of the electronically focused phased array transducers have made US competitive in some situations with chest X-ray, fluoroscopy, and CT scan (47).

Small flexible catheter-based transducer -miniature transducers- originally designed for intravascular ultrasonographic applications, have been used in conjunction with flexible endoscopy of the genitourinary and gastrointestinal tracts because of their ability to produce images beyond the luminal surface, providing information about the exact location of masses as well as such normal structures as arteries, veins and lymph nodes (27).

Endosonography is now an established technique evaluating lesions adjacent to or arising from the wall of the upper gastrointestinal organs (23).

In the respiratory tract the technical problems of endobronchial ultrasound are much more complex compared to other organs, primarily because air present in the tracheobronchial lumen and lung parenchyma interfering with penetration of the ultrasound signal. Its use in topical anesthesia is further complicated by respiratory movements, cough, tip displacement, etc.. For these reasons, the technique could not be established for a long time **(**10).

The use of a catheter-based miniaturized ultrasound transducer for the study of the tracheobronchial tree as part of a fiberoptic bronchoscopic examination was first described by Hürter and Hanrath of Aachen, Germany in 1990 (38), followed by Becker of Heidelberg, who published preliminary reports in 1994, after Olympus introduced significant technical improvements to devices in use (5).

Becker's work was presaged by early Japanese reports in EBUS from Ono and his colleagues in 1993 and 1994 (58, 59), followed by several publications and significant technical advances (41, 42, 66).
Goldberg and his colleagues evaluated the role of endoluminal ultrasound guidance for diagnosis during routine FFB for patients with known or suspected pulmonary neoplasm. The result of this first American study was published in 1994 (27).
Endobronchial ultrasound was introduced into clinical hospital practice in 2000, as a new diagnostic procedure visualizing bronchial and peribronchial tumors, mediastinal lymph nodes and adjacent vascular structures, with the aim of assessing bronchial wall and extraluminal pathology. Since major European publications deal with EBUS application in general anesthesia (8, 19, 36), its use in routine bronchoscopy in topical anesthesia needs to be evaluated more closely.

1.2 Principles of ultrasonography

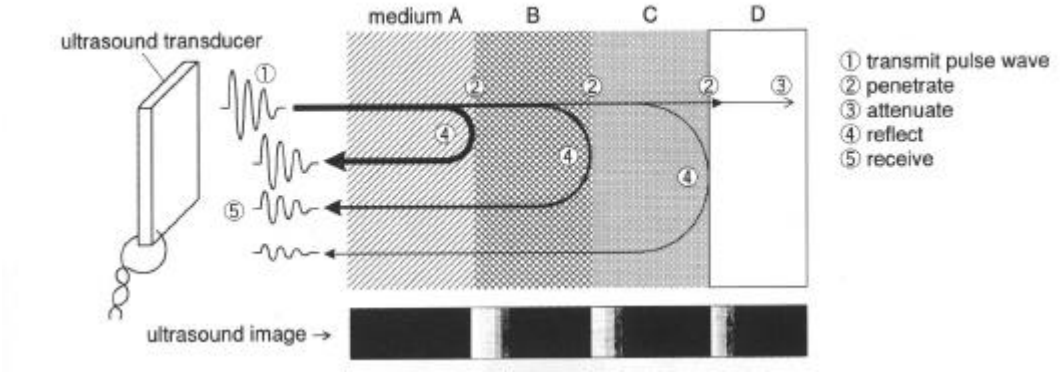
1.2.1 Principles of wave length

Imaging by ultrasound depends on differences in transmission, absorption, scattering and reflection of ultrasonic waves by tissues of different impedance. Frequencies beyond the hearing range of more than 20,000 Hz are defined as ultrasonic waves. In medical application, frequencies in the MHz range are used for creating images.
The frequency is the number of oscillations per unit of time, expressed in the unit of Hz. An increase in frequency means a decrease in the wave length. The medical diagnostic ultrasound waves have frequencies between 2 and 20 MHz (30 MHz is still being investigated) and wave lengths from 0.8 to 0.15 mm (10).

1.2.2 Principles of ultrasound imaging

Ultrasound is attenuated when it travels through a medium, and the attenuation rate increases as the frequency increases. Since ultrasound cannot penetrate the air due to the high attenuation ratio, it is necessary to fill the space between an ultrasound transducer and observation subject with a medium such as water. The ultrasound transducer produces an ultrasound image by converting electrical and ultrasound signals based on the principles that the ultrasound is partially transmitted and partially reflected at the boundary of the medium (43).

Figure 1: Principles how ultrasound image is made *(43)*



In non-technical terms, the intensity of the received waves is transformed into brightness (echogenicity or echodensity) on a black and white screen and the time elapsed from sending to reception is depicted as distance from the ultrasonic probe. Water has very low resistance and ultrasound waves travel with high speed, whereas air and bony structures are almost impenetrable and reflect the ultrasonographic waves almost completely. The processor is set to the speed of 1.540 meter/second in average water containing tissue of 37 °C as standard for its calculation. Differences from this standard are shown as brightness or darkness. Thus, if a tissue contains a lot of water, the sound waves travel faster and it appears darker. The effect of deeper penetration through fluid is called enhancement. The opposite effect is complete reflection by impenetrable tissues, which causes a shadow behind the obstacle (10).
The ultrasonic image does not strictly reflect anatomic structure but is a composite of reflection attenuation, dispersion, thermal transformation, etc., that are dependent on the specific properties of different tissues with respect to the individual impendence (10).

1.2.3 Factors influencing the quality of ultrasound image

Three major factors influence the quality of the ultrasonic image: contact of the ultrasonic probe with the tissue, depth of penetration of the ultrasonic wave and spatial resolution of the different structures (32).
The lower the frequency of the ultrasonic wave, the higher the depth of penetration and vice versa; the higher the frequency, the higher the resolution of structures. These technical implementations have to be taken into account when applying ultrasound for diagnostic purposes and in interpretation of ultrasonic images (10).

1.3 Ultrasound device

Different systems have been tested in vitro, a Japanese group applied special ultrasonic bronchofiberscopes that have a curvilinear scanner with 7.5 MHz at one side of the tip. The image was of comparatively low resolution and showed a very limited sector of the peribronchial structures. The maximum diameter of these devices is 6.3 mm (58, 59). For 360° imaging of the mediastinal structures, the instrument has to be rotated around its axis during the procedure, and the different planes have to be reconstructed like CT images. As by this procedure a direct coherent circular image of the mediastinal structures could not be produced, a different solution by applying miniaturized probes that are used for endoscopic and cardiovascular endosonography was tried (32).

The initial miniaturized Olympus probes operated with 7.5 MHz. Later, probes of 12 and 20 MHz became available (UM-2R/3R, driving unit MH-240 and processor EU-M 20 and 30; The first probe had a diameter of 3 mm, and the mechanical signal transducer at the tip was rotating at approximately 400 rpm and produced a 360° image perpendicular to its axis. Because of its large diameter, it was mainly applied during rigid bronchoscopy using a metallic tube as guide. Later, models of 12 and 20 MHz with a diameter of 2.5 mm could be introduced via biopsy channels of at least 2.8 mm through the flexible fiberoscopes (10).

Endovascular ultrasonic probes (CVIS, Sonotron Company Milwaukee, USA) had been already used in ultrasonic investigation of the pulmonary artery. These probes have an outer diameter of 10 F (12 MHz) and 8 F (20 MHz). The axial resolution is 0.12 mm and the radial resolution 0.23 mm. Rotation of this mechanical transducer is 600 rpm. Therefore, it produces less motion artifacts than the early Olympus probes. The ultrasonic wave is reflected from the transducer by a mirror with an 30° angulation of its surface. Thus, the ultrasonic image is slightly tilted forward from the tip of the ultrasonic probe (10).

1.4 Technique of endobronchial ultrasound

EBUS is applied under either general anesthesia using rigid bronchoscopy or local anesthesia with oxygen supplementation and sedation using a fiberoptic bronchoscope (10, 19, 39, 69).

The main problem of application inside the airways is coupling of the ultrasonic probe to the tracheobronchial wall. Lobar and smaller peripheral bronchi present no significant problems in this respect, but due to the surrounding air and the relatively rigid cartilaginous wall, this is impossible in the central airways. In these, with the naked probe one gets only a very limited sectorial view. This is why a flexible introducer catheter equipped with a balloon at the tip (MH-246R) was developed for the Olympus probes. Once this balloon is filled with water, it completely fills the airway and provides a complete 360° view of the mediastinal structures. The

water simultaneously serves as enhancing medium for the ultrasonic waves. Thus, under favorable conditions, the depth of penetration even for the 20 MHz waves may be up to 5 cm. Because of their higher resolution, these probes now are preferable to the 7.5 and 12-MHz probes. So far, it is not possible yet to equip the CVIS catheter with a similar device. Thus, their use is restricted to the peripheral airways and to the lung tissue (10).

Since the first balloon catheters had a diameter of 3.5 mm, they could not be introduced through the biopsy channel of ordinary bronchoscopes. They had to be applied through rigid bronchoscopes, parallel to an ordinary flexible fiberscope or via a new flexible Olympus bronchofiberscope with an outer diameter of 7 mm (Olympus BF-ST 30). The biopsy channel of the latter instruments is large enough to allow the probe to be passed. Nowadays the slimmer diameters US probe (UM-BS 2O-26R) with balloon catheter are available which can be introduced through the biopsy channel of 2.8 diameter of routine fiberoscopes together with the balloon sheath (MAJ-643R) (10).

Once the probe is placed inside the airways under visual control, the balloon is filled until close contact to the wall is established. This can be achieved without any problems peripherally and in the main bronchus as long the contralateral lung is ventilated. EBUS in the trachea or in a main bronchus after contralateral pneumonectomy causes complete occlusion of the airway. Under local anesthesia this can be tolerated for very short periods only under sufficient sedation and after careful preoxygenation (preferably via an orotracheal tube) (10). General anesthesia allows up to 3-4 minutes of apnea for investigation of the mediastinal structures (21). Although some argue that this procedure is justified with respect to the useful additional information that can be obtained (10), others make the point that flexible bronchoscopy looses much appeal if its use would require general anesthesia. (Personal communication, J.A. Nakhosteen).

1.5 Imaging artifacts

Artifacts can occur due to the following mechanisms:

a) Slow imaging processing

The comparatively slow rotation speed and imaging processing by US compared to the respiratory movements and pulsations cause the contours of any structure to move when the US beam reaches the same position after one full rotation cycle, leading to an edge between the images. Thus, the contours of the structure appear to have multiple edges or artificial elongation (comet-like extension) (7,10).

b) Insufficient contact

The insufficient contact between the balloon and the bronchial wall leads to multiple repeated reflections of the balloon echo. This is the most frequent artifact resulting from reflections at the inner surface of the balloon. It may vary with the

material. Obviously, not all types of latex are equally penetrable for the ultrasonic wave (7, 10).

c) Interference

The interference of the video signal of the video endoscopes leads to a radiation corona overlying the US image (7, 10).

d) Air bubbles

Air inside the fluid filled balloon leads to bright reflexes and the balloon is elongated (rabbit ear shape) (7, 10).

d) Irregularly rotating US probe

Friction of the tip of the US probe inside the balloon sheath causes multiple indentations of image structures (10).

The artifacts are not synchronous with the physiological movements, they are easily recognized, and after some time of accommodation, no longer interfere with the diagnostic process.

As the central airways are surrounded by strongly reflecting structures like lung tissue, vertebral column, calcified cartilages or lymph nodes, artifacts may also occur due to these strong reflections. Frequently, lymph nodes may show distorted triangular contours at the far side. Depending on their echogencity, the distal contours may be blurred. This is also true for the left atrium and the pulmonary vein. Detailed analysis of chambers of the heart and its valves however is not possible because of the limited range of the 20 MHz probe (7, 10).

1.6 Sonographic anatomy

1.6.1 The tracheobronchial wall and lung parenchyma

The tracheobronchial wall is highly echogenic and has a peculiar ultrasonographic laminar structure (79).

1.6.1.1 Laminar structure of the tracheobronchial wall

Since the extent of bronchial wall involvement in extraluminal and early lung cancer pathology is of major concern in endobronchial staging, the exact definition of mucosal layers has been a major focus of attention in EBUS studies.

In the digestive system, it has been demonstrated that the wall is depicted as a laminal structure with EUS. The anatomical structures corresponding to each echo layer have been defined. However, anatomical structures corresponding to each laminar EBUS layer have not been fully determined yet (82).

Hürter and Hanrath reported that the bronchial wall has unilaminar and trilaminar structures next to one another corresponding to membranous and cartilaginous parts of the bronchial wall (39).

Steiner and coworkers (79), using either 12.5 or 20 MHz ultrasonic probes reported

that the normal bronchial wall appeared as three echo layers. They were interpreted as hyperechogenic mucosa, hypoechogenic muscularis, and hyperechogenic adventitia.

Using 20 MHz ultrasonic probes, others reported that the tracheobronchial wall was represented as a 7-layer sonographic structure of the central airways. The mucosa on the inner surface shows a very bright echo that is further enhanced by the adjacent balloon. The submucosa is comparatively echo poor and clearly distinguishes the mucosa from the supporting structures of the tracheobronchial wall. The internal structures of the cartilage itself and of the intercartilagenous connective tissue are equally echo poor and cannot be differentiated from each other. But the strong echo of the endochondrium and of the perichondrium can always be seen in the intact structure. The adjacent external sonographic double layer structures of the supporting connective tissue and of the adventitia are easily missed under low power magnification due to the bright reflex of the perichondrium. However, no histological evidence of these hypotheses was demonstrated (10).

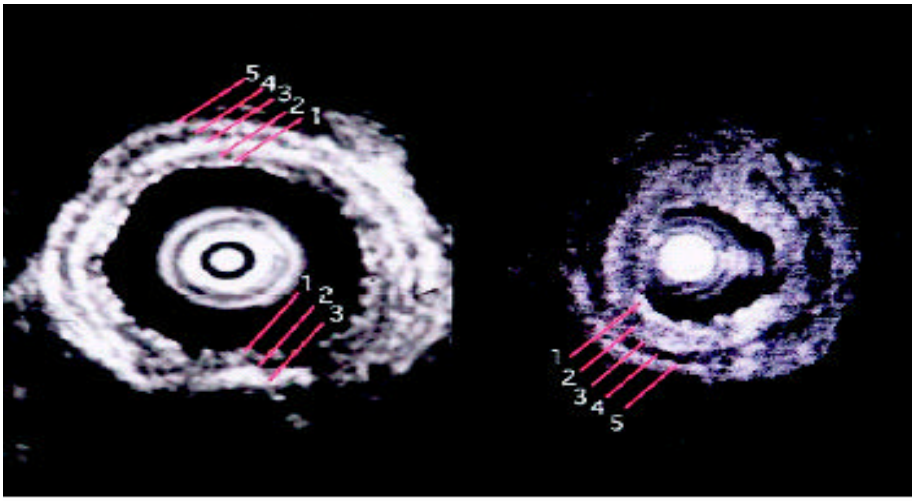
On the other hand Kurimoto and co-workers (42) identified the laminar structure comparing images of normal bronchial structure obtained by EBUS and histo-pathological tissue by conducting Needle-puncture experiment, demonstrating the histological anatomical structures corresponding to each layer using 20 MHZ ultrasound probes. They reported that the cartilaginous portion of extrapulmonary bronchi and the intrapulmonary bronchi is depicted as a 5-layer structure and that the membranous portion of the extrapulmonary bronchi appears as 3-layer structure. The fourth layer (hypoechoic), which represents the cartilage of the cartilaginous portion of the extrapulmonary bronchi and the intrapulmonary bronchi, and the second layer (hypoechoic), which represents the smooth muscle of the membranous portion, can often be clearly pointed out. These layers are considered to be the key to correct determination of depth of tumor invasion.

A precondition for obtaining the precise laminar structure by ultrasound is in positioning the probe at the center of the lumen so that the ultrasound enters the bronchial wall at right angles. This is confirmed when the first layer is a hyperechoic, not hypoechoic marginal echo (42).

Table 1: Transbronchial ultrasound imaging of tracheobronchial wall and its corresponding structures (42, 82).

	Ultrasound imaging (20MHz) **Layer**	**Ultrasound imaging (20MHz)** **Echo-intensity**	**Corresponding anatomical structures**
Cartilagenous Portion	First (inner)	Hyper	Marginal echo containing the mucous epithelium and some inner part of the submucosal tissue.
	Second	Hypo	Submucosal tissue.
	Third	Hyper	Marginal echo (inner-side border of the cartilage) containing some inner part of the cartilage.
	Fourth	Hypo	Cartilage.
	Fifth (outer)	Hyper	Marginal echo (outer-side border of the cartilage) containing the adventitia.
Membranous Portion	First (inner)	Hyper	Marginal echo containing the mucous epithelium and some inner part of the submucosal tissue.
	Second	Hypo	Submucosal tissue. (Smooth muscle)
	Third (outer)	Hyper	Marginal echo (outer-side border of the submucosal tissue) containing the adventitia.

Figure 2: EBUS layers of tracheobronchial wall *(43)*



a) *b)*

a) EBUS-layers of tracheal wall, anteriorly the cartilaginous portion (5 layers), posteriorly the membranous portion (3 layers).
b) Layers of the cartilaginous portion of the bronchial wall (5 layers) by EBUS.

1.6.1.2 Lung parenchyma

The normal lung parenchyma is characterized by a dense pattern of reflections (highly echogenic) due to the multiple air/soft-tissue interfaces found in normal lung (79).
Masses in the periphery or central portions of the lungs contain different echo texture than surrounding normal lung. Bronchial carcinoma of all histological types has an echo poor texture i.e. less echogenicity both in vivo and in vitro, than surrounding tissue. This can easily be differentiated from the highly echogenic normal bronchial wall and lung parenchyma.
Endobronchial sonography identifies endobronchial and peribronchial tumor growth as well as infiltration of the bronchial wall. In some patients, however, the echotexture is complex reflecting areas of increased echogenicity believed to represent areas of necrosis and hemorrhage (27, 39).

1.6.2 Mediastinum

1.6.2.1 Orientation in the mediastinum

Orientation within the mediastinum is difficult (15). Besides the complex anatomy of the mediastinal structures and motion artifacts by respiration and pulsation, this is mainly due to the frequently unusual plains of the sonographic image, predetermined by the airway angles. Inside the trachea, the ultrasonic image equals

the horizontal plane represented by CT scanning of the mediastinum. Passing into the main bronchi, the image continuously tilts towards a more sagittal plane, especially in the left main bronchus. In the peripheral part of the upper lobe bronchi, an inverse horizontal plane is reached (10).

1.6.2.2 Nodal anatomy

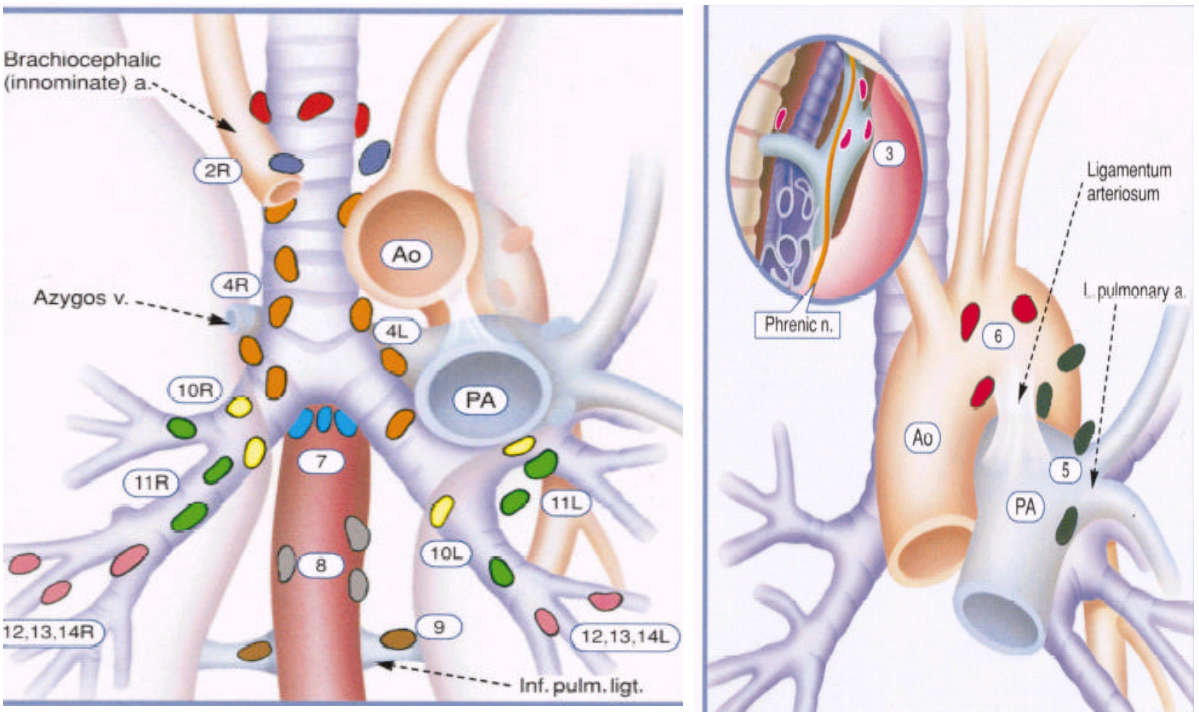
Lymph nodes appear denser; a hyperechogenic center can be recognized in some cases representing the reflective fatty hilus of the node (79). This typical pattern suggests normality and has been identified in nodes in other areas of the body (30). The nodal anatomy can be elicited from figure 3.

1.6.2.3 Other mediastinal structures

The esophagus appears as an oval-shaped multi-layer structure dorsally to the trachea, main carinal bifurcation and the left main bronchus. The esophagus is a distinct landmark for orientation.
The vessels are easily recognized by their low echo and pulsation (79).

To understand EBUS, it is necessary to understand the positional relationship between the organs around the bronchi.

Figure 3: Regional lymph node stations for lung cancer staging (51)



Superior Mediastinal Nodes

- **1** Highest Mediastinal
- **2** Upper Paratracheal
- **3** Pre-vascular and Retrotracheal
- **4** Lower Paratracheal (including Azygos Nodes)

N_1 = single digit, ipsilateral
N_2 = single digit, contralateral or supraclavicular

Aortic Nodes

- **5** Subaortic (A-P window)
- **6** Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

- **7** Subcarinal
- **8** Paraesophageal (below carina)
- **9** Pulmonary Ligament

N_1 Nodes

- **10** Hilar
- **11** Interlobar
- **12** Lobar
- **13** Segmental
- **14** Subsegmental

N_2 Nodes = 1-9

N_2 Nodes = 10-14

1.7 Clinical applications of EBUS

1.7.1 Staging of Bronchial carcinoma

1.7.1.1 Primary tumor (T)

a) Determination of depth of tumor invasion of the tracheobronchial wall

In every case of macroscopic alteration of the mucosa, concomitant alterations in the sonographic structure were found. In many instances, even if the mucosa seemed to be intact macroscopically, submucosal tumor spreading was found by endobronchial ultrasound. In some instances, it could be followed extending beyond the bronchial wall into the parabronchial structures (32).

Early published reports comparing the depth of invasion in ultrasonograms with histopathological findings suggest that EBUS can be a useful diagnostic tool in evaluation of tumor invasion to the tracheobronchial wall (41, 42, 82).

Early Carcinoma: Frequently, tumors that are not visible by high-resolution CT scan are defined as early carcinoma. The patho-anatomical definition of early cancer is lack of infiltration beyond the submucosa (11).

EBUS is supposed to improve the prediction for suspicious lesions of autofluoresence or white-light-bronchoscopy. The additional information on the bronchial wall and the surrounding structures may play a role in early carcinoma detection if these observations – at present speculative - are confirmed (33).

b) Intraluminal Extension

Herth and Becker reported, that in advanced bronchial carcinoma endoluminal ultrasound provides valuable information for therapeutic decisions. In complete airway obstruction, they were able to differentiate the basis and the surface of the tumor. By passing the stenosis, they could assess patency of the distal airways. This information was of importance for endobronchial desobliteration, especially if the pulmonary artery was not simultaneously occluded (32).

c) Peripheral pulmonary lesions

?Localization:

EBUS is helpful in localizing and guiding the biopsy of peripheral lesions (27, 41).

Lesions behind mediastinum and diaphragm, small lesions, low attenuation lesions and lesions behind another shadow may all be better visualized by EBUS (41).

? Qualitative diagnosis:

Kurimoto and his colleagues reported that opposed to benign masses a malignant pattern has no bronchioles, no vessels and heterogenous echogenicity in the tumor (41).

It is also claimed that by analyzing the spectrum of US signals, it might be possible to predict the histology of peripheral lesions (57).

d) Infiltration of Mediastinal Structures: (regional involvement)
Even more important in preoperative staging is the diagnosis of infiltration of the organs in the mediastinum such as the aorta, vena cava or the main pulmonary artery. By radiological methods, this frequently proves difficult. EBUS could demonstrate direct infiltration of the esophageal wall by US of the left main bronchus or the distal trachea. EBUS proved to be extremely valuable in diagnosis of infiltration of the esophagus by bronchogenic carcinoma.
Intratracheal ultrasound was especially helpful in diagnosing external infiltration of the tracheal wall by tumors of the mediastinal surface of the lung or by primary mediastinal tumors. Here, EBUS proved to be superior to radiological examination (34).

1.7.1.2 Involvement of lymph nodes (N)

Lymph node localization and enlargement is easily detected by EBUS, lymph nodes down to a size of 2-3 mm can be visualized (11, 39, 69, 79). In a limited prospective in vitro study it was not possible to find reliable criteria for the malignant infiltration, neither with regard to the echogeneity nor to homogeneity of the internal structure or with respect to boundary to the surrounding structures (10). This is in contrast to other localizations, for example in E.N.T tumors (31, 48).
?EBUS assisted Transbronchial Aspiration Needle of mediastinal adenopathy:
As with the Olympus system simultaneous visual control of the biopsy needle is very limited, echography mainly serves for localization of the lymph nodes. TBNA is performed sequentially after prior sonographic localization. This is easy as the cartilages and airway branches allow exact anatomical localization and guidance of the subsequent needle aspiration biopsy (10).
The addition of endobronchial ultrasound for improvement of these procedures has been investigated. Preliminary results showed that it might reduce the number of attempts, improve results and increase the diagnostic yield. It was useful in sampling small lymph nodes down to 3 mm, and provided lower complication rate and further safety by on site visualization of blood vessels preventing inadvertent puncture (10, 19, 75).

1.7.2 Mediastinal masses

Mediastinal masses can be visualized by EBUS and subsequently approached by transbronchial/transtracheal needle biopsy if they are localized in close proximity to the central airways or if some fluid-containing structure provides an acoustic window. Primary mediastinal or bronchogenic cysts in close contact to the airways are easily differentiated from solid tumors by their echo-poor internal structure that is frequently septated. With solid masses, endosonography is superior to radiological procedures in differentiation of compression and infiltration of the wall

of the airways. This applies for example to goiter and thyroid carcinoma. In tumors of the mediastinum, which are usually localized ventrally to the trachea and the left main bronchus, access via the apical segment of the left upper lobe is preferable due to its close anatomical relation (10).

1.7.3 Large intrathoracic vessels

The large intrathoracic vessels adjacent to the central airways can be recognized due to their low echo structure and their pulsation. The importance of sonographic diagnosis in direct tumor invasion has been discussed above.
Especially in early infancy and childhood, compression of the airways by vascular anomalies is comparatively frequent. EBUS detected such anomalies, even if extensive previous cardiovascular diagnostic procedures did not show the pathology. Thus, in the future EBUS might be a standard procedure in the diagnosis of pediatric malformations. This applies also to extensive thoracic deformities where compression of the airways by deviation of the heart, the large intrathoracic blood vessels and the thoracic wall can be diagnosed by EBUS preventing more invasive radiological procedures like angiography (10).

1.7.4 Pleural Space

If an atelectasis or pleural effusion provides an acoustic window, the pleural surface and mediastinal structures may be visualized. Thus, solid formations of the visceral and mediastinal pleura or on the pericardium can be seen (10).

1.7.5 Endobronchial ultrasound in interventional bronchoscopy

In exploration of central airway stenosis, sonography was useful in assessment of its extent and cause in order to choose the best method for interventional procedures, i.e. dilatation, laser or stent implantation as well as control of the therapeutic effect. In bronchoscopic treatment of malignant tumors with curative intent such as photodynamic therapy and endoluminal high-dose radiation, it is important that the lesion is not extending beyond the bronchial wall. Here, endobronchial sonography proved superior to all other diagnostic procedures, according to some authors (32).
In bronchoscopic palliative brachytherapy of malignant tracheobronchial tumors, EBUS determined the extent to which the lesion had affected the bronchial wall, thus was helpful in choosing the appropriate dose of irradiation suitable for the extent of the lesion, follow up and evaluation of the treatment response (58).
Correct endoscopic judgment of the healing process of an anastomosis after a so-called bronchoplastic surgical procedures (sleeve resection) can be problematic. Thus, it is sometimes difficult to differentiate superficial necrosis with mucosal swelling and fibrin deposition from imminent dehiscence.

Endobronchial ultrasound proved to be very useful in assessment of the surrounding structures (6).

1.8 Patient Tolerance

The procedure is well tolerated by the majority of the patients. Up till now, no serious side effects were recorded (19, 27, 39, 69, 70, 75, 82).

Cough and hypoxemia were reported by Scherer (69, 70) and Falcone (19) in a limited group of patients.

a-Coughing: coughing interferes with the US examination, rendering coupling of the probe with the bronchial wall difficult (69).

b-Hypoxemia: oxygen desaturation can occur in main bronchi or trachea, intermittent balloon inflation in the main bronchi was usually tolerated without desaturation below 90%. Hypoxemia per se never prevented collection of information (69).

1.9 EBUS learning curve:

The acquisition of good quality images and their interpretation is to a large extent dependent on the experience and the skill of the bronchoscopist. With increasing number of examinations, the information obtained by the ultrasound images increases rapidly with a steep learning curve in few months.

Familiarization with the topography of the mediastinum organs and accustoming to the particular view of the ultrasound anatomy is a prerequisite to reliable interpretation of the pictures. (19, 69)

1.10 Cost-effectiveness:

The sum of investment in any new machine is relatively large; the most important is cost of individual examination. Compensation for one EBUS examination is the sum total of: one conventional bronchoscopy, transbronchial flexible needle biopsy and ultrasound examination of one organ:

DM 100.- + 30.- + 20.- = DM 150.- (77 EUR)

(Prices are based on the current fee schedules for medical services in Germany (GOÄ) (54).

The assertion that EBUS is cost-effective (10), still remains to be validated by wider use in bronchial endoscopy.

1.11 Study hypothesis

From the above discussion it is clear that most European studies on EBUS have been done in general anesthesia, using the rigid bronchoscope as a conduit for flexible scope to guide the ultrasonic probe to regions of interest. Since most routine diagnostic bronchoscopies are done in topical anesthesia, however, we studied the use of EBUS in topical anesthesia while aiming to validate the indications evolved using rigid procedures. Hence, this study aims to test two hypotheses:

1. EBUS provides valuable additional information for assessment of lung cancer, compared to bronchoscopy and computer tomography, and hence improves diagnostic rate.
2. The use of EBUS in bronchoscopy under topical anesthesia is practicable despite some prolongation in the examination time.

2. Patients, Materials and Methods

2.1 Recruitment of patients

For this prospective study, we recruited 50 consecutive patients with suspected lung cancer undergoing diagnostic and/or staging FFB from October 2000 till October 2001.

2.2 Inclusion criteria

Patients should be able to give informed consent and have no contraindication for conventional fiberoptic bronchoscopy.
Suspected lung cancer patients should have suspicious shadow(s) and/or mediastinal adenopathy in computed chest tomography ± chest x-ray.

2.3 Investigations

The following investigations were performed routinely:
full history and clinical examination, coagulation and routine blood studies,
chest x-rays and computed chest tomography with contrast medium is done and evaluated prior to the endoscopic examination by the referring radiologist and bronchoscopist separately,
fiberoptic bronchoscopic examination using 2.8-channel bronchofiberscope (Olympus 1T 40),
endobronchial ultrasonographic examination under topical anesthesia during bronchoscopy to the areas of interest (details below).
Samples taken for cyto-/histological examination were documented in an accompanying examination protocol.

2.4 Materials

2.4.1 Specifications of the fiber bronchoscope (OES-BF 1T40, Olympus Optical Co. Ltd, Germany) are detailed below.

Table 2: Specifications of the fiber bronchoscope

Optical system	Field of view	120°
	Depth of view	3~50mm
Insertion tube	Outer diameter	Ø 6.0mm
Distal end	Outer diameter	Ø5.9mm
Working length	550mm	
Instrument channel	Inner diameter	Ø 2.8mm
Bending section	Range of the tip bending	UP180°, Down 130°
Total length	840mm	
High frequency compatibility	Yes	

Main technical features of the EBUS system are as follows.

Figure 4: System used for EBUS application (7).

2.4.2 Ultrasonic probe (UM-BS 20-26R, Olympus Optical Co. Ltd, Germany.)

Table 3: Functions, size and compatible endoscopes for ultrasonic probe		
Ultrasonic Functions		
Display mode	B-mode	
Scanning method	Mechanical, radial scanning	
Scanning direction	Perpendicular, to the direction of axis 360 degrees	
Frequency	20 MHz	
Contact method for site in question	Balloon method	
Probe driving unit (MH-240)	To drive ultrasonic probe in connection with the EU- M30	
Size		
Working length (mm)	2050	
Total Length (mm)	2140	
Balloon Sheath outer diameter (mm)	Ø 2.5	
Insertion tube diameter (including MAJ-643R balloon sheath)	Ø2.6	
Compatible Endoscopes		
Scopes	Channel inner diameter	
Flexible	Ø 2.8 (mm) or over	
Rigid	Minimum capacity 9 Fr	

2.4.3 Incorporated balloon sheath (MAJ-643R Olympus)

Table 4: Features of balloon sheath	
Balloon inflation with	Distilled water
Precautions	No air bubbles inside
Maximum inflation diameter	Approximately 20 mm
Distal end security	O-ring mechanism

?Balloon preparation before use: The aim of the preparation is to test the balloon inflation with distilled water, making sure that it contains no air bubbles.

?Distal security mechanism of the balloon end: as soon as the amount of the injected distilled water exceeds the inflation limit of the balloon, the O-ring at the distal end is released and the distilled water is discharged from the distal end deflating the balloon. The probe needs to be removed and set up again.
This mechanism prevents the balloon from bursting and dispersing loose pieces inside the bronchus.

Figure 5: Distal end of fiber bronchoscope with protruding ultrasonic probe with inflated balloon (7)

2.4.4 Endoscopic ultrasound center (EU-M30 Olympus)

The endoscopic ultrasound center (EU-M30) controls the endoscopic ultrasonic probe inserted into the bronchi. The EU-M30 is able to receive, temporarily store and convert reflected echoes from the tissue into digital signals. The converted digital signals are displayed on the monitor.

The EU-M30 probe is compatible with the video-endoscope (Olympus EVIS-BF) system and ordinary (OES BF) bronchofiberoscope system, enabling full operation of both systems. Although simultaneous observation of the endoscopic and ultrasonic images on one monitor is possible, it is preferable to have two monitors – one for endoscopic image, and one for ultrasound signals.

2.4.5 Aspiration needle 21 G (NA-2C, Olympus)
This is a size 21 G fenestrated needle with a length of 13 mm, which is contained in a flexible catheter with a hand-operated, integrated proximal suction mechanism.

2.5 Methods

2.5.1 Patients preparation

1-An Intravenous line is introduced.
2-Premedication:
a) Atropine sulphate 0.5 mg is given intramuscularly 30 minutes before bronchoscopy as well as
b) Pethidine 50 mg intramuscularly 30 minutes before bronchoscopy.
c) 100 mg prednisolone is given intravenously 90 minutes before bronchoscopy in COPD patients to reduce the bronchial hyperreactivity (e.g. cough and bronchospam). Additional dose of prednisolone is given the night before bronchoscopy in patients with history of bronchial hyperreactivity.

3-Topical anesthesia:
Inhalation of 5ml Lidocaine 4% solution with 2.5 mg Salbutamoul solution + 0.25 mg Ipratropium bromide for 15 minutes is delivered before the procedure through an ultrasonic nebulizer.
For further topical anesthesia during bronchoscopy, 2 ml aliquots of lidocaine 2% solution are instilled via the aspirating channel of the bronchoscope, up to a total maximum of 14 ml.
4-Sedation:
Titrated intravenous midazolam sedation is performed with all patients.
Initially 3 mg are given, further increase are individually adjusted until speech becomes slurred or the patient sleeps.
A benzodiazepine antagonist (flumazenil) is available for use to reverse occasional excessive sedative effects of midazolam.
5-Oxygen supplement and patient monitoring:
Administration of low flow (1 – 3 L/min) humidified oxygen transnasally, with pulse oxymetric monitoring is administered to all patients.
The arterial oxygen saturation is continuously monitored during and immediately following the bronchoscopy and EBUS examination.

2.5.2 Bronchoscopic – EBUS procedure

With the patient in a recumbent position, the Olympus BF 1T 40 is introduced transnasally when possible, otherwise transorally. The bronchoscopic examination starts with careful inspection of the airways.

Then EBUS examination is performed as follows:
A 20 MHz radial mechanical type ultrasound probe combined with a balloon (UM-BS 20-26R) connected to an ultrasound unit (Driving unit MH-240 and Processor EU-M30, Olympus) is inserted through the working channel of fiberoptic bronchoscope, just beyond the tip of the FFB to the areas of interest under direct vision. The balloon is inflated with distilled water until the bronchial lumen is fully occluded, thus ensuring a complete coupling between transducer and the bronchial wall. A motor in the ultrasound unit rotates the transducer within the catheter, producing a cross-sectional 360° ultrasound image, which is oriented at a right angle to the axis of the catheter. The endoscopic and ultrasonic images are immediately available for viewing on the monitor (real time). Individual freeze-frame images are printed out. All examinations are recorded by videotape for later analysis and storage.
? *Scanning of the trachea:* In the trachea partial inflation of the balloon up to 60 seconds is performed, while pushing the probe towards the suspected site of tracheal wall, during which anatomical and pathological structures are quickly visualized. Then a freeze frame image is taken and analyzed more closely after balloon deflation.
? *Scanning of the central bronchi:* During EBUS scanning of the central bronchi, the bronchial lumen is obstructed between 30 to 120 seconds with the inflated balloon, during which anatomical and pathological structures are visualized. Then a freeze frame image is taken and meticulously studied after balloon deflation.
? *Scanning of peripheral bronchi:* In the peripheral bronchi, the lumen can be occluded for longer durations than central bronchi. In more peripheral smaller caliber bronchi, a 360° coupling without air interposition can be achieved some times without balloon inflation.
? Localization of a lesion in relation to the bronchial lumen:
After deflation of the balloon, the level of the ultrasonic transducer probe (black in color) is recorded in relation to the adjacent anatomical landmarks (e.g. cartilages, bronchial branches). The anatomical position of the suspected lesion is described as its clock position on the ultrasonic image. (i.e. for location of the suspected lesion in relation to the tracheobronchial tree is best visualized by imaging the interior of the airways as a clock face.)

2.5.3 Transbronchial needle aspiration

Transbronchial needle aspiration from the suspected lesions using a 21 G aspiration needle is sequentially done after prior EBUS localization. Other bronchoscopic samples (bronchial biopsy, transbronchial lung biopsy, bronchial brushing and bronchial wash) are taken whenever needed.

T.B.N.A Technique:

The "jabbing method" is used to insert the needle through the airway wall as described by Wang (89). With the tip of the scope straight and at midtrachea, the needle is inserted through the scope while its tip is inside the metal hub. When the metal hub is visualized, the needle is advanced and locked into place. The whole catheter, with the locked needle, is withdrawn to a point where only the very distal tip of the needle is visible through the bronchoscope. Then the bronchoscope is advanced to the target area. When the puncture site is identified and reached, the tip of the scope is bent maximally toward the puncture site. While the assistant fixes the scope at the nose or mouth, the operator grasps the proximal portion of the catheter and then the needle is thrust through the intercartilaginous space with a quick firm jab to the catheter.

2.6 Complications

A-Complications related to the EBUS procedure:

Complications of the procedure were recorded and graded as mild, moderate or forcing to abandon the procedure:

1-Cough: [Mild (less than 3 episodes), moderate cough or cough terminating the examination].

2- Desaturation:

?Mild (oxygen saturation 90 -95%)→ No effect on examination.

?Moderate (oxygen saturation 85 - 89%)→ Affected examination (prolongation of duration -other effects.)

?Aborted examination. (oxygen saturation <85%)

The patient tolerance score is plotted based on complications encountered:

1- Complete tolerance (no complications).

2- Partial tolerance (mild to moderate complications).

3-No tolerance (procedure aborted).

B-Complications related to TBNA is recorded if occurred.

2.7 Instrument handling difficulties

Instrumental handling difficulties as difficulties in the balloon sheath preparation before and during use, imaging artifacts, image adjustment difficulties and orientation difficulties related to the instrument or any other encountered during study would be registered.

2.8 Statistical analysis

The data collected are tabulated and analyzed statistically; the following methods are used to express the results obtained:

?The diagnostic ability of EBUS to detect central, peripheral and combined lesions: In the context of testing the diagnostic ability of EBUS to detect central, peripheral and combined lesions, combined FFB (with histology and/or cytology) and CT findings were considered as gold standard.

EBUS detection rate (DR) of central tumors = truly positively detected central lesions / truly positively + falsely negative detected central lesions.

EBUS DR of peripheral tumors = truly positively detected peripheral lesions / truly positively + falsely negative detected peripheral lesions.

The previous method is used to calculate EBUS DR of combined central and peripheral tumors.

To test the significant difference in the detecting capability of EBUS between central and peripheral tumors, the chi-squared (X^2) significance test was used; a P-value is produced and gives the probability of the observed results under the null hypothesis.

?Testing the additional information provided by EBUS versus FFB & CT:

In the perspective of testing the additional information provided by EBUS the interest was on the additional data EBUS could provide and not suspected radiologically or endoscopically, in the form of further lymph nodes, bronchial wall invasion and its depth and blood vessel impression or infiltration.

Additional information provided by EBUS = number of patients in whom an additive information was detected by EBUS (e.g. LNs & /or bronchial wall invasion and its depth & /or blood vessel impression or infiltration) and not suspected by FFB & CT / number of all patients in whom additive information was examined

Additional information provided by FFB & CT = number of patients in whom an additive information was detected by FFB & CT by failed to be detected by EBUS / number of all patients in whom additive information was examined.

To test the significant difference in the additional information provided by EBUS versus FFB & CT, the chi-squared (X^2) significance test was used; a P-value is produced and gives the probability of the observed results under the null hypothesis.

The additional information was evaluated on a per-patient basis, not per single additive information, as the former is more indicative of consequences following this additive information in each case.

? Testing LNs DR:

EBUS & CT LNs DR = number of LNs detected by both EBUS & CT / total number of LNs examined.

EBUS LNs DR = number of LNs detected by EBUS only / total number of LNs examined.
CT LNs DR = number of LNs detected by CT only / total number of LNs examined.
Total EBUS LNs DR = number of LNs detected by EBUS & CT + EBUS only / total number of LNs examined.
Total CT LNs DR = number of LNs detected by EBUS & CT + CT only / total number of LNs examined.
To test the significant difference in detection of LNs between EBUS and CT, the chi-squared (X^2) significance test was used; a P-value is produced and gives the probability of the observed results under the null hypothesis.
?Diagnostic yield of EBUS-assisted TBNA of EBL and LNs:
Diagnostic yield of EBUS-assisted TBNA of EBL = number of detected and diagnosed EBL by EBUS-assisted TBNA / total number of EBL examined by EBUS-assisted TBNA.
Diagnostic yield of EBUS-assisted TBNA of LNs = number of detected and diagnosed LNs by EBUS-assisted TBNA / total number of LNs examined by EBUS-assisted TBNA.

The 95% confidence interval (95% CI) is calculated to assess the clinical significance of the estimated range of the result.
? Patient tolerance score: is plotted on the basis of complications encountered.
Complete tolerance = Number of patients examined by EBUS without complications / total number of patients examined by EBUS
Partial tolerance = Number of patients examined by EBUS with presence of mild to moderate complications / total number of patients examined by EBUS.
No tolerance = Number of patients in which EBUS examination was aborted / total number of patient examined by EBUS.
? Calculating the proportion of the EBUS examination from the total time of bronchoscopy = Duration of EBUS examination / total examination time x 100
In the current study, for statistical calculations the following program was used:
EpiCalc2000 Statistical Program, version 1.02, Joe Gilman and Mark Myatt, 1998. Brixton Books.
Different detection rates (DR) presented in this study were compared using
the uncorrected chi-square and p-value for a series of proportions (expressed as percentages) and sample sizes.

The method used to calculate the chi-square statistic is described in:
Kirkwood BR, Essentials of Medical Statistics, Blackwell Scientific Publications, 1988, ISBN 0-632-01052-5, pp. 91-92

The method used to calculate the p-value for the chi-square statistic uses the method described by Lau (Lau CL, Algorithm AS 147. A Simple Series for the Incomplete Gamma Integral, Applied Statistics, 29,113 - 114, 1980) and is adapted from an algorithm presented in:
Cooke D, Craven AH, Clarke GM, Basic Statistical Computing (Second Edition), Edward Arnold, 1990, ISBN 0-340-53919-4, pp. 84-94
The 95% confidence interval (95% CI), was calculated with the help of:
Ciba Geigy Scientific Tables, 1980, 2nd edition, Basle, Switzerland.

3. Results

3.1 Overview on results of all cases studied

3.1.1 Patients characteristics and lesions location, biopsy technique and final pathology

Out of 50 patients with suspected lung cancer in this study, 36 were male and 14 were female. Their ages ranged between 36-89 years, with a mean age of 62.4 ± 12.3 years (Table 5).

Table 5: Patients characteristics and lesions location, biopsy technique and final pathology

Case	Age (Y)	Sex	Location	Biopsy /Lesion	Final Pathology
1	74	M	C	TBNA /LN	Inflammatory
2	54	F	C	TBNA /PBL	Adenocarcinoma
3	41	F	C	TBNA /PBL	Adenocarcinoma
4	63	M	C	TBNA /PBL	SCLC
5	73	M	C	TBNA /LN	Adenocarcinoma
6	61	M	P	TBLB & BW/ PL	Squamous cell CA
7	70	F	C	TBNA /PBL & LN	Squamous cell CA
8	75	M	C	TBNA /PBL	Mixed cell carcinoma
9	43	F	C	TBNA /PBL & LN	Adenocarcinoma
10	70	M	C	TBNA /PBL	Mixed cell carcinoma
11	64	M	C	BB / BL	Mixed cell carcinoma
12	45	M	C	TBNA /LN	Inflammatory
13	49	M	C	TBNA /LN	SCLC
14	63	M	C	TBNA /PBL	NAD
15	45	M	C	TBNA /BL	SCLC
16	70	M	P	TBNA /PBL	Squamous cell CA
17	76	M	C	TBNA /PBL	Severe Dysplasia
18	40	F	C	TBNA &BAL /LN	Sarcoidosis
19	58	F	P	TBNA /PBL	Inflammatory
20	45	F	P	TBLB /PL	Adenocarcinoma
21	62	M	C	TBNA /PBL	NAD
22	64	M	P	TBNA&TBLB /LN & PL	Adenocarinoma
23	45	M	P	TBNA& TBLB /2 LN &PL	SCLC
24	89	F	C	BB / BL	Large cell carcinoma
25	63	M	P	TBLB / PL	SCLC
26	64	M	C	TBNA /PBL	SCLC
27	76	M	P	TBNA /PBL	Squamous cell CA

Case	Age (Y)	Sex	Location	Biopsy /Lesion	Final Pathology
28	71	M	C	TBNA /PBL	Adenocarcinoma.
29	73	M	C	TBNA /PBL	Squamous cell CA
30	63	M	C	BB / BL	SCLC
31	64	M	C&P	TBNA/LN	Inflammatory (TB)
32	74	M	C&P	TBNA /PBL & PL	Squamous cell CA
33	54	F	C	TBNA /LN	Adenocarcinoma
34	75	M	C	TBNA /LN	NRS
35	57	F	P	BAL &TBNA / PL &LN	PL=NAD & LN=NRS
36	52	M	C	---------	**
37	69	F	P	TBLB / PL	Adenocarcinoma
38	59	F	C	TBNA /LN	Inflammatory
39	70	M	C	TBNA /LN	Inflammatory
40	36	M	C	TBNA /BL & PBL	Squamous cell CA
41	47	F	P	TBLB / PL	Adenocarcinoma
42	69	M	C	TBNA&BB / LN & BL	Squamous cell CA
43	64	M	C	TBNA / LN& PBL	Adenocarcinoma
44	59	M	C	TBNA / LN	Squamous cell CA
45	81	M	C	BB / BL	SCLC
46	82	M	P	Brush / PL	Adenocarcinoma
47	56	F	P	TBLB &TBNA / PL & LN	Adenocarcinoma
48	78	M	P	TBLB / PL	Squamous cell CA
49	58	M	C	TBNA / LN	Inflammatory
50	67	M	C	TBNA / LN	Adenocarcinoma

M = male, F = female, C = central lesion, P = peripheral, LN = lymph node, PBL = Peribronchial lesion, BL= bronchial lesion, PL = peripheral lesion, TBNA = Transbronchial needle aspiration,
TBLB = Transbronchial lung biopsy, BB = Bronchial biopsy, BW = Bronchial wash, BAL = Bronchoalveolar lavage, Brush = protected catheter brush, SCLC = Small cell lung cancer, NAD = no abnormality detected, NRS= Non-representative sample, TB= Tuberculosis, CA = carcinoma, ** = no tumor infiltration to the trachea, in a case of cancer esophagus, confirmed surgically.

3.1.2 Results of additive information provided by FFB & CT / EBUS and EBUS explanation of FFB findings (Table 6)

Table 6: Results of additive information provided by FFB & CT / EBUS and EBUS explanation of FFB findings

Case	FFB and CT provided more data than EBUS	EBUS explanation of the FFB findings	EBUS provided additional information		
			Lymph nodes	Bronchial wall invasion	Blood vessel infiltration or impression
1	1 LN	- ve	2	-	-
2	1 LN	+ ve	3	-	Impression
3	-	+ ve	1	Invasion from outside the bronchial wall	-
4	-	+ ve	-	Invasion of cartilage	-
5	1 LN	- ve	-	-	-
6	1 PL	+ ve	1	-	-
7	-	+ ve	-	Beyond adventitia	-
8	-	+ ve	1	Invasion from outside the bronchial wall	-
9	1 LN	- ve	1	-	-
10	-	+ ve	-	Beyond adventitia	-
11	-	- ve	-	Beyond adventitia	-
12	-	- ve	-	-	-
13	-	+ ve	-	Beyond adventitia	Impression
14	-	+ ve	-	Beyond adventitia	-
15	-	+ ve	1	Beyond adventitia	-
16	-	+ ve	1	Invasion from outside the bronchial wall	-
17	-	+ ve	1	Beyond adventitia	-
18	-	- ve	1	-	-
19	-	- ve	-	-	-
20	-	- ve	1	-	-
21	-	- ve	-	Beyond adventitia	-
22	1 LN	+ ve	-	Beyond adventitia	-
23	-	- ve	3	Invasion from outside the bronchial wall	-
24	2 LN	- ve	-	-	-

Case	FFB and CT provided more data than EBUS	EBUS explanation of the FFB findings	EBUS provided additional information		
			Lymph nodes	Bronhial wall Invasion	Blood vessels infiltration or impression
25	-	+ ve	1	-	-
26	-	+ ve	2	Invasion of adventitia & LN invading bronchial wall	-
27	-	- ve	-	-	-
28	-	- ve	-	-	-
29	-	+ ve	-	-	-
30	-	- ve	-	-	-
31	-	+ ve	3	-	-
32	-	- ve	-	-	-
33	-	- ve	-	-	-
34	-	- ve	-	-	-
35	1 PL	- ve	1	-	-
36	1 LN	- ve	1	-	-
37	-	+ ve	-	Invasion of cartilage	-
38	-	- ve	1	-	-
39	-	- ve	2	-	-
40	-	+ ve	-	Beyond adventitia	-
41	-	- ve	-	-	-
42	-	+ ve	-	-	-
43	-	+ ve	1	Beyond adventitia	-
44	-	- ve	1	-	-
45	-	+ ve	-	Invasion of cartilage	-
46	-	- ve	-	Beyond adventitia	
47	1 LN	- ve	1	Beyond adventitia	-
48	-	- ve	-	-	-
49	-	- ve	-	-	-
50	-	- ve	1	-	-

LN = lymph node, PL = peripheral lesion, FFB = Flexible fiberoptic bronchoscopy, CT = computerized tomography, + ve = positive findings, EBUS helped in explanation of bronchoscopic findings and – ve = negative bronchoscopic findings.

3.2 Pathological results of all studied cases

Pathological verifications were as follows (Table 7): 36 patients had lung cancer, 7 patients had inflammatory lesions (5 were lymphocytic hyperplasia of enlarged LN, one case of tuberculous lymphadenitis and another case with a non-specific inflammatory lesion), a case of sarcoidosis, and one patient had severe dysplasia suspicious of malignancy. In three cases, pathological results showed no abnormality. A non-representative sample had been obtained in one case.

In the case of cancer of the esophagus, no tumor infiltration to the trachea wall had been detected with EBUS and this was confirmed later surgically.

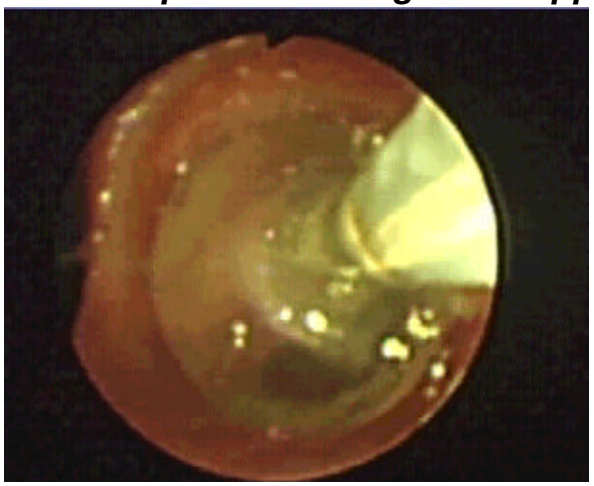
Table 7: Pathological results of all studied cases.

Pathological results	N	Total
Malignant:		36
Adenocarcinoma	14	
Squamous cell carcinoma	10	
Small cell lung cancer	8	
Large cell lung cancer	1	
Mixed cell type	3	
Inflammatory:		7
Lymphocytic hyperplasia of lymph nodes	5	
Tuberculous lymphadenitis	1	
Non–specific inflammatory lesion	1	
Others:		7
Sarcoidosis	1	
No abnormality detected	3	
Severe dysplasia suspicious of malignancy	1	
Non-representative sample	1	
* Cancer esophagus	1	

*A case of esophageal cancer (number 36): No tumor infiltration of the central airways was postulated with EBUS and confirmed surgically.

In follow up, all inflammatory lesions were free from malignancy.
(2 out of 5 lymphocytic hyperplastic LN were confirmed by mediastinoscopy, the other 3 were followed up without evidence of malignancy for more than 6 months. A para-cardiac space occupying lesion with non-specific inflammatory results proved to be organized pneumonia with complete resolution and no further recurrence until 7 months later.)
Follow up of NAD cases confirmed one case as free from malignancy (true negative; Lt upper lobe lung shadow and enlarged LNs, on thoracotomy were found to be chronic organized pneumonia, anthracosis and chronic lymphadenitis). 2 further cases proved to be malignant (false negative).
Malignancy was revealed on further diagnostic work up of the case with severe dysplasia (false negative).

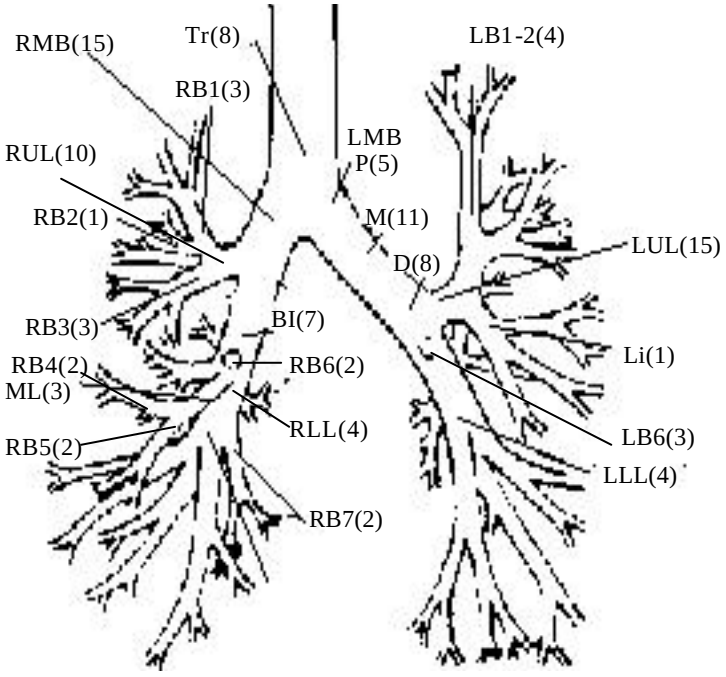
Figure 6: Actual endoscopic view during EBUS application.



US probe with inflated balloon at its distal end at the region of the proximal right main bronchus and main carina, notice the complete coupling between the inflated balloon and bronchial wall for achievement of good image quality.

3.3 EBUS Applications sites

Figure 7: Number of EBUS applications in each position in 50 patients.



The numbers of EBUS applications in different positions were 114 applications in 50 patients (Figure 6, 7) (table 8).

Table 8: Distribution of EBUS application sites			
Trachea (T) =N 8			
Application site	N	Application site	N
Lt. tracheobronchial tree:	52	Rt. tracheobronchial tree:	54
Lt. main bronchus (LMB)		Rt. main bronchus (RMB)	15
proximal(P) LMB	5	Rt. upper lobe bronchus (RUL)	10
middle(M) LMP	11	Apical (RB1)	3
distal(D) LMP	8	Posterior (RB2)	1
Lt. upper lobe bronchus (LUL)	15	Anterior (RB3)	3
Lt. apico-posterior (LB1&2)	4	Bronchus intermedius (B.I)	7
Lingula (Li)	1	Middle lobe bronchus (ML)	3
Lt. lower lobe bronchus (LLL)	4	Medial (RB5)	2
Lt. superior basal (LB6)	3	Lateral (RB4)	2
Lt. anterior basal (LB8)	1	Rt. lower lobe bronchus (RLL)	4
		Superior basal (RB6)	2
		Medial basal (RB7)	2

3.4 Structures identified by EBUS

In all the 50 cases, satisfactory images could be obtained, recorded and studied.

3.4.1 Blood vessels

Blood vessels were recognized as echo-free or relatively hypoechoic structures with variable appearances. Arteries were identified by strong obvious pulsation. Veins had weaker pulsatile changes. Differentiation between arteries and veins was sometimes difficult, especially in the right and left lower lobes, because of the wide variation in the positions and the numerous small caliber branches of the pulmonary arteries and veins in these areas.

Also some cardiac structures were identified as the left and right atrium.

3.4.2 Esophagus

The esophagus appeared as an oval, triangular or linear-shaped multi-layered structure, dorsal to the trachea and the left main bronchus.

3.4.3 Lymph nodes

Lymph nodes appeared as hypoechogenic structures with discrete borders in their usual anatomical position. They are ovoid, rounded, triangular or elliptical in shape. However, there are exceptions. A hyperechogenic center was recognized in one case representing the hilum of the node. In another, the nodes appeared as hypodense irregular structures without the characteristic lymph node configuration.

The outer border of pathologically enlarged lymph nodes were sometimes beyond the EBUS range, thus making it difficult to measure lymph node diameters in all cases, but when measured it ranged between 0.4 cm to 2.5 cm.

3.4.4 Tumor

The detected masses appeared as hypoechoic structures with different degrees of hypoechogenicity, having irregular margins and taking abnormal shapes with no respect to the surrounding anatomical structures.

3.4.5 Normal lung parenchyma

Appeared hyperechogenic.

3.4.6 Laminar structure of the bronchial wall

The multi-layers of the bronchial wall are not easily identifiable in many instances. The third marginal layer (inner-side border of the cartilage or cartilage-endochondrium) and the fourth layer (bronchial cartilage) appear as hyperechogenic, hypoechogenic layers respectively, near the middle part of the bronchial wall. This was a helpful landmark for identifying the layers of bronchial wall. Bronchial wall layers lying towards its inner aspect (i.e. between it and the bronchial lumen), are the first and second layers mucosa and submucosa. The layer towards its outer aspect is the fifth layer (adventitia). Depth of tumor invasion was identified by its relation to the third and fourth layers.

3.5 Locations of lesions (central, peripheral or combined)

The lesions were classified into central, peripheral or combined lesions based on combined FFB and radiological (CT) findings.

Central lesions are either visible endoscopic bronchial masses or radiologically apparent extraluminal masses up to the level of second–order bronchi.

Peripheral lesions start at the third order or more distal bronchi.

Combined lesions are cases where central and peripheral lesions detected (Table 9).

Table 9: Location of lesions in 50 patients based on combined FFB and CT findings.

Location	?	Malignant	Inflammation	Others
Central	34	23	5	6
Peripheral	14	12	1	1
Central &Peripheral	2	1	1	0
Total	50	36	7	7

? = sum

Out of 50 cases studied by FFB and CT (Table 10), EBUS detected all the 34 central lesions (100%), out of 14 cases with peripheral lesions 12 were detected with EBUS (86 %), while 2 cases were not detected (14%). The 2 combined lesions were detected with EBUS (100%).

Table 10: EBUS detection of lesions in the 50 cases studied

Localization	FFB & CT	EBUS		
		N	DR (%)	95% CI
Central	34	34	100	89.4-100
Peripheral	14	12	86	57.2-98.2
Combined	2	2	100	15.8-100

N = number. DR = detection rate. CI = confidence interval.

In 36 cases pathologically verified lung cancer (Table 11), EBUS detected all 23 cases with central lesions (100%) and 11 out of 12 peripheral lesions (92%) and failed in detecting one case (8%). A case with combined central and peripheral lesions was detected (100%). Thus EBUS detected 35 out of 36 pathologically verified lung cancer (97%) and failed in detecting one peripheral lesion (3%). EBUS has equal detecting capability for central and peripheral lesions (Table 12).

Table 11: EBUS detection of central and peripheral lesions in 36 cases pathologically verified lung cancer

Localization	N	**Detected**			**Non-detected**	
		N	DR (%)	95% CI	N	DR (%)
Central tumors	23	23	100	85.2-100		
Peripheral tumors	12	11	92	61.5-99.8	1	8
Combined C& P tumors	1	1	100			
Total	36	35	97	85.4-99.9	1	3

C = Central P = Peripheral N = number DR = detection rate CI = confidence interval

Table 12: Comparison of EBUS capability to identify central and peripheral lesions in 36 cases pathologically verified lung cancer

Central tumors			Peripheral tumors			
Detected lesions	DR (%)	95% CI	Detected lesions	DR (%)	95% CI	P-value
23/23	100	85.2-100	11/12	92	61.5-99.8	P > 0.05

There were non-significant difference (P > 0.05) in EBUS detection rate between central and peripheral tumors, thus EBUS has equal detecting capability in detecting central and peripheral tumors.

**Clarification and specification of 4 central lesions:*
In four cases with central lesions, EBUS was more precise than CT in detecting and clarifying these lesions. In 3 of these cases, CT detected the lesion as central mass lesion without further details. By EBUS, these lesions were more precisely identified as enlarged lymph nodes with specification of their number, size, location and surroundings structures.
In the fourth case, CT identified the lesion as a subcarinal soft tissue mass suspicious of mediastinal lymphadenopathy. By EBUS, this lesion was more precisely identified and assessed to be a central right upper lobe bronchus tumor with Rt. and Lt. subcarinal lymphadenopathy.

Characterizing a lesion as a lymph node takes into account similar sonographic patterns of lymph nodes in other areas of the body and appearance of cytologically verified nodes from previous EBUS experience. Similarly, tumor identification was based on characteristic sonographic patterns of histologically proven tumors.

3.6 Additional information provided by EBUS

In all areas examined by EBUS and other conventional methods (CT and FFB), agreement about the main features of disease process was reached, but the main interest was on the additional data EBUS provided compared to other methods.
In 35 out of 50 cases (70%) EBUS provided additional data more than FFB and CT. On the other hand, FFB and CT provided additional data more than EBUS in 10 out of 50 cases (20%) (Table 13).

Table 13: Additional data provided by EBUS /FFB &CT in 50 patients							
Cases	EBUS provided additional data more than FFB & CT			FFB & CT provided additional data more than EBUS			
N	N	R (%)	95% CI	N	R (%)	95% CI	P-value
50	35	70	55.4-82.1	10	20	10.2-33.7	P<0.005

N = number. R = rate. CI = confidence interval.
Statistically the additional data provided by EBUS were highly significant as compared to the additional data provided by FFB and CT (P < 0.005) (Table 13).

In pathologically verified lung cancer, EBUS provided additional data more than FFB and CT in 25 out of 36 cases (69%). On the other hand, FFB and CT provided additional data more than EBUS in 7 out of 36 cases (19%)(Table 14).

Table 14: Additional data provided by EBUS versus FFB & CT in 36 cases of pathologically verified lung cancer							
Cases	EBUS provided data in addition to FFB & CT			FFB & CT provided data in addition to EBUS			
N	N	R (%)	95% CI	N	R (%)	95% CI	P-value
36	25	69	51.9-83.7	7	19	8.19-36	P < 0.005

N = number. R = rate. CI = confidence interval.
Statistically the additional data provided by EBUS were highly significant as compared to the additional data provided by FFB and CT (P < 0.005) (Table 14).

The additional data provided by EBUS as opposed to other conventional methods (FFB and CT) were in position and number of lymph nodes, bronchial wall invasion and the differentiation between compression or infiltration of blood vessels.

3.6.1 Lymph nodes

The lymph nodes studied were classified into three groups according to the method of detection: LNs detected by CT and EBUS, by EBUS only, or by CT only.

Criteria for LNs detected by EBUS and CT: Characterizing a lesion identified by EBUS as a lymph node takes into account that it takes a typical similar sonographic pattern of lymph nodes in other areas of the body and in previous EBUS experience and taking usual site of lymph node station. The same LNs were also detected by CT and cytological confirmation was obtained in a group of them.

Criteria for additional LNs provided by EBUS only: Characterizing an additive LN identified by EBUS only as a typical similar sonographic pattern of lymph nodes in other areas of the body and in previous EBUS experience. It presents at a usual lymph node station with cytological verification obtained in a group of them. In addition, confirmation was achieved by mediastinoscopy in two of them.
Criteria for LNs detected by CT only: LN detected by CT and failed to be identified by EBUS (No suggestive sonographic pattern of LN).

Totally 86 lymph nodes were detected, 45 lymph nodes (52%) were detected by CT and EBUS, 32 lymph node (37%) by EBUS only and 9 lymph node (11%) by CT only (Table 15).

Table 15: Lymph nodes detected by EBUS/CT in 50 patients

LN	Detected by EBUS and CT			Detected by EBUS only			Detected by CT only		
N	N	DR (%)	95% CI	N	DR (%)	95% CI	N	DR (%)	95% CI
86	45	52	41.3-63.2	32	37	27-48.3	9	11	4.9-18.4

N = number. DR = detection rate. CI = confidence interval.

In all studied cases, the total number of LN detected by EBUS was 77 out of 86 (90%) LN studied, while the total number of LN detected by CT was 54 out of 86 (63%) (Table 16).

Table 16: Comparison between total number of LN detected by EBUS to CT in 50 patients

LN	Total number of LN detected by EBUS			Total number of LN detected by CT			
N	N	DR (%)	95% CI	N	DR (%)	95% CI	P-value
86	77	90	81.1-95.1	54	63	51.7-72.9	P <0.005

N = number. DR = detection rate. CI = confidence interval.
In all studied cases, the total number of LNs detected by EBUS when compared with those detected by CT showed a highly significant difference (P < 0.005) (Table 16).

The LNs detected by EBUS only were 32 LNs, while the LNs detected by CT only were 9 LNs in all studied cases (Table 17). [LNs numbering is after reference (51).]

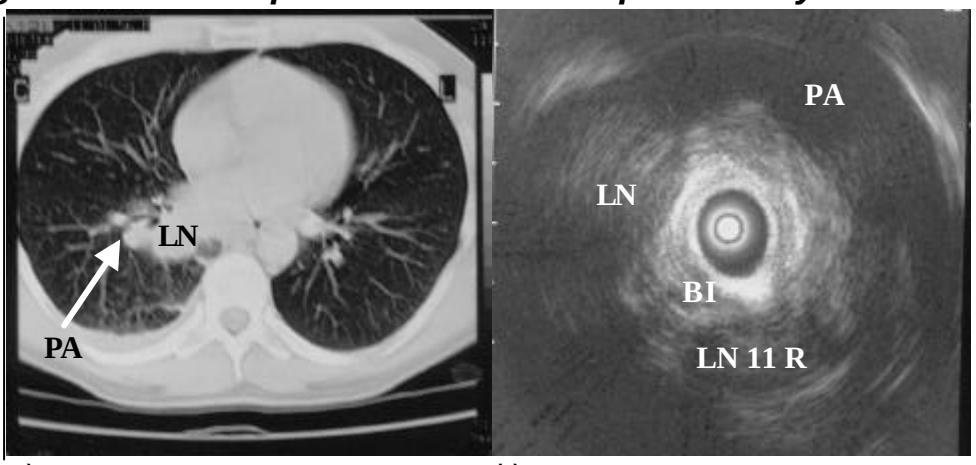
Table 17: Localization of lymph nodes detected by EBUS only or by CT only in all studied cases		
LN localization	**By EBUS only (32 LNs)**	**By CT only (9 LNs)**
Rt lower paratracheal LN (4R)	-	5
Lt subaortic (Aorto-Pulmonary) LN (5L)	7	-
Lt para-aortic LN (6L)	-	2
Rt subcarinal LN (7R)	1	1
Paraoesophageal LN (8)	1	-
Rt hilar LN (10R)	6	1
Lt hilar LN (10R)	1	-
Rt interlobar LN (11R)	2	-
Lt interlobar LN (11L)	5	-
Rt lobar LN (12R)	4	-
Rt segmental LN (13R)	2	-
Lt segmental LN (13L)	3	-

In 36 cases pathologically verified lung cancer, 55 lymph node were detected, 28 lymph nodes (51%) were detected by CT and EBUS, 20 lymph nodes (36%) by EBUS only and 7 lymph nodes (13%) by CT only (Table 18).

Table 18: Lymph nodes detected by EBUS/CT in 36 cases pathologically verified lung cancer									
LN	**Detected by EBUS & CT**			**Detected by EBUS only**			**Detected by CT only**		
N	**N**	**DR** (%)	**95% CI**	**N**	**DR** (%)	**95% CI**	**N**	**DR** (%)	**95% CI**
55	28	51	37.1-64.7	20	36	23.8-50.4	7	13	5.3-24.5

N = number. DR = detection rate. CI = confidence interval.

Figure 8: An example of an additive LN provided by EBUS only



a) *b)*

a) CT scan cut shows pulmonary artery (PA) and an enlarged Rt hilar LN surrounding bronchus intermedius.
b) EBUS in bronchus intermedius (BI), showing Rt hilar LN medially, pulmonary artery (PA) and an additive enlarged Rt interlobar LN (#11R) postero-lateral not seen in CT.

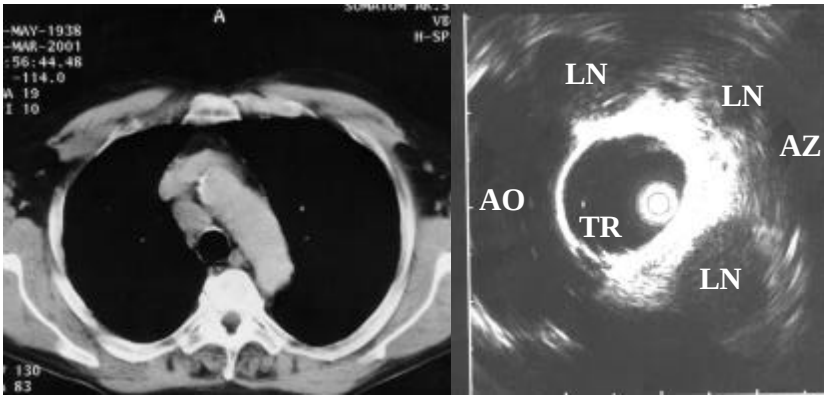
In 36 cases of pathologically verified lung cancer, the total number of LNs detected by EBUS was 48 out of 55 (87%) LN studied, while the total number of LNs detected by CT was 35 out of 55 (64%) (Table 19).

Table 19: Comparison between total number of LN detected by EBUS to CT in 36 cases with pathologically verified lung cancer.

LN	Total number of LN detected by EBUS			Total number of LN detected by CT			
N	**N**	**DR (%)**	**95% CI**	**N**	**DR (%)**	**95% CI**	**P-value**
55	48	87	75.5-94.7	35	64	49.6-76.2	P < 0.005

N = number. DR = detection rate. CI = confidence interval.
In 36 cases pathologically verified lung cancer, the total number of LNs detected by EBUS when compared with those detected by CT showed a highly significant difference (P < 0.005) (Table 19).

Figure 9: An example of EBUS application in the trachea.



a) *b)*

a) CT scan cut showing an enlarged big Rt lower paratracheal LN (#4 R) lying anterior to the trachea and a smaller node (#4R) posteriorly.
b) EBUS in the trachea showing more detailed nodal distribution with 2 enlarged Rt lower paratracheal LN (#4 R) lying anterior to trachea in addition to a posterior node. (AO= Aortic arch, AZ= Azygos vein and TR = Trachea)

The LNs detected by EBUS only, in 36 pathologically verified lung cancer cases were 20 LNs, while 7 LNs were detected by CT only (Table 20).

Table 20: Localization of lymph nodes detected by EBUS only or by CT only in pathologically verified lung cancer

LN localization	By EBUS only (20LNs)	By CT only (7LNs)
Rt lower paratracheal LN (4R)	-	4
Lt subaortic (Aorto-Pulmonary) LN (5L)	6	-
Lt para-aortic LN (6L)	-	-
Rt subcarinal LN (7R)	1	1
Rt hilar LN (10R)	1	1
Lt hilar LN (10R)	1	-
Rt interlobar LN (11R)	1	-
Lt interlobar LN (11L)	4	-
Rt lobar LN (12R)	3	-
Lt segmental LN (13L)	3	-

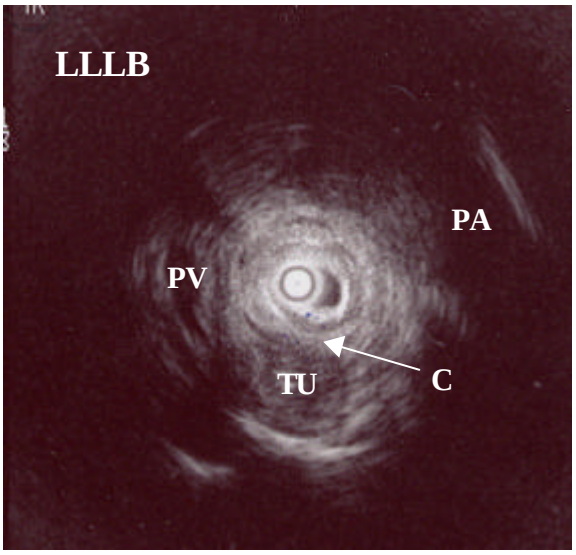
3.6.2 Bronchial wall invasion

Criteria of identification of bronchial wall invasion by EBUS additionally:

Characterizing tumor invasion of a bronchial wall as additional information provided by EBUS takes in account the characteristic sonographic patterns and alterations of tumor in bronchial wall observed by EBUS and not by CT and its histological verification to be malignant through bronchoscopic biopsy. However, biopsy could not confirm the exact depth of invasion, which was ascertained by

EBUS images only.
In pathologically verified lung cancer patients (36), tumor invasion of the bronchial wall was identified in 21 cases.
The distribution of extent was as follows:
- *Invasion beyond the adventitia: 13 cases.*
Tumor invading all bronchial wall layers and extending beyond the adventitia.
- *Invasion of the adventitia and lymph node invading the bronchial wall: 1*
Tumor invading up to adventitia associated with lymph node invading from outside the bronchial wall layers up to the submucosa, but with intact mucosa (case 26).
- *Invasion of cartilage: 3 cases.*
Tumor invading up to the cartilage. The tumor has a special appearance, it invades submucosa and cartilage, lying between the intact mucosa and adventitia. (in cases 4, 37 and 45).
- *Tumor invading from outside the bronchial wall: 4 cases.*
Tumor invading from outside the bronchial wall up to the cartilage (all cartilage layers are invaded) with intact mucosa and submucosa (cases 3,16 and 23).
In case number 8, tumor invades from the outside of the bronchial wall up to bronchial cartilage (fourth layer) with intact marginal echo at inner-side border of cartilage (third layer), mucosa and submucosa.

Figure 10: An example of bronchial wall invasion and depth diagnosis.



EBUS in Lt lower lobe: Localised area of hypoechogenic tumor mass invading from outside the bronchial wall up to bronchial cartilage (fourth layer) with intact marginal echo at inner-side border of cartilage (arrow) (third layer), mucosa and submucosa. The pulmonary artery (PA) and vein (PV) of the Lt lower lobe appear as an echo free area easy to differentiate during motion.

3.6.3 Infiltration or Impression of blood vessels

In 2 cases impression of pulmonary arteries (Lt upper lobe pulmonary artery and Lt lower lobe pulmonary artery) by enlarged lymph nodes were identified and was based on the sonographic pattern of the impression of vessels observed in other EBUS experience which is characterized by indentation of calibre of vessel with regular margins by close contact to the lesion and failure of CT to identify it.
In all the cases studied no tumor-infiltration of pulmonary vessels had been detected.

3.6.4 Infiltration of mediastinal structures

In all cases studied no infiltration of mediastinal structures was detected.

3.7 Visualization of extraluminal tissue changes causing abnormal bronchoscopic findings

EBUS was helpful in explanation of the bronchoscopic findings in 22 cases (44%) of all cases, while in 36 pathologically verified lung cancer patients it was helpful in 19 cases (53%). EBUS helped in elucidating the cause of carinal widening, extrabronchial compression, submucosal invasion, bronchial stenosis or narrowing, and abnormal mucosa (Table 21). In 3 non-malignant cases, extraluminal tissue changes were observed, 2 of them proved to be malignant in follow up, while the third case proved to be chronic organized pneumonia after thoracotomy.

Table 21: EBUS help in explanation of bronchoscopic findings

Cases	N	R (%)	95% CI
All studied cases (50)	22	44	30-58.8
Pathologically verified lung cancer (36)	19	53	35.5-69.6

3.8 Cases without further information provided by EBUS

Radiology and bronchoscopy provided more data than EBUS in 10 cases out of the 50 cases studied (20 %) and in 7 cases out of 36 pathologically verified lung cancer patients (19%).
These data were as follows:
9 lymph nodes in 50 patients (previously enumerated),
2 peripheral lesions in 50 patients (previously enumerated).

3.9 EBUS-assisted TBNA of EBL

EBUS-assisted TBNA was performed in 44 lesions in 36 out of 50 cases studied. The main indication of TBNA was cytological diagnosis of PBL (19), enlarged LNs (21), peripheral (2) and bronchial lesions (2). TBNA was performed in more than one location in the same patient whenever the diagnostic purpose necessitate.

EBUS-assisted TBNA of extrabronchial lesions EBL (PBL+LNs) was diagnostic in 36 out 40 EBL (90%). 28 were malignant EBL (70%), 8 were benign EBL (30%), while in 4 EBL (10%) were non-diagnostic (Table 22).

In case number 29, EBUS assisted TBNA secured a definitive cytological diagnosis (squamous cell carcinoma) after previously negative pathological results obtained by mediastinoscopy to a left extrabronchial lesion in the aortopulmonary window.

Table 22: Cytological diagnosis of EBUS assisted TBNA of EBL

EBUS-assisted TBNA of EBL	Diagnostic			Non-diagnostic		
N	N	R (%)	95% CI	N	R (%)	95% CI
40	36	90	73.9-96.9	4	10	3.1-26.1

N = number. R = Rate. CI = confidence interval.

3.9.1 EBUS-assisted TBNA of LNs

In 19 patients, EBUS assisted TBNA of LNs were performed in 21 enlarged mediastinal, hilar and intrapulmonary LNs. Of these 13 were detected by EBUS only and 8 by both EBUS and CT.

Diagnosis by EBUS-assisted TBNA of LNs was achieved in 19 lymph nodes (90%), while in 2 LNs (10%) EBUS-assisted TBNA of LNs was non-diagnostic (Table 23). 12 LNs (63%) were tumor-invaded and in 7 LNs were benign (37%). 12 of the 19 diagnosed LNs were detected by EBUS only (63%), 7 (37%)of them were malignant.

Table 23: Results of EBUS-assisted TBNA of LNs

EBUS-assisted TBNA of LNs	Diagnostic			Non-diagnostic		
LNs	N	R (%)	95% CI	N	R (%)	95% CI
21	19	90	68.3-98.7	2	10	1.23-31.7

N = number. R = Rate. CI = confidence interval.

2 EBUS-only detected benign lymph nodes (case 1 and 39) had their histology confirmed later by mediastinoscopy.
No complications were recorded from TBNA procedures.

?Change of staging and therapeutic consequences:
7 malignant LNs were additively detected by EBUS only and diagnosed by EBUS-assisted TBNA in 5 cases (Cases No. 9, 23, 44, 47 & 50).
The nodal descriptors (N) changed from N_0 to N_1, N_1 to N_2 and N_0 to N_2 in 1, 2 and 1 case respectively. In the fifth case, there was no change in the nodal descriptors (N). The nodal descriptors (N) changes in the 4 cases lead to changes in patients' tumor stages in 2 cases. However, this change had no therapeutic consequences on patients, as they were functionally inoperable. There was no change in tumor descriptors (T) by addition of EBUS in the present study.

3.10 Sedation
The mean value of midazolam sedation given was 6 ± 3.5 mg.

3.11 Complications and patient tolerance
All complications encountered were either mild or moderate oxygen desaturation in 6 and 1 respectively, mild and moderate cough (9 and 3) and 2 cases of tachycardia. No bleeding was recorded (Table 24).

Table 24: Complications of EBUS in all studied cases.

Complications	Desaturation		Cough		Bleeding		Tachycardia	
	N	%	N	%	N	%	N	%
Mild	6	12	9	18	0	0	2	4
Moderate	1	2	3	6	0	0	0	0
Aborted examination	0	0	0	0	0	0	0	0
Total	7	14	12	24	0	0	2	4

A patient tolerance score was plotted based on complications encountered (Table 25):
1-Complete tolerance (no complications) in 33 cases (66%).
2-Partial tolerance (mild to moderate complications) in 17 cases (34%).
3-No tolerance (procedure aborted) were not encountered.

Table 25: Patient tolerance to EBUS in all studied cases.			
Tolerance	N	R(%)	95% CI
Complete tolerance	33	66	51.2-78.9
Partial tolerance	17	34	21.1-48.8
No tolerance	0	0	

N = number. R = Rate. CI = confidence interval.

3.11.1 Duration of EBUS and FFB examination

When time of EBUS and FFB were recorded (34 cases), the percentage of the EBUS examination from the total time of bronchoscopy was calculated as 44% (Table 26).

Table 26: Duration of the procedures in 34 cases	
Duration	Mean value
FFB (including EBUS)	34 min
EBUS	15 min
Percentage of EBUS duration	44%

3.11.2 Instrument handling Difficulties

3.11.2.1 Difficulties in the balloon sheath preparation before use

Although the instruction manual steps for balloon sheath preparation were followed exactly, it was always difficult to achieve a fully inflated balloon without air bubbles inside.

Also the attachment of the balloon O-ring section to the ditch section of the ultrasonic probe with the balloon applicator (MaJ-564) or manually was difficult.

3.11.2.2 Difficulties in the balloon sheath during use

a) Dislocation of the attachment between the balloon O-ring section to the ditch section of ultrasonic probe occurred twice during the present study.

b) Perforation of the balloon occurred twice during the present study.

3.11.2.3 Image artifacts

The most commonly met artifact were in the form of:

a) Radiating images, appearing as broken black lines from the center to the periphery.

b) Multiple repeated reflections artifacts due to the balloon echo occurred when there was insufficient contact between the balloon and the bronchial wall.
c) Multiple edges between the images.

3.11.2.4 US image adjusting difficulties

Adjusting the ultrasound image is only possible in real-time mode, thus adding more time to the examination to adjust image quality while the balloon is completely inflated. Freeze-frame images cannot be adjusted. This sometimes lead to inadequate image picture quality.

3.11.3 Orientation difficulties related to the instrument

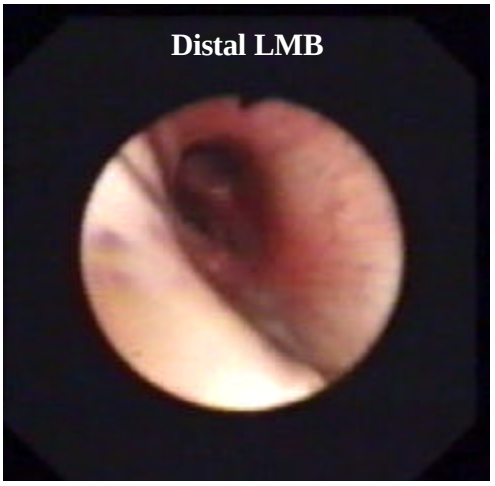
a) The subscreen containing the endoscopic picture was too small to see the relation of the ultrasound probe in the bronchus examined.
b) The movement of the bronchoscope with the ultrasound probe is in 2 directions only. So in order to orient in 4 directions (medial, lateral, anterior and posterior), the bronchoscope with the ultrasound probe needs to be rotated in another plane perpendicular to the first, occasionally leading to loss of orientation.

3.12 Typical case demonstration

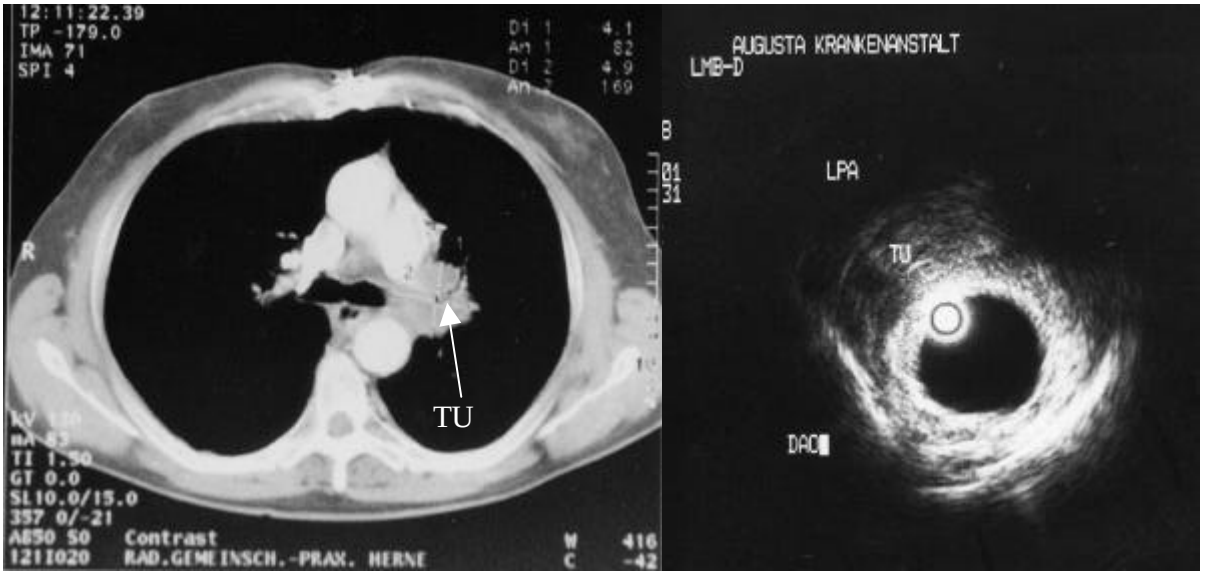
Case 1:

A 76 male patient, with a smoking history of 60-pack year was referred to our department after undergoing diagnostic mediastinoscopy for a mass in the aorto-pulmonary window with negative pathological results. Endoscopic, CT and EBUS findings are presented. EBUS identified the position of the lesion in relation to the bronchial lumen, assisting in the location of transbronchial puncturing. Through EBUS assisted TBNA squamous cell carcinoma was diagnosed.

Figure 11: An example of EBUS assisted TBNA of an extrabronchial lesion



a) Endoscopically, the distal Lt. main bronchus (LMB) shows no abnormality



b) c)

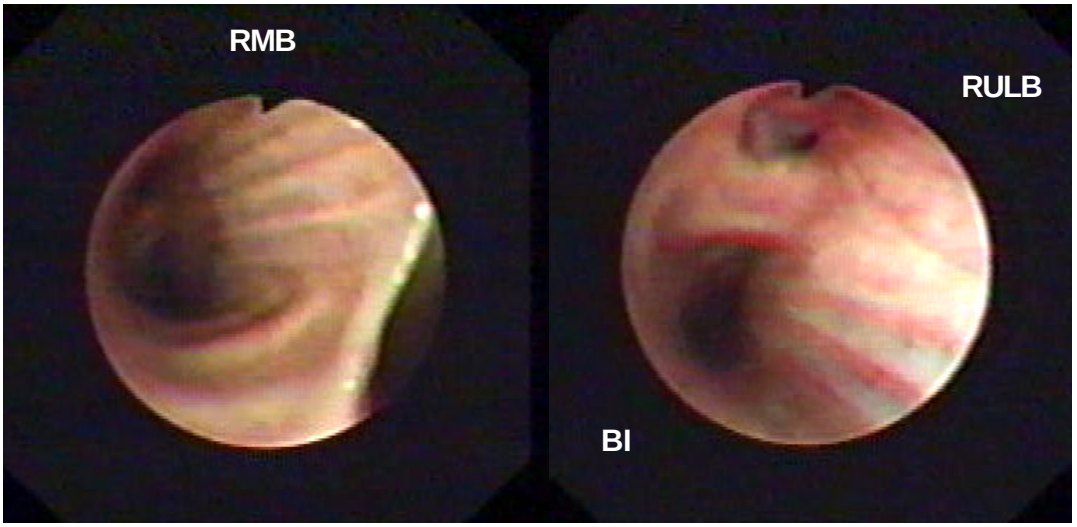
b) The CT scan cut shows a tumor mass (TU) in the region between pulmonary artery anteriorly and descending aorta posteriorly.

c) EBUS in Lt. main bronchus: Antero-laterally there is an echo free area of the left pulmonary artery (LPA) that showed vigorous pulsation during examination, postero-laterally there is an echo free area of the descending aorta (DAO), in-between there is a hypoechogenic irregular area suspicious of the tumor mass (TU).

Case 2:

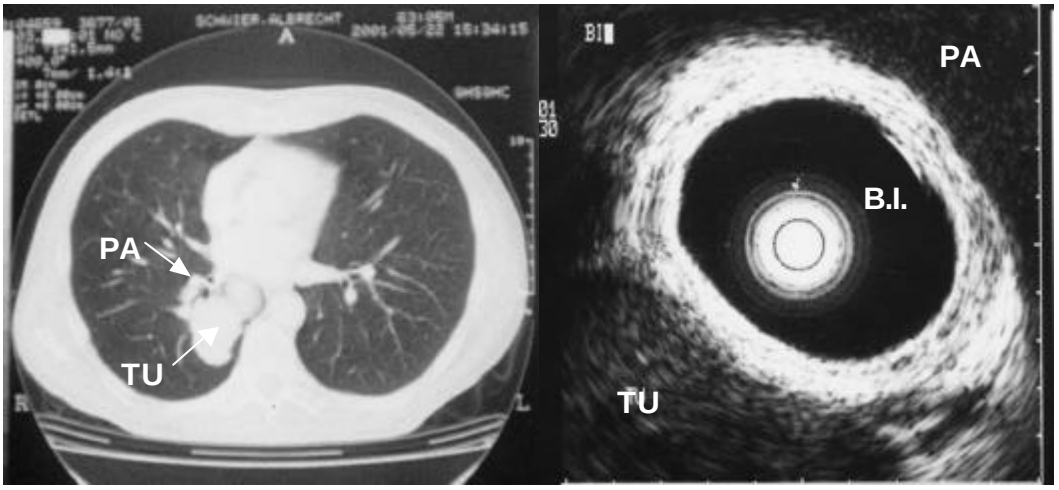
64 year male non-smoker patient, presented with a space occupying lesion in the Rt. middle mediastium. Endoscopic, CT and EBUS findings are presented.

Figure 12: An example of EBUS help in explanation of bronchoscopic findings and an additive LN detected by EBUS only.



a) *b)*

a) Rt main bronchus (RMB) endoscopically without abnormality.
b) Dorsal wall of bronchus intermedius (BI) with extraluminal compression.



c) *d)*

c) CT scan cut shows pulmonary artery (PA) anterior to bronchus intermedius and a tumor mass dorsally.
d) EBUS in bronchus intermedius explained the endoscopic appearance of extraluminal compression by on site identifying an underlying hypoechogenic

tumor mass (TU), additionally defining the exact relation of lesion to pulmonary artery (PA), which appears as an echo free area anteriorly.

e) *f)*

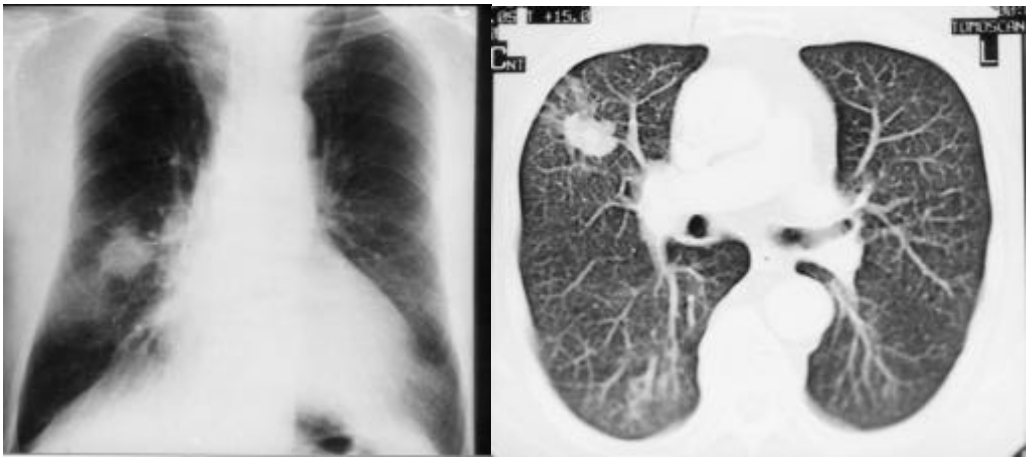
e) CT scan cut shows pulmonary artery (PA) anterior to Rt. main bronchus, with no evidence of enlarged LN in this area (circle).

f) EBUS in Rt. main bronchus (RMB), echo free area of the pulmonary artery (PA) anterior and azygos vein (AZ) posterior. An additional enlarged Rt. hilar LN (#10R) measuring 12 x 10 mm is seen laterally, changing the patient's nodal stage after TBNA.

Case 3:

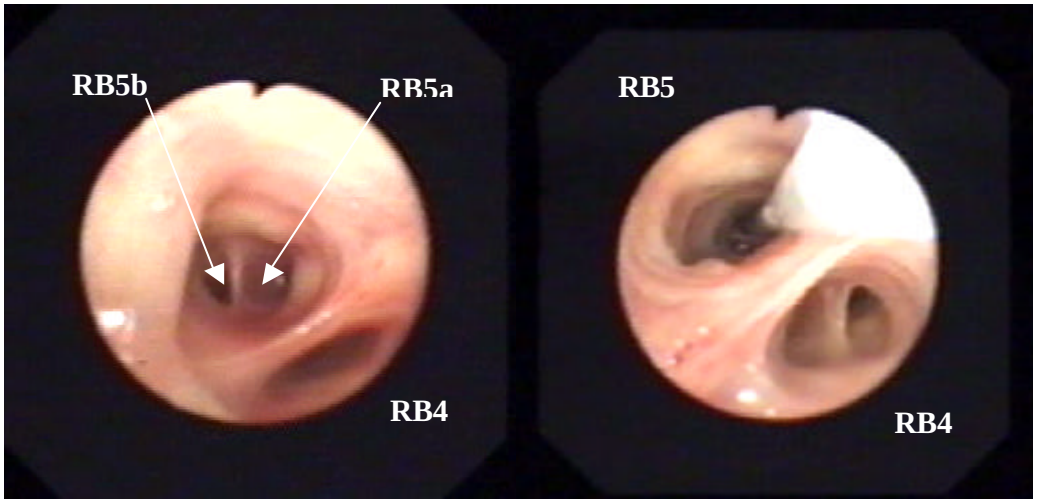
76 year male patient, with a well known history of COPD and a smoking history of 80 pack years, presented with a rounded lung shadow in Rt middle radiological lung zone. Chest x-ray, endoscopic, CT and EBUS findings are presented.

Figure 13: An example of a peripheral lung lesion



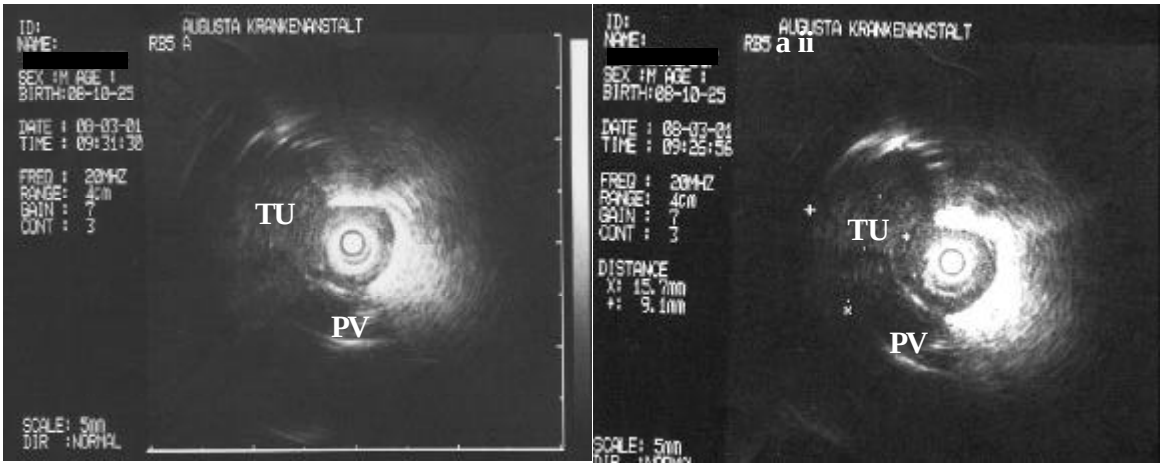
a) b)

a) Chest x-ray postro-anterior view showing a rounded lung shadow in Rt middle lung field.
b) CT scan cut showing the same peripheral shadow in the region of the medial segment of the middle lobe.



c) c)

c) Endoscopic view showing no abnormality.
(RB5 = medial segment of Rt middle lobe, RB5a and RB5b are dorsal and ventral subsegments. RB5a(ii) is a further dorsal subdivision. RB4 = lateral segment of Rt middle lobe.)
d) Endoscopic view while advancing the EBUS probe.



e) EBUS in RB5a: Showing hypoechogenic irregular area suggestive of tumor mass (TU), and an echo free area of a pulmonary vein (PV), which was identified by its weak sluggish pulsations during motion.

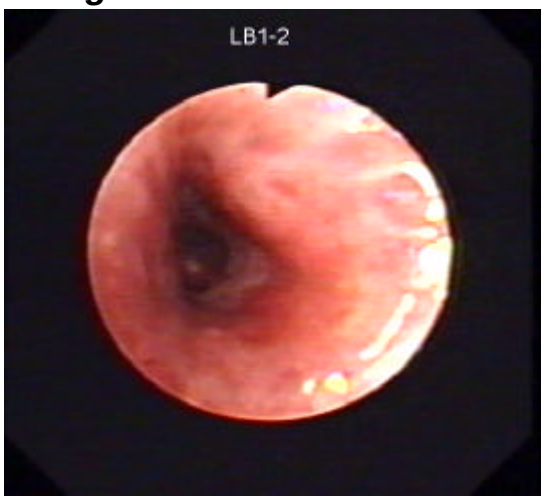
f) EBUS in RB5a ii: after advancing the probe more distally, showing hypoechogenic irregular area of suggestive tumor (TU) measuring 15.7 x 9.1 mm, with an echo free area of a pulmonary vein (PV).

Through TBNA of the peripheral lesion squamous cell carcinoma was diagnosed.

Case 4:

A 70 year old male patient, with a smoking history of 60-pack years and a well known history of chronic bronchitis, presented with a suspicious shadow in the Lt upper radiological lung zone. . Endoscopic, CT and EBUS findings are presented.

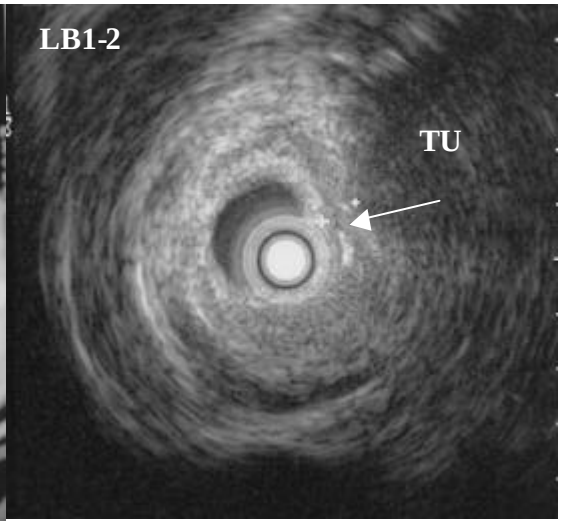
Figure 14: An example of a peripheral lung lesion with bronchial wall invasion, EBUS definition of depth of invasion and explanation of bronchoscopic findings.



a)

a) Endoscopically the apico-posterior segment bronchus of Lt upper lobe (LB1-2) is narrowed with mucosal redness and hypervascularization.

b)



c)

b) CT scan cut shows a tumor mass in the apico-posterior segment of Lt. upper lobe (LB 1- 2).

c) EBUS in the apico-posterior segment bronchus of Lt upper lobe (LB1-2) explains the cause of endoscopic appearance by identifying the underlying tumor mass (TU). This

is an example of invasion of the bronchial wall from outside, invasion is up to the bronchial cartilage with intact mucosa and submucosa (arrow).

4. Discussion

4.1 Lung cancer status

Lung cancer is the most common cause of cancer death for both men and women in the United States, and it is a growing worldwide problem, especially in developing countries, killing over 85% of those it afflicts within five years. The dimensions are of epidemic proportion and reflect the general failure of conventional diagnosis and treatment (13, 55, 74). In Germany 42,000 newly diagnosed patients are recorded annually, of whom only 6,000 are expected to survive five years (56).

In the past, there were few good options for the detection, prevention, or treatment of lung cancer. This led to considerable pessimism regarding the care of patients with the disease. In the recent past, however, there have been many advances in understanding the biology, early detection, staging, prevention, and treatment of lung cancer, which together with improved nursing and home care, are bringing about a reassessment of the nihilistic attitude of physicians toward lung cancer patients (13).

4.2 Inefficiency of conventional methods

The art of bronchoscopy has progressed at a rapid pace over the last 30 years. From its humble beginnings as a mere curiosity, the bronchoscope has become an essential component in the struggle against lung cancer (63).

Improvements in flexible bronchoscopic optics and image acquisition technology, as well as in the tissue sampling capabilities of the procedure, have expanded its applications, resulting in an overall diagnostic yield for NSCLC and SCLC in excess of 95% for visible lesions (1, 76).

At the same time limitations of bronchoscopy are well recognized. The view of the bronchoscopist is limited to the lumen and the internal surface of the airways (9). Many pathological processes of airways involve the submucosal and the peribronchial structures including mural and extramural tumors and metastatic enlarged lymph nodes. Some of these processes are suspected from indirect signs such as discoloration and swelling of the mucosa, pathological vascularization, leveling of the cartilage relief or impression, displacement or destruction of the airway wall, while others can not be suspected as they show no endoscopic signs (9, 49). Thus, the diagnostic yield tends to be much lower in submucosal and peribronchial diseases than for the exophytic lesions (49).

The inability to directly visualize peripheral lesions together with other factors contribute to the lower diagnostic rate of peripheral masses at bronchoscopy (18).

In bronchoscopic evaluation of tracheobronchial wall infiltration by cancer of the esophagus, macroscopic abnormalities of airway invasion are infrequently seen, sole bronchoscopic inspection is not reliable. Extensive bronchoscopic sampling

may be helpful (64). However in the absence of macroscopic signs, they are blind procedures.

The success of endobronchial therapies such photodynamic therapy is strongly influenced by the depth of the infiltration of the tumor into bronchial wall or extrabronchial invasion, information never reliably obtained by endoscopic views and even random biopsies alone (50).
Therefore there is an essential need to overcome these limitations through extending the view of the bronchoscopist beyond the tracheobronchial lumen (32).

Imaging modalities play an integral role in diagnosing, staging, and following patients with lung cancer (60). The role in the diagnosis is focused on preprocedural planning, aiding in establishing an appropriate approach for bronchoscopic biopsy (79).
Aided by standard chest radiography, CT and fluoroscopy during bronchoscopy, it is possible to further localize peripheral lesions, extraluminal tumor or lymph nodes that are amenable to transbronchial biopsy, but in spite of radiographic guidance and visible deformity, the precise locations of peripheral lesions, extraluminal masses or lymph nodes viewed through the bronchoscope may not be obvious. It is also usually not possible to identify major pulmonary and mediastinal blood vessels (27). This is attributed to the fact that CT or magnetic resonance imaging can help with the prebronchoscopic planning, but on application of cross-sectional imaging to the actual bronchoscopic procedure it is limited. This is also evident in new techniques such as virtual bronchoscopy, which may help the bronchoscopist with prebronchoscopic planning, but up till now no applied technique has effectively linked the bronchoscope with the CT images to aid the procedure itself (77).
In addition Solomon and his colleagues (77) speculated that the limitation encountered from C-arm fluoroscopic guidance of peripheral lesion is due to the fact that the lesion lies in three-dimensional space while the fluoroscopy image at any time is two-dimensional only (even though this limitation can be overcome by rotational fluoroscopy). Solomon's observations reinforces the essential need to extend the bronchoscopic view beyond the lumen during the bronchoscopic procedure.

Staging is critical for treatment of lung cancer. Computed tomography is one of the most commonly performed imaging modalities in assessment of lung cancer, evaluating local extent, mediastinal invasion and in staging of mediastinal lymph nodes. Despite its safety and utility, a number of limitations to use CT as a sole staging test exist. CT has its limitation in evaluating tracheobronchial wall structure and thus cannot reveal the exact depth of the tumor invasion (82). Similarly the

sensitivity of CT in the detection of invasion of vital mediastinal structures e.g. great vessels, trachea and esophagus is low, with reports of sensitivity in the ranges of 60-75% (1). The CT ability to show lymph node enlargement clearly is not sufficient, due to the movement and the partial volume effect of the pulmonary artery and vein, aortic arch and the left atrium (20). Thus not all mediastinal nodes can be detected by CT (17). The short-axis diameter greater than 1 cm criteria used as an indicator of pathologic enlargement is a nonspecific criterion for malignancy, as the incidence of metastases in normal sized nodes (<1 cm) on CT were 21% in patients with non small cell lung cancer who underwent thoracotomy in a recent study (2, 60).
Another study (25), comparing the imaging TNM [(i)TNM] determined by CT findings and pathological TNM [pTNM] determined by pathological examination of the resected tumors and lymph nodes, in the staging of bronchogenic carcinoma, reported the following: the agreement between (i)TNM and pTNM was only 35.1%. The primary tumor (T) was correctly staged in 54.1%, over-staged in 27.0% and under-staged in 18.9% of the patients. Sensitivity and specificity of CT regarding hilar and mediastinal lymph node staging were 48.3 and 53.3%, the nodal (N) factor was correctly determined by CT scan in 35.1%, over-staged in 44.6%, and under-staged in 20.3% of the patients. Thus even with present-day CT scanners (i) TNM provides no accurate staging of bronchogenic carcinoma.

Even as invasive procedures as mediastinoscopy, considered the ‘‘gold standard’’ of preoperative mediastinal evaluation, cannot evaluate all mediastinal compartments or lymph node groups, and a significant percentage (up to 33%) of patients with bronchogenic carcinoma who have a negative mediastinoscopy prove to have mediastinal nodal metastases at surgery (28, 78).
The use of TBNA can eliminate the need for mediastinoscopy for evaluating right paratracheal, mediastinotomy (especially for left paratracheal and aorticopulomonary window lesions) and open thoracotomy (in particular for posterior subcarinal lesions). In the literature TBNA diagnostic results can be expected in between 50% to 80%, clearly there is room for improvement. Furthermore, not all investigators have been able to consistently reproduce these results and it remains underutilized (53).

For these reasons, it is necessary to improve the diagnostic tools for bronchoscopic staging of the mediastinum, through new procedures.

4.3 Endosonography

Endosonography has been proven to be superior in imaging beyond the luminal surface, providing information about the exact location of masses as well as such

normal structures as arteries, veins, and lymph nodes. It is well established in other fields of medicine (88, 91). This is especially true for gastrointestinal endoscopy, where EUS has its place in staging of carcinoma of the esophagus, cardia and colorectum exerting decisive influences on therapeutic decisions (3, 40, 83).
Recent trials using EUS for nodal staging of lung cancer were hindered by inability to assess N3 disease in the anterior mediastinal compartment due to interposition of the trachea (29).
After overcoming technical problems EBUS became available for clinical practice and early reports are encouraging (6, 27, 79).

In the light of previously enumerated limitations in conventional diagnostic methods of lung cancer, the use of EBUS was evaluated to assess its use in overcoming these limitations.

4.4 The present study as it relates to reports in literature

In a prospective study involving 50 patients with suspected lung cancer, two hypotheses were tested: EBUS provides valuable additional information for assessment of lung cancer compared to bronchoscopy and CT; and the use of EBUS in bronchoscopy under topical anesthesia is practicable and applicable in spite of some prolongation in the examination time.
Fifty consecutive patients with suspected lung cancer undergoing diagnostic and/or staging fiberoptic bronchoscopy under topical anesthesia were recruited. All the patients without contraindications for conventional fiberoptic bronchoscopy had a clinical history together with shadow(s) or mediastinal adenopathy in computed chest tomography ± chest x-ray suspicious of lung cancer. These subjects provided the basis for EBUS addition to the usual routine bronchoscopic workup performed for assessment of lung cancer.

4.4.1 EBUS examination anesthesia, sedation, application sites and duration

In contrast to other reports applying EBUS in general anesthesia (8, 19, 36), in this study it was applied under topical as it is customary in routine, ambulatory endoscopy.
In the present study, prebronchoscopic patient preparation and topical anesthesia were no different to the usually applied methods in our bronchology unit. In addition to 100 mg prednisolone given intravenously 90 minutes before bronchoscopy, 2.5 mg Salbutamoul solution + 0.25 mg Ipratropium bromide solution were added to the lidocaine 4% solution inhalation in COPD patients to decrease cough and bronchospasm. Cautiously titrated i.v. midazolam sedation was given under continuous oxygen supplement and pulse-oxymetric monitoring throughout the procedure.

The mean value of midazolam sedation given was 6 ± 3.5 mg; no complications related to midazolam sedation were recorded and no benzodiazepine antagonist was needed.

The number of EBUS applications in different locations was 114 in 50 patients. No difficulty in reaching all desired locations with the ultrasound probe was recorded (Table 8, Fig. 7).

The positions of EBUS applications were selected on the basis of the radiological and/or endoscopic findings, surveying these regions until the lesion was reached, under consideration of the standard positions stated in the literature (7).

A similar selection concept based on radiological and/or endoscopic findings prior to EBUS examination were reported by Goldberg et al. (27) and Steiner et al. (79).

The mean duration of EBUS was 15 minutes, it constituted 44% of bronchoscopy time in the present study (Table 26). In comparison to other studies under topical anesthesia, EBUS examinations ranged between 5-15 minutes and constituted between 20-60% of bronchoscopy time (19, 69), while under general anesthesia EBUS examinations ranged between 3.1-14.4 minutes (36). The added time in the present study is expected with spontaneously breathing patient under conscious sedation with strong respiratory movements, coughing, and clearing of secretions which lead to delay localization and acquisition of good documentation. In addition to, EBUS application in more than one site in each patient and cautious examination to achieve the best patient tolerance during the examination.

4.4.2 EBUS detection of anatomical-pathological structures, central and peripheral lesions

Different anatomical-pathological structures could be identified by EBUS including blood vessels, esophagus, normal lung parenchyma, lymph nodes and tumors. Each has a peculiar sonographic pattern, which were similar to previous EBUS studies (27, 32, 79).

Some difficulties were encountered in the differentiation between arteries and veins especially in the right and left lower lobes even after a trial to synchronize the arterial pulsations with pulse-oxymetry. This can be attributed to the wide anatomical variation in the positions and the numerous adjacent small caliber branches of the pulmonary arteries and veins in right and left lower lobes, with the possibilities of transmitted pulsations to veins. Similar difficulties were reported by Herth and Becker (32) and Scherer et al. (69), even after application of echo contrast medium it was difficult (32).

In one case, the detailed internal echo structure of a lymph node revealed a central hyperechogenicity lying against the hypoechoic background representing fat surrounding the nodal hilum. This picture represents a typical sonographic pattern of normal nodal architecture previously demonstrated in other areas of the body

and in peribronchial lymph nodes (27, 30, 79). In another case the lymph nodes appeared as hypodense irregular structures in the usual anatomical site, it was thought that this pattern might occur when the node metastases had invaded through the node capsule (extra-nodal metastases) (61).
A search for a sonographic echo-pattern or suspicious size of the enlarged LNs suggestive of malignant infiltration or benign enlargement was non-productive, as the gold standard for involvement of LNs by metastases is cyto-histological evidence. Becker and Herth in an invitro study were not able to find reliable sonographic signs for malignant infiltration (32).

The suspected lesions were classified into central, peripheral or combined lesions based on combined FFB and CT findings (Table 9). In all cases, studied EBUS detected 34/34 central lesions (100%), 12/14 peripheral lesions (86 %), and 2/2 with combined central and peripheral lesions (100%) (Table 10).
In the 36 cases with pathologically verified lung cancer, EBUS detected all the cases with central lesions i.e. 23/23 (100%), 11/12 peripheral lesions (92%) and the case with combined central and peripheral lesions (100%). Thus, EBUS only failed in detecting one peripheral lesion (3%). EBUS was highly efficient in detecting all tumors, with equal detecting capability for central and peripheral tumor sites (Table 11& 12).
Several studies showed nearly similar results to the present study, taking in consideration the differences in systems used for EBUS applications.
Hürter and Hanrath (39), in their early experience with EBUS application in patients with lung cancer, could identify 69/74 of the central lesions (93%) and 19/26 of the peripheral lesions (73%) by EBUS. However, they used 20 MHz ultrasound transducer-containing catheter without a balloon sheath, different from the method applied in the present study, and used a similar definition of central and peripheral lesions, but based on endoscopy only.
Goldberg et al. (27), in a series of 25 patients with known or suspected lung cancer, using 12.5 or 20 MHz US probes as that used by Hürter and Hanrath (39), applied the same definition of central and peripheral lesions adopted in the present work. They could identify 19/19 of the central lesions (100%), 4/6 of the peripheral lesions (67%) by EBUS, because of the difficulty to maintain adequate contact with the bronchus, 2 cases could not be detected.
Steiner et al. (79), used the same system and frequency applied by Goldberg et al., (27), but tried to eliminate the air around the transducer by injecting sterile water in the chamber between the catheter and the transducer. They could identify 15/15 of the central lesions (100%) by EBUS, 20/22 of the peripheral lesions (91%) and all the cases with combined central and peripheral lesions 7/7 (100%) in 44 cases with clinical and radiological evidence of central and peripheral thoracic masses.

4.4.3 Additional information provided by EBUS

In all areas examined by EBUS, CT and FFB, agreement about the main features of the primary disease processes was achieved, but the main interest was on the additional data EBUS could provide in addition, in the form of further lymph nodes, depth of tumor invasion, blood vessel impression or infiltration. Also it helps in explanation of the bronchoscopic findings and its assistance of TBNA.

4.4.3.1 Lymph nodes

The lymph nodes studied were classified into three groups according to the method of detection: LNs detected by CT and EBUS, by EBUS only, or by CT only. Characterizing a lesion as a lymph node takes into account similar sonographic patterns of lymph nodes in other areas of the body (30), and appearance of cytologically verified nodes from previous EBUS experience.

In the search for draining lymph nodes proximal to the primary lesions, EBUS detected nodes not present in CT prior to bronchoscopic-EBUS procedure. Thus, EBUS may identify additional proximal LNs, which might be helpful in staging. The total lymph nodes detected by EBUS in pathologically verified lung cancer patients, were variably distributed, including mediastinal, hilar and intrapulmonary LNs groups. Their position in relationship to the bronchial lumen, depicting shape, border and size, longitudinal and cross diameter, delineating surrounding structures as pulmonary and mediastinal vessels was a help in performing TBNA. The outer border of LN were sometimes beyond the EBUS range, making it difficult to measure the exact cross diameters in all cases, but when measured it ranged between 0.4 to 2.5 cm. Similar reports contain fine sonographic images of a variety of LN groups, and LN size as small as 3 mm (11, 27, 41, 70, 75, 79).

Sagawa and his coworkers (65) compared the diagnostic value of CT with that of transtracheobronchial ultrasonography (TUS) in the evaluation of mediastinal lymphadenopathy in 5 patients with resectable lung cancer. They found that the sizes of LN measured by TUS were similar to or slightly smaller than the sizes as measured by CT. Hilar and right paratracheal LN were clearly observed with TUS, but were sometimes unclear with CT.

EUS also proved to be superior to CT in the detection of mediastinal lymph nodes and it was possible to visualize nodes as small as 5 mm (29).

In addition, not all mediastinal nodes could be detected by CT (17, 20) and that imaging TNM (using CT) was congruent with pathological TNM, as regarding the nodal (N) factor in only 35.1%, of the patients (25). All this supports the ability of EBUS to identify additional LNs and to clarify and delineate masses and LN better than CT in the present study.

In the pathologically verified lung cancer patients, seven LNs had been detected by CT only and not by EBUS. In 4 lower paratracheal LN, failure of detection could be attributed to impaired patient tolerance to the procedure in the trachea, and to incomplete coupling between the balloon sheath and tracheal lumen. However, in the last three examinations of the trachea, detection of lower paratracheal LNs was successful. This might be attributed to a different examination technique. By pushing the US probe towards the suspected site of lower paratracheal LN on the tracheal wall before the balloon inflation, so an image can rapidly be captured.
Scherer et al. (70), reported similar difficulties during examination of paratracheal LN, where full inflation of balloon in the trachea for achievement of good coupling was not tolerated by patients. The tracheal examination had to be terminated prematurely in 34%.
Lack of patient tolerance was responsible for failure of depicting one subcarinal LN, while in one Rt hilar LN the EBUS image itself was inconclusive. The para-aortic LNs could not be detected, as they are beyond EBUS detection range. Wang (90) stated that these LNs are beyond reach of TBNA as well. When involved by lung cancer, they are often associated with involvement of subaortic or left hilar LN, then they can be reached by EBUS assisted TBNA easily.

4.4.3.2 Depth of tumor invasion

The most acceptable available definition for identifying the laminar structure of the tracheobronchial wall described by Kurimoto et al. (42), has been used in the present study (Table 1). Frequently the multi-layers of the normal bronchial wall are not easily identifiable. The third marginal layer (inner-side border of cartilage or cartilage-endochondrium) and the fourth layer (bronchial cartilage) appear as hyperechogenic, hypoechogenic layers respectively, near the middle part of the bronchial wall and this is a helpful landmark for identifying the remaining layers of bronchial wall. The depth of tumor invasion could be identified by its relation to the bronchial cartilage, which could be detected and pointed out clearly.
In the 36 pathologically verified lung cancer patients, tumor invasion of the bronchial wall had been identified as an additional information provided by EBUS over CT and FFB in 21 cases. Invasion beyond the adventitia was documented in 13 cases, up to the adventitia in one case associated with lymph node invading the bronchial wall, invasion of cartilage in 3 cases, and tumor invading from outside the bronchial wall in 4 cases.

All these areas were confirmed to be malignant histologically through bronchoscopic biopsy (forceps or needle), this however could not confirm the exact depth of invasion. In addition, all the cases diagnosed were non-operable, so the

correlation between the images of the depth of invasion obtained by EBUS and histology could not be performed.

It has been reported previously that high frequency ultrasound endoscopy proved to be superior to CT and MRI in demonstrating detailed structures of wall of various tubular organs and in evaluation of the depth of tumor invasion of the wall (16). In both gastrointestinal and respiratory systems, the accuracy of evaluation of the tumor invasion were much higher than CT, with EUS it was 89%, where as by CT it was only 59% (84), while for EBUS it was 94%, and for CT it was only 51% (34).

The definition of the detailed layers of the normal bronchial wall and the detailed depth of tumor invasion by EBUS varies between experimental and clinical studies.

Under favorable conditions in experimental studies, as needle-puncture experiment preformed by Kurimoto et al. (42), the details of laminar structure of normal tracheobronchial wall could be easily identified on specimens from human tracheas and bronchi, demonstrating the histological anatomical structures corresponding to each sonographic alteration. In addition, the detailed depth of tumor invasion by EBUS could be classified into four levels: submucosa, cartilage, adventitia and beyond adventitia, from resected lung cancer specimens.

Recently and in agreement to the present study, Miyazu et al. 2001 (50), using the same sonographic definition of the laminar structure of the tracheobronchial wall and 20 MHz ultrasound probe, demonstrated that it was difficult to detect all the layers of normal bronchial wall and consequently the four levels of the depth of tumor invasion by EBUS in a clinical study. As the cartilage layer was clearly more evident than any other layer in agreement with other EBUS studies (42, 82) the depth of tumor invasion could be categorized into two levels, whether the cartilage is involved or not. This categorization seemed practicable when applied to 3 resectable invasive lung cancers (cartilage involved). The histopathological findings after resection were congruent with the EBUS evaluation. In two other patients with early lung caner (cartilage not involved) a decision for photodynamic therapy was made. EBUS results determined the choice of therapy.

EBUS has its clinical implication on centrally located early lung cancer staging and treatment strategy. In conjunction with new methods as combined automated sputum cytometry and cytology for detection (54, 56), autofluorescence bronchoscopy for localizing and delineating tumor margins (56, 81), EBUS can determine depth of tumor invasion and enlargement of regional lymph nodes (42, 36). The decision as to which therapeutic modality (surgical or endobronchial) should be applied for cure (81, 50) may depend on whether the cartilage is involved or not (50).

In the present study, tumor invading from outside the bronchial wall had been described when most of the sonographic pattern of tumor (hypoechoic) was lying outside the bronchial wall and involved wall structures. (i.e. extramural-intramural invasion), this pattern of invasion which was not described before by Kurimoto et al. (42). It is only of importance in surgical resection decision making of mediastinal tumors, paratracheal tumors, thyroid tumors and metastatic lymph nodes. If the adventitia is not involved it can be assumed that the patient is operable. Herth and Becker 2001(34) had the same concept in central tumor growth, in which EBUS allowed the differentiation between tumor invasion and impression with much higher accuracy (94%) than CT (51%) and added that patients judged radiologically initially as inoperable tumor, could be operated after EBUS evaluation. In a recent study in 2001(85), EBUS was potentially more useful in diagnosing tracheal invasion by thyroid cancer, compared with conventional CT and/or MRI.
In the new TNM staging of lung cancer 1997 (52), superficial tumors with their invasive component limited to the bronchial wall are classified T1 even if they are in the main bronchus. Defining this entity non-invasively is possible through EBUS imaging of the bronchial wall only.

Kurimoto et al., 1999 (42) added information on the limitations of the EBUS estimation of tumor invasion at present time: it can be difficult due to poor definition on the luminal side of the cartilage at 20 MHz, attenuation by the balloon, difficult visualization at bronchial spurs and the need for a thick flexible bronchoscope because of the balloon sheath. In addition, they considered several measures to deal with these problems as examination at a higher frequency for example, 30 MHz, improvement of balloon quality, diagnosis by making longitudinal slices of the bronchi with a three-dimensional ultrasound system and making the probe thinner.

4.4.3.3 Infiltration or impression of mediastinal structures

Impression of pulmonary arteries by enlarged lymph nodes were identified by EBUS in 2 cases, in addition infiltration of mediastinal vessels or structures was excluded by EBUS in all areas examined.
Herth and Becker (32, 34), could either diagnose or exclude infiltration or impression of mediastinal structures as aorta, vena cava, esophagus or pulmonary artery which frequently proved to be difficult by radiological methods, and was an important point in the preoperative staging process.
EBUS played an important role in preoperative decision-making. In a case of esophageal cancer (case 36), this meant the exclusion of tumor infiltration into the trachea, as there was a clear sonographic demarcation between the esophageal

tumor and the tracheal adventitia. This is of value in both tumors originating from the esophagus with possible infiltration of the tracheobronchial wall or tumors originating from the distal trachea or left main bronchus with possible infiltration of esophagus. In the previous two situations, EBUS proved to be superior to radiology (34, 82).

Summing up the previously discussed additional data (lymph nodes, depth of bronchial wall invasion, blood vessel infiltration or impression) in the pathologically verified lung cancer cases, EBUS provided additional data to FFB and CT in 25 patients (69%), while FFB and CT were superior to EBUS in 7 patients (19%). Statistically the additional data provided by EBUS more than FFB and CT were highly significant as compared to the data that by FFB and CT provided more than EBUS (Table 13).

4.4.4 Explanation of abnormal bronchoscopic findings

EBUS was also helpful in explanation of the bronchoscopic findings in 19 cases out of 36 pathologically verified lung cancer patients (53%) (Table 21). EBUS helped in elucidating the cause of carinal widening, extrabronchial compression, submucosal invasion, bronchial stenosis or narrowing, and abnormal mucosa. EBUS could identify underlying enlarged LNs, extrabronchial tumor, intramural tumors related to these bronchoscopic findings. EBUS thus provides immediate information, even in absence of CT about the underlying cause of indirect bronchoscopic tumor signs during bronchoscopy, delineating surrounding structures e.g. blood vessels. An important feature is the identification of the relationship between the lesion and the bronchial lumen thus aiding TBNA.

4.4.5 EBUS-assisted TBNA

EBUS-assisted TBNA of EBL had diagnostic rate of 90%, of which 70% were malignant and 30% were benign. There were no complications recorded related to TBNA (Table 22). Early previous experience with standard TBNA in the study unit had a diagnostic rate 33% (37), thus EBUS assistance improved the diagnostic yield. However Falcone et al., (18) gave lower diagnostic rates for EBUS-assisted TBNA 60% (21 cases were diagnostic out of 35), but this could be more related to the trial in small diameter LNs.

EBUS-assisted TBNA of lower paratracheal, subcarinal, subaortic, hilar, and intrapulmonary LN had been performed aiming to obtain cytological diagnosis of enlarged LNs, even in the technically more difficult sites as aortopulmonary area due to its proximity to major vessels (90). Subaortic LNs could be easily and safely sampled after EBUS localization.

In all cases of TBNA, technical precautions were taken to abolish any risk of

contamination of samples by bronchial secretions and debris that is characterized by scattered, rare neoplastic cells against a background of bronchial secretions (75). In addition, careful sampling was adhered to in cases of close proximity of the primary tumor to punctured LN. Thus, the incidence of false positive aspirate is likewise rare, and no necessary further surgical confirmation is needed (14, 67, 68)

An adequate cytological specimen is characterized by absent or a paucity of columnar epithelial cells and a large number of lymphocytes and malignant cells to confirm the diagnosis of malignancy, while absence of lymphocytes in the specimen is considered inadequate sample (49, 68).

EBUS-assisted TBNA of LNs was diagnostic in 90 %, of which 63% were malignant and 37% were benign, in these 12 LNs were detected by EBUS only (63%), in which 7 (37%) of them were malignant (Table 23).

Herth and Becker reported that EBUS-assisted TBNA of LNs had improved the yield of TBNA, a diagnostic yield of 82% had been reached, in which 64% were malignant and 36% were benign and added that in further experience the yield was close to 90% (35). An initial study in 1996 (75) comparing US-directed TBNA and standard TBNA of mediastinal adenopathy, found USTBNA exhibits a similarly high diagnostic yield (84%) to standard TBNA in setting of rapid on-site cytopathology evaluation. USTBNA reduced the number of aspirates and provided easier biopsy approach in paratracheal LN in particular while sampling smaller nodes. The authors attributed these results to their very high sensitivity for standard TBNA, to the presence of on-site cytopathology and technical difficulties imposed by using initial 12.5 or 20 MHz US catheters intended for intravascular use (75). However, only subcarinal and paratracheal LNs were included and difficult risky areas like aortopulmonary window (subaortic LNs) were not included.

A recent study in 2001 (24) aimed to demonstrate the usefulness of CT fluoroscopic guidance in improvement the yield of TBNA of subcarinal and precarinal LNs in whom previous standard TBNA was non-diagnostic. A high diagnostic yield 87.5% had been reached in which 75% were malignant and 25% were benign. However there was a need for an attending radiologist, cytologist, and the procedure had been performed within a regular interventional CT time slot of one hour in CT suite, this in addition to the relatively high risk of radiation exposure.

In the benign group of the previous study (24), 6 out of 7 patients had lymphocytes only in the specimen. Follow-up showed only one of these 6 patients to have malignancy. Similarly in the present study, in the benign group, 5 out of 7 patients had lymphocytes only in specimen (lymphocytic hyperplasia of LNs), 2 of them undergone mediastinoscopy which confirmed the cytological diagnosis of EBUS assisted TBNA, while the other 3 were followed up with no evidence of malignancy in period more than 6 months. The presence of 5 lymphocytic

hyperplasia of LNs may be attributed to geographical predominance of anthracosis and / or silicosis in the study region.

4.4.6 Change of staging and therapeutic consequences:

EBUS was helpful in local nodal staging. EBUS-assistance to the conventional TBNA technique could successfully change nodal descriptors (N) in 4 cases. However, there was no change in tumor descriptors (T) by addition of EBUS as there was no detection of infiltration of mediastinal structures or vessels as well as early carcinoma detection in all cases studied.

EBUS addition to the conventional methods of staging of lung cancer lead to an overall change in patients cancer stage in 2 cases only out of 36 verified lung cancer cases, but without any subsequent therapeutic consequences, as the two cases were functionally inoperable.

In a population studied with the intent to characterize otherwise difficult to reach lymph node localizations or radiologically ill-defined tumor margins EBUS addition for local staging would have better subsequent effects on the patients' stage, future therapy plan and considerable cost savings from unneeded surgical procedures. With the data presented feasibility of EBUS-examination in local anesthesia with precision surpassing CT and FFB can be assumed.

4.4.7 Complications and patients tolerability

The majority of complications were mild and infrequent. These included desaturation 6 cases (12%), cough 9 cases (18%) and 2 sinus tachycardias (4%). Moderate complications were rarely observed; desaturation 1 case (1%), cough 3 cases (6%), and no examination was aborted. No serious complications were encountered, and these could be considered as side effects rather than complications (Table 24). Occasionally repeated cough lead to desaturation leading to tachycardia, which is not surprising, considering the large number of EBUS applications (114 in 50 patients).

Patient tolerance score was plotted based on complications encountered, complete tolerance in 33 cases (66%), partial tolerance in 17 cases (34%) and no examination abortion (Table 25).

Initial reports applying EBUS through ultrasound transducer-containing catheter without a balloon sheath under topical anesthesia observed no complications in general. This may be related to the US probe used and also a lack of emphasis on complications analysis (27, 39, 79).

An initial trial was conducted applying the Olympus probes with a balloon sheath using rigid bronchoscopy under general anesthesia in more than 1000 patients from 1994- June 1996. Technical problems as the large diameter of the initial probes precluded the use of flexible scopes (8). However after solving the initial technical

problems, EBUS is still used under general anesthesia on a wide scale. In a recent study published in 2001 (36), documenting all patients who performed EBUS additionally to bronchoscopy between January and December 1999, EBUS was applied under general anesthesia in 603 out of 648 patients studied (93%) through combined rigid and flexible bronchoscopy approach and through flexible bronchoscopy under local anesthesia in the remaining 7%, using US probes identical to that used in the present study. Side effect encountered were rare compared to the present study, 34 patients (5%) developed desaturation and needed supplementary oxygen during the examination, transitory cardiac arrhythmia occurred only during the application of the probe in the left lower lobe bronchus, in 18 patients (17%) patients out of 103 cases, mostly they were sinus tachycardia. The authors make no reference to possible complications of general anesthesia.
Similar side effects, had been reported by Scherer et al. 1999 (69) in their initial experience applying EBUS under topical anesthesia using probes identical to that used in the present study, in which cough occurred in 15-20% of examined cases. Contrary to the present study coughing prevented acquisition of the desired information mandating premature termination in 8-12%. In 10% of examined cases desaturation occurred and mandated repeated deflation of the balloon to improve the oxygenation.
Falcone et al. 2000 (19), describing the Italian experience of EBUS in 70 patients, 62 under topical anesthesia and 8 cases under general anesthesia, experienced much better patient tolerance than the present study. In 93.6% there was complete tolerance, in 6.4% partial tolerance related to coughing, bleeding and hypoxia and the examination was never prematurely terminated in all the examined cases. Comparison between this study and the present study is difficult, as the criteria for selection of patients, use of general anesthesia, the number and the positions of application sites in each patient had not been discussed, also the number of the side effects observed in the present study was recorded by complication entity (i.e. several complications may be present in one patient, but recorded each as a separate entity). Other recent reports (50, 82), applying EBUS under topical anesthesia, even in the trachea (82) noted no difficulties in application but without giving further details.

4.4.8 Instrument handling difficulties

In evaluation of the role of this new diagnostic procedure, it is important to note instrument handling difficulties, with the aim of minimizing these difficulties for new generations of the instrument, which will be more accurate and more easily handled. This point had not been previously focused on in literature, which may be related to the short period of availability (since 2000) of the instrument in the daily hospital practice, and the limited number of centres, which apply this new

technology. The difficulties in handling as previously enumerated were in balloon sheath preparation before and during use, imaging artefacts, instrument adjustment problems and instrument orientation problems. Imaging artefacts are expected as with any imaging instrument, and after adequate practice with EBUS application it infrequently hinders the diagnostic process. The most common artefacts are multiple repeated reflections of the balloon echo. This can be corrected by providing sufficient contact between the balloon and the bronchial wall thus achieving good coupling. These imaging artefacts are not synchronous with the physiological movements, they are easily recognised, and after some time of accommodation, they no longer interfere with the diagnostic process.
Orientation of mediastinum sonographic anatomy in relation to the bronchial lumen is the primary most difficult task in EBUS application, but improves with practice. Also, complex anatomy of mediastinum and unusual planes of EBUS which follow bronchial tree may cause some problems.
The subscreen provided for observation of endoscopic image simultaneously with the ultrasound image, is too small to see the position relationship of ultrasound probe in the bronchus examined. This difficulty had been overcome by having two adjacent monitors, one for each of the endoscopic image and the ultrasound signal.
In addition loss of the examiner orientation is one of the difficulties that is observed during training with EBUS, it occurs due to the need to rotate the bronchoscope with the probe frequently for wall approximation. A help is the following technique: during the examination the US probe is directly pushed into contact with the suspected site, then the balloon is inflated, and when the suspected lesion appears directly in contact with the probe, then the lesion is placed into its correct orientation in relation to the endoscopic image by rotating the ultrasound image rather than the bronchoscope. Image adjustment problems had been solved recently in a newly launched generation of ultrasonic processors.
The difficulties of balloon sheath, requiring time and effort still needs technical solutions.

In contrast to other imaging modalities, EBUS application has the following advantages: it is safe (although requiring high degree of endoscopic expertise), carries no risk of exposure to ionising radiation nor intravenous injection of contrast material, provides real-time images in the hands of bronchologists, with immediate gain of information about extraluminal structures. Subsequently appropriate management decision can be made in one procedure without time lag.

Other innovative imaging technologies, whose exact role in clinical practice is yet to be defined, include virtual bronchoscopy (26, 62, 87), positron emission tomography (72, 80, 86) and CT fluoroscopy (24, 46). Whether -and to which

extent- these procedures will prove to be clinically relevant, cost-effective, and complementary to EBUS remains to be seen.

It was shown by the data presented that EBUS application under topical anesthesia is a well tolerated procedure, associated with mild infrequent side effects, providing valuable beneficial additional information to bronchoscopy and CT in assessment of cases of bronchial carcinoma; further expected technical improvements will allow EBUS to play an important role in diagnostic and interventional bronchoscopy in the near future.

4.5 Future EBUS aspects

Further technical improvements for EBUS application include the following: Addition of a biopsy channel into a balloon-integrated bronchoscope to enable simultaneous sonographically guided needle biopsy (10, 79). First integrated systems are in the prototype stage. A new ultrasonic fiberoscope prototype is now available, with a rotating built-in transceducer at the tip surrounded by a balloon allowing a 300 degrees radial scan (19). Replacing the 20 MHz probe with a 30 MHz ultrasound device will probably allow demonstration of a more detailed structure of the tracheobronchial wall (82). Prototypes are being assessed. A further innovation is the addition of Doppler sonography for analysis of vascularization, which could be helpful in the control of bronchial anastomosis after surgical procedures (10). Further, computerized analysis of tissue characterization could be useful for the detection of malignancy of early carcinoma or lymph node metastases. (1, 35, 40)

Three dimensional image, image fusion techniques and EBUS-guided therapy are expected future developments (57).

5. Summary, conclusions and recommendations

Conventional methods used for diagnosis of lung cancer are still inadquate for objectively estimating the exact depth of tumor invasion to bronchial wall, nodal staging, infiltration of mediastinal structures and extent of early lung cancer. Endobronchial ultrasound (EBUS) was introduced into clinical hospital practice in 2000, as a new diagnostic procedure visualizing bronchial and peribronchial tumors, mediastinal lymph nodes and adjacent vascular structures, with the aim of assessing bronchial wall and extraluminal pathology. Since major European publications deal with EBUS application in general anesthesia, its use in routine bronchoscopy under topical anesthesia has been addressed more closely in this study. Hence the primary question we attempted to answer has been, is the addition of EBUS under topical anesthesia to bronchoscopy practicable and does it improve diagnosis in bronchial cancer beyond computer tomography (CT) and bronchoscopy alone?

50 consecutive patients were recruited with suspected lung cancer (suspicious shadow(s) and / or mediastinal adenopathy in chest CT) undergoing diagnostic and/or staging flexible fiberoptic bronchoscopy. In all patients, EBUS was performed as an adjuvant to bronchoscopy using midazolam sedation, lidocaine mucosal anesthesia and supplemental oxygen. A 20-mega Hz radial mechanical ultrasound probe integrated with a balloon, connected to ultrasound unit is advanced through the 2.8-millimeter working channel FFB to area of interest, where the balloon is inflated to provide a medium for ultrasound transmission. Agreement of EBUS findings with FFB/ CT and cyto-histology, additional information provided by EBUS, complications, patients tolerability under topical anesthesia were assessed.

Out of the 50 cases with suspected lung cancer, 36 cases were pathologically verified. In 36 lung cancer cases, EBUS findings coincided with those of FFB and CT in main features of the disease process. EBUS provided additional information in 25 cases (69%), in which 20 additive lymph nodes were detected, depth of tumor invasion was determined in 18 cases and compression of pulmonary arteries in 2 cases. In addition, it was helpful in explanation of bronchoscopic findings in 19 cases (53%) and exclusion of mediastinal structures infiltration. On the other hand, FFB and CT provided additional information in 7 cases (19%). In all studied cases, EBUS assisted transbronchial needle aspiration biopsy had diagnostic yield in extraluminal lesions up to 89% and 90% in mediastinal and intrapulmonary adenopathy. EBUS addition could change the nodal descriptors in 4 cases and patient stage in 2 cases, but without any subsequent therapeutic consequences. The complications encountered in all studied cases were either mild (6) or moderate (1) desaturation, mild (9) or moderate (3) cough and 2 cases of tachycardia. The procedure is completely tolerated by most of the patients (66%). There is an average increase in examination time of 15 minutes, constituting 44% of total time of bronchoscopy.

EBUS application under topical anesthesia is a well tolerated procedure, associated with mild infrequent side effects, providing valuable beneficial additional information to bronchoscopy and CT; hence its addition can improve the diagnosis and assessment of bronchial cancer. Further expected technical improvements are still needed, which may allow EBUS in the near future to play a more important role in diagnostic and interventional bronchoscopy.

Prospective multicentre studies are needed for critical assessment of EBUS in operable lung cancer patients, correlating EBUS image findings with postoperative anatomical and pathological findings in same areas examined. A more applicable definition of depth of tumor invasion, the use of 30 MHz probes, the use of double lumen bronchoscopy, the cost effectiveness of procedure and the role of EBUS in peripheral lesions are recommended to be further studied. The sound indications of this new technology need to be settled, in the diagnostic investigation path of lung cancer.

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