

Real-Time, Endobronchial Ultrasound-Guided, Transbronchial Needle Aspiration For Sampling Mediastinal Lymph Nodes

FJF Herth, MD (1); R. Eberhardt, MD(1); P. Vilmann, MD (2);
M. Krasnik, MD (3); A. Ernst, MD (1, 4)

(1) Department of Pneumology and Critical Care Medicine, Thoraxklinik, University
of Heidelberg, Germany,

(2) Department of Surgical Gastroenterology and

(3) Department of Cardiothoracic Surgery, Gentofte University Hospital,
Copenhagen, Denmark,

(4) Interventional Pulmonology, Beth Israel Deaconess Medical Center, Harvard
Medical School, Boston, USA

Conflict of Interest Statement

The prototype endobronchial ultrasound probe was loaned to the authors by Olympus Ltd., Tokyo, Japan for the duration of this study. None of the authors has any financial stake in Olympus Ltd., of Tokyo, Japan.

Corresponding author:

Prof. Felix JF Herth, MD, DSc, FCCP

Department of Internal Medicine, Pneumology and Critical Care Medicine

Thoraxklinik, University of Heidelberg

Amalienstr. 5

D-69126 Heidelberg

Tel +49-6221-396-600/601

Fax +49-6221-396-602

Felix.Herth@thoraxklinik-heidelberg.de

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in [THORAX] editions and any other BMJPG Ltd products to exploit all subsidiary rights, as set out in our licence (<http://thorax.bmjournals.com/ifora/licence.pdf>).

ABSTRACT

Purpose: Transbronchial needle aspiration (TBNA) is an established method for sampling mediastinal lymph nodes to aid in diagnosing lymphadenopathy and in staging lung cancers. Real-time, endobronchial ultrasound (EBUS) guidance is a new method of TBNA that may increase the ability to sample these nodes and, hence, to determine a diagnosis. We conducted a descriptive study to test this new method.

Methods: Consecutive patients referred for TBNA of mediastinal lymph nodes were included in the trial. When a node was detected, a puncture was performed under real-time ultrasound control. The primary endpoint was the number of successful biopsies. Diagnostic results from the biopsies were compared to operative findings. Lymph node stations were classified according to the recently adopted American Thoracic Society scheme.

Results: From 502 patients (mean age 59 years, range 24 to 82 years; 316 men), 572 lymph nodes were punctured, and 535 (94%) resulted in a diagnosis. Biopsies were taken from lymph nodes in region 2l (40 nodes), 2r (53 nodes), 3 (35 nodes), 4r (86 nodes), 4l (77 nodes), 7 (127 nodes), 10r (38 nodes), 10l (43 nodes), 11r (40 nodes) and 11l (33 nodes). Mean (SD) diameter of the nodes was 1.6 cm (0.36 cm) and the range was 0.8 to 3.2 cm (SD \pm 0.36; range 0.8 to 4.3). Sensitivity was 94%, specificity was 100%, and the positive predictive value was 100% calculated per patient. No complications occurred.

Conclusion: EBUS TBNA is a promising new method for sampling mediastinal lymph node. Compared to conventional TBNA, it appears to permit more and smaller nodes to be sampled and it is safe.

Keywords: lung cancer, transbronchial needle aspiration, endobronchial ultrasound, mediastinal lymphadenopathy

INTRODUCTION

Non-small cell lung cancer (NSCLC) usually metastasizes first to hilar and mediastinal lymph nodes. Subsequently, hematogenous metastasis to distant sites may occur. Because survival is inversely correlated with stage, a meticulous staging procedure is required to determine the treatment and prognosis.[1][2]

Mediastinal lymph node staging can be divided into imaging and sampling phases. Computed tomography, magnetic resonance imaging, and positron-emission tomography may be used to image mediastinal lymph nodes.[4] Pathologic sampling of suspicious lesions can be performed by mediastinoscopy, thoracoscopy, transthoracic needle aspiration, transbronchial needle aspiration (TBNA), and endoscopic ultrasonography with needle aspiration.[4][5][6][7]

For many years, mediastinoscopy has been regarded as the reference standard for sampling mediastinal lesions, but it is invasive, costly, and requires general anaesthesia. Although a standard cervical mediastinoscopy permits access to paratracheal lymph node stations (levels 2R, 2L, 4R, and 4L) and to the anterior subcarinal lymph node station (level 7), access to the posterior and inferior mediastinum is limited and requires either extended cervical mediastinoscopy or a thoracoscopy.[8]

To overcome the limitations of mediastinoscopy in accessing paratracheal and para-bronchial lymph nodes (stations 2, 3, 4, 7, 10 and 11), a new bronchoscope has been developed. This bronchoscope is equipped with a linear array transducer that allows real-time ultrasonic guidance of fine-needle, transbronchial biopsy. We used this new bronchoscope for 27 months, during which we developed a method we call real-time, endobronchial ultrasound-guided, transbronchial needle aspiration (EBUS-TBNA) and evaluated its clinical utility for visualizing and sampling mediastinal and hilar lymph nodes under direct endobronchial ultrasound guidance. Here, we describe our experience with this method.

MATERIALS AND METHODS

The study and prospective data collection was approved by the Institutional Review Boards at Thoraxklinik Heidelberg and Gentofte University Hospital, where

all patients were examined by the authors. Written informed consent was obtained from all the patients in the study.

Between June 2002 and September 2004, patients with mediastinal or hilar lymphadenopathy referred for TBNA were enrolled in the study. The main indications for TBNA were the sampling and diagnosis of enlarged lymph nodes of unknown origin and lung cancer staging, especially the exclusion of N3 nodes.

A chest radiograph and computed tomography scan of the chest (plain and contrast enhanced) were routinely performed in all patients.

Conventional flexible bronchoscopy (model BF-7160 bronchoscope; Olympus; Tokyo, Japan) was first performed in a standard fashion to examine the tracheobronchial tree, followed by EBUS-TBNA using the new ultrasound biopsy bronchoscope (model XBF-UC260F-OL8; Olympus Ltd., Tokyo, Japan). Both bronchoscopy procedures were performed by the same operator.

All patients in whom a specific diagnosis was not determined from biopsies obtained through EBUS-TBNA underwent a surgical biopsy procedure (mediastinoscopy).

Real-Time, Endobronchial Ultrasound-Guided, Transbronchial Needle Aspiration

The Prototype Linear Array Ultrasonic Bronchoscope

Endobronchial ultrasound was performed using a prototype linear array ultrasonic bronchoscope. The instrument is similar to a standard bronchoscopic videoscope, with an outer diameter of 6.9 mm, a 2.0-mm instrument channel, and 30-degree oblique forward-viewing optics. An electronic convex array ultrasound transducer is mounted at the distal tip (Figure 1) and is covered by a water-inflatable balloon sheath. Scanning is performed at a frequency of 7.5 MHz and with a penetration of 50 mm. The angle of view is 90°, and the direction of view is 30° forward oblique. Image processing is performed by an Olympus ultrasound processor (EU-60).

A dedicated 22-gauge needle (XNA-202C Olympus Ltd.) was developed to perform transbronchial aspiration (Figure 2). The needle is also equipped with a stylet, which is withdrawn after passing the bronchial wall, avoiding contamination

during TBNA. The needle is mounted at the biopsy channel inlet of the endoscope before puncture. The needle exits the outer covering of the insertion tube at 20°. The needle can be visualized through the optics and on the ultrasound image.

The Biopsy Procedure

The probe was introduced through the mouth and vocal cords to the main carina. With the balloon partially inflated (0.3 to 0.5 ml of water), the regional lymph node stations of the middle mediastinum and hilar regions (stations 2, 3, 4, 7, 10, and 11) [3] were systematically imaged and measured (short-axis diameter) during slow withdrawal and rotation of the transducer.

Fine-needle aspiration was performed by passing the dedicated prototype 22-gauge needle through the airway wall and into the lymph nodes under real-time ultrasound guidance. Needle punctures were performed using the 'jabbing' method.[5] Integrated power Doppler ultrasound was used to visualize and avoid potentially intervening vessels immediately before needle puncture (Figures 2 and 3).

The aspirate was placed onto at least 4 glass slides, air-dried, stained, and classified. Papanicolaou staining and light microscopy were performed by a cytopathologist who was blinded to the details of the patients. No rapid onsite cytology was performed. Two aspirates per node were obtained.

Diagnoses based on samples obtained through EBUS TBNA were confirmed by open thoracotomy, thoracoscopy, or clinical follow-up. A positive cytologic result of malignancy was accepted as evidence of cancer, and the patients were treated accordingly.

Statistical Methods

The primary endpoint of the study was the percentage of biopsies obtained that contained evaluable lymphocytes. The secondary endpoint was the percentage of confirmed diagnoses made possible with EBUS TBNA. Diagnostic sensitivity, specificity, and accuracy were calculated using the standard definitions: the proportion of true positive results, true negative results, and all correct results, respectively. The unit of analysis was the patient.

RESULTS

Of the 502 patients who underwent TBNA, 186 were women and 316 were men (mean age 58.9 years, range 24 to 82 years). One hundred- eighty-nine patients were examined under moderate sedation with midazolam (medium dose 3.5 mg per patient) and topical anaesthesia (1% and 2% lidocaine as needed). Three hundred - thirteen patients were examined under general anaesthesia and jet ventilation. The decision on which kind of anaesthesia to use was up to the discretion of the operator and mainly dependant on which other procedures were planned for the same setting. There was no difference amongst institutions.

Among these patients, 572 lymphnodes were identified by CT to be enlarged more than 1 cm and were punctured (1.14/ patient, range, 1 to 3). Mean (SD) lymph node size was 1.6 cm (0.36), and the range was 0.8-to 3.2 cm as measured during the EBUS examination.

The procedure time for EBUS TBNA was 12.5 minutes (range 8-21 minutes). There was no difference in time required between types of anesthesia.

Of the 572 nodes, 535 (93,5%) were successfully biopsied and a specific diagnosis was established. The overall diagnostic yield was 93.5% (Table 1). Six patients patients did have lymphocytes in the specimens, but no specific diagnosis. Surgical biopsy in these cases confirmed sarcoidosis in 2 and malignancy in 4 patients. Table 2 lists the results of all biopsies.

Among the 37 nodes (6%) in which the biopsy did not result in a diagnosis (including lymphocyte positive nodes), 35 were found on surgery to have a malignancy and 2 had sarcoidosis.

The results were not different when controlling for the type of anaesthesia used. In patients who received a general anaesthetic, the accuracy was 94.8%, PPV was 100% NPV was 11%, sensitivity was 95% and specificity was 100%. In patients who received moderate sedation, the accuracy was 93.6%, PPV was 100%, NPV was 14%, sensitivity was 93.5% and specificity was 100%.

Analysing the diagnostic yield for the 502 patients, rather than nodes, we were able to establish a definitive diagnosis in 470 (93%) patients. The sensitivity, specificity, and accuracy were thus 94%, 100%, and 94%, respectively. The PPV was 100% and the NPV 11%.

No complications were associated with EBUS-TBNA.

DISCUSSION

Chest physicians often need to assess enlarged mediastinal lymph nodes.[1][2] Lymph nodes may be enlarged for a variety of inflammatory, infectious, or malignant reasons, and it is important to ascertain a diagnosis or, in case of malignancy, to determine the stage of disease before making treatment decisions.[9]

Mediastinoscopy has long been the mainstay of mediastinal lymph node sampling, but it has several disadvantages. As a surgical procedure, it requires general anaesthesia and the use of an operating room. It is also difficult to perform a second time in a given patient. Additionally, the reach of the procedure is limited, in that lymph nodes in the posterior carina and hilar stations are generally inaccessible. Lastly, although it is currently the reference standard, mediastinoscopy's specificity and sensitivity are not optimal.[8][9][10].

Interest in non-surgical staging has been increasing ever since endoscopic needle aspiration of mediastinal lymph nodes has been possible.[11][12][13] Transbronchial needle aspiration is an established bronchoscopic technique, but it remains underused, and the biopsy yield varies widely, perhaps because of the long learning curve and its associated frustrations. Additionally, conventional TBNA is a fairly blind technique that does not allow the target to be visualized, making smaller lymph nodes and nodes in some locations more difficult to access.

The introduction of endoesophageal-ultrasound- and endobronchial-ultrasound-guided needle aspiration and the resulting increase in yield has further enhanced this diagnostic instrument.[7][14][15][16][17][18][19]

Endoscopic imaging with simultaneous ultrasound scanning has several advantages over mediastinoscopy: there is no need for surgery or general anaesthesia, it can be done repetitively in the same person and, depending on which endoscopic modality is used, lymph node stations not surgically accessible are within reach.[15][18][20][21] Before the development of the real-time EBUS-TBNA bronchoscopy, TBNA was limited to "blind" needle puncture guided by static computed tomography scans. This method is highly operator-dependent, and the successful sampling rate varies between 20% and 80%.[7][8][9] More recently, we

[17][18] demonstrated that a mechanical radial ultrasound mini-probe, introduced through the working channel of a flexible bronchoscope, can be used to localise target lymph nodes before sequential blind biopsy. This method increased sampling success to 86%.[11] Although this technique has improved TBNA yields, it does not allow real-time, ultrasound-guided control of needle puncture: inadvertent puncture of vascular structures is a risk.

In this report, we have shown that real-time, endobronchial-ultrasound guided, fine-needle aspiration can be used to identify and aspirate lymph nodes adjacent to the trachea and main bronchi from lymph node stations 2, 3, 4, 7, 10, and 11 with a sampling success rate of greater than 90%. The data also supports the recommendations that negative TBNA needs to be followed up with a more definitive diagnostic procedure (as evidenced by the low NPV).

We did note some drawbacks with the bronchoscope. The direction of view of the scope is 30° forward oblique, making manipulation difficult. From our experience, this new bronchoscope requires at least 10 manipulations for an experienced bronchoscopist to be able to smoothly insert it and to obtain clear images.

Also, the subaortic and paraesophageal lymph nodes (locations 5, 6, 8, 9) were not accessible with EBUS-TBNA. However, most mediastinal and hilar lymph nodes are present along the airway, so they should be accessible using EBUS-TBNA. For lymph nodes not accessible with EBUS-TBNA, endoscopic-guided, fine needle aspiration may need to be performed.[7][14][15][16]

To date, 3 papers have been published on this procedure. Krasnik et al.[22] reported on 11 patients in whom 15 lesions were punctured, without complications. The lesions were located as follows: 4 in region 10L, 4 in region 10R, 1 in region 4L, 3 in region 4R, 1 in region 1, 1 in region 7, and 1 in region 2R. The lesions ranged from 7 mm to 80 mm. Biopsies obtained through EBUS-FNA showed malignant cells in 13 lesions and benign cells in 2.

Yasufuku et al.[23] examined 70 patients with mediastinal (n=58) and hilar lymph nodes (n=12). The sensitivity, specificity, and accuracy of EBUS- TBNA in distinguishing benign from malignant lymph nodes were 95.7%, 100%, and 97.1%, respectively. There were no complications.

In a recent paper by Rintoul et al.[24] EBUS-TBNA was used in 18 patients. Cytology revealed node (N)2/N3 disease in 11 patients and provided a primary diagnosis in 8 patients. Cytology results for EBUS-TBNA samples were negative in 6 patients, and mediastinoscopy or clinical follow-up confirmed this result in 4. Sensitivity, specificity, and accuracy for EBUS-TBNA were 85%, 100%, and 89%, respectively.

Our study establishes the method of performing real-time EBUS-TBNA in a large group of patients and confirmed our assumption that the use of EBUS for TBNA results in a high success rate for accessing lymph nodes and a high diagnostic yield. It allowed for reliable biopsy of even small nodes and nodes in difficult locations. When using EBUS, lymph node location and size did not influence the success of actually “hitting” the intended node. This is in contrast to conventional TBNA, where there is a significant difference in diagnostic success depending on node location. This gives additional credence to the assumption that imaging guidance is beneficial for TBNA.

Conclusions

We believe that TBNA of the mediastinal and hilar lymph nodes under direct, real-time EBUS guidance using the new ultrasound bronchoscope is a safe and effective means of obtaining biopsies from these nodes.

References

1. Sihoe AD, Yim AP. Lung cancer staging. *J Surg Res* 2004;117:92-106.
2. Spira A, Ettinger DS. Multidisciplinary management of lung cancer. *N Engl J Med*. 2004; 350:379-92.
3. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. *Chest* 1997;111:1718-23.
4. Toloza EM, Harpole L, Detterbeck F, McCrory DC. Invasive staging of non-small cell lung cancer: a review of the current evidence. *Chest* 2003; 123:157-66.
5. Garpestad E, Goldberg S, Herth F, et al. CT fluoroscopy guidance for transbronchial needle aspiration: an experience in 35 patients. *Chest* 2001; 119:329-332
6. Mehta AC, Kavuru MS, Meeker DP, Gephardt GN, Nunez C. Transbronchial needle aspiration for histology specimens. *Chest* 1989;96:1268-72.
7. Vilmann P, Hancke S. A new biopsy handle instrument for endoscopic ultrasound guided biopsy. *Gastrointest Endosc* 1996;43:238-42.
8. Hoffmann H. Invasive staging of lung cancer by mediastinoscopy and video-assisted thoracoscopy. *Lung Cancer* 2001;34:3-5.
9. Luke WP, Pearson FG, Todd TR, Patterson GA, Cooper JD. Prospective evaluation of mediastinoscopy for assessment of carcinoma of the lung. *J Thorac Cardiovasc Surg* 1986;91:53-6.

10. Coughlin M, Deslauriers J, Beaulieu M, Fournier B, Piraux M, Rouleau J, Tardif A. Role of mediastinoscopy in pretreatment staging of patients with primary lung cancer. *Ann Thorac Surg* 1985;40:556-60.
11. Gasparini S, Zuccatosta L, DeNictolis M. Transbronchial needle aspiration of mediastinal lesions. *Monaldi Arch Chest Dis* 2000;55:29-32.
12. Mehta AC, Meeker DP. Transbronchial needle aspiration for histology specimens. In: Wang KP, Mehta AC, editors. *Flexible Bronchoscopy*. Cambridge: Blackwell Science, 1995:199-205.
13. Wagner ED, Ramzy I, Greenburg SO, Gonzalez JM. Transbronchial fine needle aspiration: reliability and limitations. *Am J Clin Pathol* 1989;92:36-41.
14. Wiersema MJ, Vilmann P, Giovannini M, Chang KJ, Wiersema LM. Endosonography guided fine needle aspiration biopsy: Diagnostic accuracy and complication assessment. *Gastroenterology* 1997;112:1087-95.
15. Pedersen BH, Vilmann P, Milman N, Folke K, Hancke S. Endoscopic ultrasonography with guided fine needle aspiration biopsy of a mediastinal mass lesion. *Acta Radiol* 1995;36:326-8.
16. Silvestri GA, Hoffman BJ, Bhutani MS, Hawes RH, Coppage L, Sanders-Cliette A, Reed CE. Endoscopic ultrasound with fine-needle aspiration in the diagnosis and staging of lung cancer. *Ann Thorac Surg* 1996;61:1441-6.
17. Herth F, Becker HD, Ernst A. Conventional vs endobronchial ultrasound-guided transbronchial needle aspiration: a randomized trial. *Chest* 2004; 125: 322-5.
18. Herth FJ, Becker HD, Ernst A. Ultrasound-guided transbronchial needle

- aspiration: an experience in 242 patients. *Chest* 2003;123:604-7.
19. Okamoto H, Watanabe K, Nagatomo A, Kunikane H, Aono H, Yamagata T, Kase M. Endobronchial ultrasonography for mediastinal and hilar lymph node metastases of lung cancer. *Chest* 2002; 121:1498-506.
 20. Herth F, Becker HD. Endobronchial ultrasound of the airways and the mediastinum. *Monaldi Arch Chest Dis* 2000;55:36-45.
 21. Falcone F, Fois F, Grosso D. Endobronchial ultrasound. *Respiration* 2003;70:179-94.
 22. Krasnik M, Vilmann P, Larsen SS, Jacobsen GK. Preliminary experience with a new method of endoscopic transbronchial real time ultrasound guided biopsy for diagnosis of mediastinal and hilar lesions *Thorax* 2003;58:1083-8.
 23. Yasufuku K, Chiyo M, Sekine Y, Haged PN, Shibuya K, Iizasa T, Fujisawa T. Real-time endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes. *Chest* 2004; 126:122-8.
 24. Rintoul RC, Skwarski KM, Murchison JT, Wallace WA, Walker WS, Penman ID. Endobronchial and endoscopic ultrasound-guided real-time fine-needle aspiration for mediastinal staging *Eur Respir J* 2005; 25: 416-21.

Table 1. Results of Real-Time, Endobronchial Ultrasound-Guided, Transbronchial Needle Biopsies in 502 Patients with Mediastinal Lymph Nodes, by Location.

Lymph Node Station	Nodes n	Lymphocytes positive n	Diagnosis Established from Biopsy, n	Nodes Diagnosed, %
2r	53	49	48	91
2l	40	36	36	90
3	35	33	32	91
4r	86	81	81	94
4l	77	75	74	96
7	127	123	122	96
10r	39	37	36	92
10l	43	42	42	97
11r	40	36	36	90
11l	33	29	28	88
Totals	572	541	535	93.5

Table 2

This table depicts the diagnosis obtained by surgery and EBUS TBNA in all 502 patients. Of those, 470 patients had a definitive diagnosis made by endoscopic means.

	Overall	Definitive Diagnosis in EBUS	
	N	N	%
Squamous cell carcinoma	148	138	93
Adeno carcinoma	156	150	96
Large cell carcinoma	56	49	88
NSCLC	10	9	90
SCLC	123	119	96
Sarcoidosis	6	2	33
Tuberculosis	3	3	100
	502	470	94

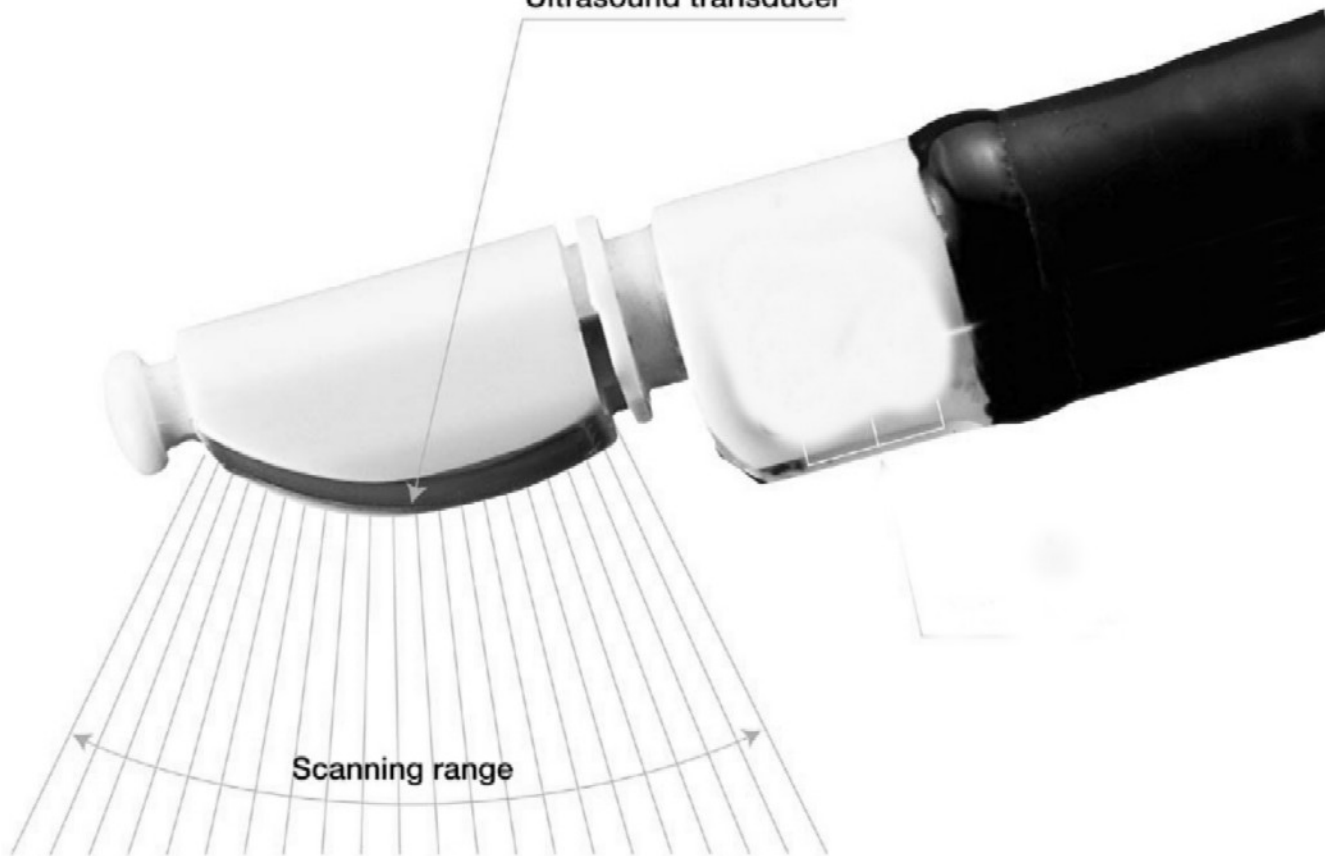
Figure Captions

Figure 1: Scheme of the tip of the EBUS-TBNA bronchoscope

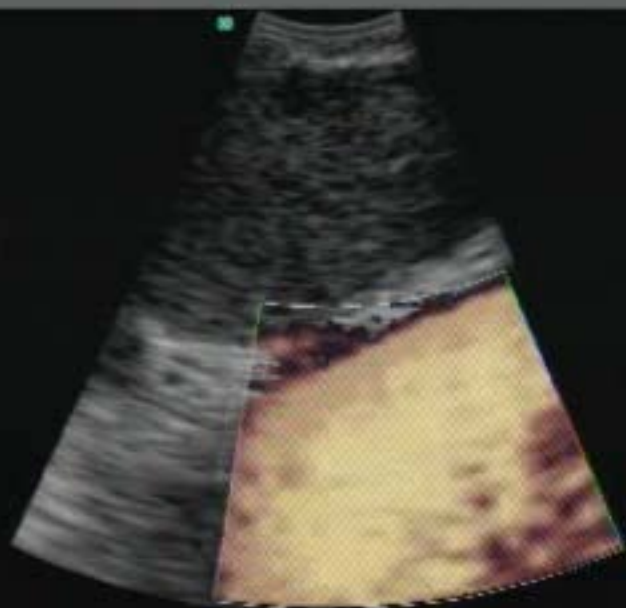
Figure 2: Colour Doppler image for detecting vessels before sampling the node

Figure 3: Endobronchial ultrasound image of the needle puncture

Ultrasound transducer



Scanning range



GI2
R8

32
3.0
cm

2003Aug05 10:10



Needle

LN

GI2



R8



42



3.0
cm