Review Article

# Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a concise review

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**Abstract:** Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) offers a minimally invasive alternative to mediastinoscopy with additional access to the hilar nodes, a better safety profile, and it removes the costs and hazards of theatre time and general anesthesia with comparable sensitivity, although the negative predictive value of mediastinoscopy (and sample size) is greater. EBUS-TBNA also obtains larger samples than conventional TBNA, has superior performance and theoretically is safer, allowing real-time sampling under direct vision. It can also have predictive value both in sonographic appearance of the nodes and histological characteristics. EBUS-TBNA is therefore indicated for NSCLC staging, diagnosis of lung cancer when there is no endobronchial lesion, and diagnosis of both benign (especially tuberculosis and sarcoidosis) and malignant mediastinal lesions. The procedure is different than for flexible bronchoscopy, takes longer, and requires more training. EBUS-TBNA is more expensive than conventional TBNA but can save costs by reducing the number of more costly mediastinoscopies. In the future, endobronchial ultrasound may have applications in airways disease and pulmonary vascular disease.

**Key Words:** Endobronchial ultrasound; transbronchial needle aspiration; fine needle aspiration cytology; non-small cell lung carcinoma; mediastinum; cancer staging; sarcoidosis; technique

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## Introduction

Endobronchial ultrasound-guided transbronchial fine needle aspiration (EBUS-TBNA) is a novel, minimally invasive method to sample peribronchial masses using real-time guidance. As cytopathologists play a crucial role in the success of this technique, it is important to understand the procedure, its indications, limitations and potential for diagnostic pitfalls.

The most important use of this technique is in the nodal staging of patients with non-small cell lung carcinoma (NSCLC) (1-9). This review will primarily focus on the comparison of EBUS-TBNA with other minimal invasive techniques used for the same purpose and the indications. It will also discuss the other use of the technique like restaging of lung cancer after chemotherapy or chemo-radiation therapy, diagnosis of mediastinal lymphadenopathy of unknown reasons.

In NSCLC, which represent about 85% of all primary pulmonary malignancies, the single most important determinant of resectability and prognosis is nodal stage. Despite constant improvements in non- invasive nodal staging by computed tomography (CT), positron emission tomography (PET) and combined PET / CT (10), all candidates for definitive surgical treatment still require cytological or histological assessment of the mediastinum (11).

While mediastinoscopy is the gold standard for preoperative staging of NSCLC, endoscopic minimally invasive sampling techniques, including transoesophageal EUS-FNA and EBUS- TBNA, are increasingly successfully used for this indication.

Accurate preoperative staging decreases the number of futile operations performed with curative intent and allows the use of chemotherapy or chemo-radiation regimens followed by restaging and potential surgery after downstaging (12-14).

## Rationale for EBUS-TBNA and brief historical summary of development

For patients with lung cancer, timely diagnosis and accurate staging are pivotal for facilitating the appropriate treatment. Staging algorithms and treatment practices have been guided by mediastinal lymph node metastases, which determine outcome (15). Radiological investigations (contrast enhanced computed tomography (CT) of the chest and upper abdomen and positron emission tomography (PET)) are limited by false negative and positive results, and therefore the need for tissue confirmation of abnormal results (16).

Factors contributing to the limitations of CT here are inter-observer variability (17), the need for an interface to allow differentiation between adjacent soft tissues (18), benign causes of enlarged adenopathy, and water dense structures such as mucoid plugs and secretions which may mimic solid structures.

CT and PET, however, do allow targeting of invasive mediastinal sampling techniques, guide further diagnostic decisions on how best to obtain tissue to confirm the diagnosis and metastatic spread in one visit, or assess suitability for radical treatment. Moreover, flexible bronchoscopy is effective at diagnosis of direct endoluminal tumors, but many lung cancers present in the mediastinum. Conventional TBNA can allow the mediastinal nodes to be sampled, but without direct vision, relying on correlation of CT imaging and anatomical knowledge. Expanding the view of nodes adjacent to the airway by imaging to allow real-time sampling under direct vision is therefore a logical development.

Transthoracic ultrasound is limited by the reflection of ultrasound wave by air prompting the development of endoluminal ultrasound. Esophageal endoscopic ultrasound guided fine needle aspiration (EUS-FNA) was developed in the 1980s for evaluation of gastrointestinal malignancies, especially the esophagus. Because of the proximity of the esophagus to mediastinal structures, EUS-FNA was used in lung cancer to sample accessible lymph nodes (19). However, airway interference prevented better vision of other lymph node stations and some stations were not accessible via the esophagus, but would be accessible from the airway, hence the development of the closely related EBUS-TBNA in the 1990s (20,21). Modifications included smaller probes to allow adequate ventilation, Initially, a radial probe was developed and then subsequently the linear probe (22,23).

## Indications for EBUS-TBNA

The most common indication for EBUS-TBNA would be:

I. Staging the mediastinum for suspected non-small cell lung cancer (NSCLC), which is important in determining outcome and treatment.

II. For diagnosis of both NSCLC and small cell lung cancer, as often there is no endoluminal tumor at bronchoscopy and this avoids the need for either a CT guided lung biopsy or mediastinoscopy (which may not be appropriate, especially if the patient is unlikely to be having surgical treatment).

III. For diagnosis of unexplained mediastinal lymphadenopathy accessible to the major airway including benign conditions such as sarcoidosis or tuberculosis.

IV. As a research tool for tissue banking samples for later studies.

## Contraindications for EBUS-TBNA

EBUS-TBNA is well tolerated, but sampling from the mediastinal nodes should not be performed with patients on warfarin (international normalized ratio (INR) should be <1.4 ideally) or clopidogrel (both should be stopped for a week before the procedure), or known coagulation or platelet function disorders because of bleeding risk in the mediastinum.

EBUS-TBNA should be postponed for at least six weeks after myocardial infarction and is contraindicated in the presence of ongoing myocardial ischemia, arrhythmias or severe hypoxemia at rest.

EBUS-TBNA is not usually clinically appropriate if lymphoma is a likely possibility.

## EBUS-TBNA tecnique

### *Procedure room*

EBUS-TBNA can be performed in an endoscopy suite or an operating room. A recent CT scan of the chest has to be available for the operator to review before and during the procedure. The operator needs to verify that the location and size of the target are in accordance with the location and size on the CT scan.

### *Anesthesia*

EBUS-TBNA can be performed with conscious sedation or under general anesthesia, reportedly with equivalent results (24). In most clinical setting, general anesthesia is preferred, particularly to sample small (less than 10 mm) mediastinal lymph nodes in the paratracheal areas, were respiratory variation and cough can interfere with proper sampling; additionally, short periods of controlled apnea can facilitate TBNA. The endotracheal tube or laryngeal mask airway should have a minimum diameter of 8 mm to accommodate the EBUS bronchoscope (6.2 mm diameter).

### *Technique*

Once the target lymph node or mass has been clearly identified with EBUS, the needle is inserted under real-time US guidance. The stylet of the needle is left in place on the first puncture to minimize bronchial cell contamination; once the needle tip is inside the target tissue the stylet is removed. The target is stabbed 10-15 times without suction and apply suction only for the last two or three stabbing motions. Prior to retracting the needle into the needle sheath, suction must be removed to minimize sample loss into the syringe. The specimen is then air-flushed on a slide, the needle is flushed with heparin-saline solution to avoid clotting and the same procedure is repeated three times at every lymph node station. A positive result should prompt using a new needle if any additional lymph node stations are to be sampled.

### *Size of needle*

At present, EBUS-TBNA only allows the procurement of cytological samples with a 22-G needle. However, abundant material can be obtained, and cellblocks prepared from such samples may allow the evaluation of histological detail. It is expected that core needles that allow histological sampling will soon also become commercially available for EBUS-TBNA (25).

### *Number and size of mediastinal lymph nodes sampled*

The number of mediastinal lymph node stations to sample depends on the purpose of the examination. Clearly, NSCLC staging requires at least sampling of three stations. Every attempt should be made to sample nodes at these sites, even if size and ultrasonographic features are normal.

### *Number of passes*

Usually, three to four aspirations per lymph node station are recommended, as the diagnostic yield curve reaches its plateau after three passes, similar to the experience with EUS-FNA of lymph nodes where a plateau appears in the third pass (26), although some authors recommend five passes for EUS-FNA of lymph nodes (27). More passes per site may be needed to reach a diagnosis of malignancy (mean of 4.4 passes) than to reach one of a benign lesion (mean of three passes) (28).

With on-site evaluation of adequacy, a smaller number of passes may be possible as the procedure is stopped once a diagnosis of malignancy, granulomatous or inflammatory condition is reached. However, in order to reduce the number of false-negative results, we believe that if no malignancy or granulomatous inflammation is identified during the rapid on-site evaluation, a minimum of three adequate aspirates per lymph node station should be performed.

### *Sampling errors*

Sampling errors may occur if the target is not appropriately identified and correlated with CT findings; this type of error is easily avoided. Non-diagnostic samples are generally contaminated with airway epithelium or blood. Proper sampling technique, as described above, is designed to reduce the rate of non- diagnostic specimens to around 5%.

False-negative samples occur at variable rates and depend on factors such as operator and cytologist experience. Even in the most experienced hands, false-negative rates of up to 15-20% can be seen. To minimize false-negative results, both the largest and the second largest node at each station should be sampled, especially in adenocarcinoma.

The most important step to minimize potential harm to the patient by a false-negative sample is to pursue an alternative biopsy technique if the treating physician has the slightest doubt about the credibility of the result. False-positive samples can occur if TBNA is performed through an area of bronchial epithelial high-grade dysplasia or carcinoma in situ.

### *Procedure time*

The mean procedure time varies from 44 to 22 minutes. However, depending on the size, difficulty in accessing the lesion, the number of passes and the skill and experience of the operator, it may take much longer (29). When no adequate specimen can be obtained, it is not clear what the

maximum number of passes should be before another target is sampled or another diagnostic modality considered.

### *Role of operator*

The results of EBUS-TBNA vary with the skill and experience of the operator (30), and maintaining competency requires frequent performance of the procedure. The American College of Chest Physicians recommends that initial training should consist of at least 50 supervised TBNA procedures to establish proficiency (31); the European Respiratory Society and the American Thoracic Society recommend that the first 40 procedures should be supervised (32).

### *Role of the cytopathologist*

The availability of an experienced cytopathologist is essential for the success of EBUS-TBNA. Interpretation of EBUS-TBNA samples requires good communication between the operator (pneumonologist, gastroenterologist or surgeon) and the cytopathologist. The best diagnostic results are achieved when clinical and imaging data are provided to the pathologist (33).

The accuracy of EBUS-TBNA, like that of conventional TBNA (34,35), percutaneous CT-guided FNA (36) and EUS-FNA (37) is improved by immediate evaluation of the sample by the cytopathologist.

The on-site cytopathologist not only ensures optimal specimen preparation and assessment of the adequacy and representativeness of the sample, but can also further triage the specimen, requesting additional studies such as flow cytometry, cultures, cytogenetic or molecular studies that have to be performed on fresh samples.

Gross examination of the aspiration material can sometimes be useful, as adequate samples frequently appear creamy (rather than bloody, watery or mucoid), may appear black due to anthracosis and the smears may show granules that are more evident towards their end (38).

The presence of the cytopathologist during the performance of the procedure helps establish good communication between the pathologist and the endosonographer, which is further useful for the integration of the pathologist into the multidisciplinary management team.

## Future developments

The technology of EBUS has other potential applications in other disease processes, and the indications for EBUS are likely to increase in the future, as the potential of this technology becomes better understood. Radial probe EBUS can provide information about the airway wall and EBUS allows real time imaging of the central pulmonary vasculature. This has been exploited in two recent studies.

Aumiller *et al*. reported a prospective pilot study illustrating the potential utility of EBUS to identify central pulmonary emboli, although this was not a blinded study and all pulmonary emboli had been diagnosed by prior CT pulmonary angiography (39). Soja *et al*. measured airway wall thickness (using a radial probe) and correlated this with asthma severity (40).

## Conclusions

EBUS-TBNA represents a new technology in the field of bronchoscopy. The primary indications for EBUS-TBNA are staging NSCLC and the diagnostic assessment of mediastinal lymphadenopathy. EBUS-TBNA also has a diagnostic role in suspected benign disease, especially sarcoidosis and tuberculosis. It is a minimally invasive option as the first sampling staging procedure in suspected NSCLC with solitary hilar nodes, discrete N2 or N3 disease, or bulky mediastinal disease.

Due to the current inferior negative predictive value of EBUS-TBNA, mediastinoscopy is still required for clarification of EBUS-TBNA negative nodes when the pre-test probability of lung cancer is high.

Currently, where radical treatment is contemplated, mediastinoscopy remains the preferred investigation for mediastinal staging, but this may well change to EBUS-TBNA with time if future larger controlled studies support a role for EBUS-TBNA in staging CT and PET negative sub-centimeter nodes.

As such it could be used as the primary staging tool in situations where re- staging (with mediastinoscopy) is likely to be needed or as an alternative re-staging procedure itself.

Those experienced or trained in the technique should perform EBUS-TBNA, and it is important not to underestimate the learning period for even experienced conventional bronchoscopists. The capital and running costs should also be thoroughly considered before setting up a service, although the principal financial argument for EBUS-TBNA will be to save money by avoiding mediastinoscopies. In the future, centers with appropriate throughput, technical expertise and funding, may seek to develop a combined EBUS-TBNA/EUS-FNA service,

giving access to all the nodal stations.

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