REVIEW ARTICLE

LINEAR ENDOSONOGRAPHY IN LUNG CANCER: A COMPREHENSIVE REVIEW

António Bugalho[1,2,3], Fernando Guedes[4], Francisco Freitas[1,5], Luis Vaz Rodrigues[6], Paul Frost Clementsen[7], Ralf Eberhardt[8], José Cepeda Ribeiro[1]

[1] Pulmonology Unit, CUF Tejo Hospital, Lisbon, Portugal
[2] Pulmonology Unit, CUF Descobertas Hospital, Lisbon, Portugal
[3] Chronic Diseases Research Centre (CEDOC), NOVA Medical School, Lisbon, Portugal
[4] Pulmonology Department, Centre Hospitalier de Luxembourg, Luxembourg
[5] Pulmonology Department, Hospital Santa Maria, Centro Hospitalar Lisboa Norte, Lisbon, Portugal
[6] Pulmonology Department, Instituto Português de Oncologia Francisco Gentil, Coimbra, Portugal
[7] Copenhagen Academy for Medical Education and Simulation (CAMES), Denmark
[8] Pulmonology and Intensive Care Medicine Department, Asklepios KlinikBarmbek, Hamburg, Germany

* **Corresponding author**: antonio.bugalho@cuf.pt

Abstract

Introduction: *The role of endobronchial ultrasound (EBUS) and trans-esophageal endobronchial ultrasound (EUS-B) in lung cancer is well established and scientifically validated. There is increasing data that endosonography is a crucial tool for the diagnosis of central lung lesions, and mediastinal staging and restaging of non-small cell lung cancer patients. The present article reviews the technical aspects of EBUS and EUS-B and focus on the last published research regarding its value in lung cancer.*

INTRODUCTION

Lung cancer is a defying disease for the scientific community, patients, and their families. It is the leading cause of cancer-related mortality in the world, with estimated 1.8 million deaths in 2020, and this number will raise in the upcoming decades.[1]

Accurate diagnosis and staging are mandatory for correct treatment. However, non-invasive procedures such as computed tomography (CT) or positron emission tomography (PET) are associated with high rates of false-positive and false-negative results. Therefore, there is a huge and increasing need for precise and minimal invasive diagnostic procedures to achieve material not only from the lung tumor but also from suspected metastases. Linear endobronchial ultrasound combined with transbronchial needle aspiration (EBUS-TBNA), and esophageal ultrasound fine needle aspiration (EUS-FNA) have replaced surgical staging as the initial preoperative tests for mediastinal tissue evaluation in patients with lung cancer.[2] These procedures are minimally invasive, performed in real-time, and are established as important diagnostic and staging procedures in the workup of lung cancer patients.[2,3] They are also used to diagnose other neoplastic and benign diseases that fall out of the scope of the present article.

Lung cancer diagnostic and staging procedures, such as EBUS and EUS, have a high performance in published studies that are mainly designed in expert centers. In real-life, in non-small cell lung cancer (NSCLC) patients, invasive mediastinal staging remains underused and of inconsistent quality.[4,5]

This review aims to provide the best current knowledge regarding endosonography in lung cancer, by revising the technique, results from recent publications and existing international guidelines.

Endobronchial ultrasound

The EBUS-TBNA bronchoscope is available since

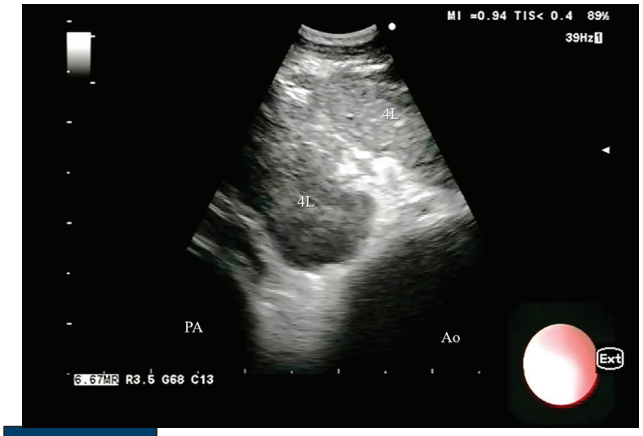

Figure 1

Ultrasound view of the left lower paratracheal lymph node station (4L). Two increased size, heterogenous lymph nodes can be identified (4L), along with the aorta (Ao) and pulmonary artery (PA).

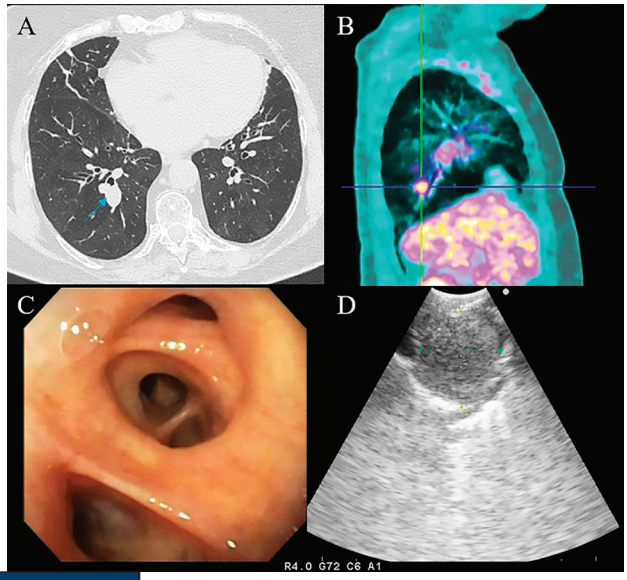

Figure 2

52 year-old women, non-smoker, with a lung lesion in the right lower lobe (A), PET positive (B). Flexible bronchoscopy could not identify this extraluminal tumor (C). Throught EBUS-TBNA the lesion was located (D) and proved to be a lung adenocarcinoma, thyroid transcription factor-1 (TTF-1) positive and PD-L1 > 50%. The patient was submitted to lobectomy.

2004. It is performed using a curvilinear scanning ultrasound bronchoscope connected to an ultrasound unit. The angle and field of view, quality of the image, the outer diameter and distal end size of the echoendoscope differ among the three commercially existing EBUS-TBNA scopes (Olympus, Pentax, Fujifilm).

Several technological improvements have been made in the last few years, such as, smaller ultrasound (US) probes; higher endoscopic resolution; better sonographic consoles and US image; increased size, resistance, angulation and cutting edge of the needles.

Esophageal ultrasound

Esophageal ultrasound with fine needle aspiration is performed either with a large curvilinear gastrointestinal ultrasound endoscope (EUS-FNA) or by using the smaller EBUS-scope in the esophagus (EUS-B-FNA). EUS has several advantages over EUS-B: the US window angle is larger; the US image is better; and the transducer is in close contact with the target due to suction with deflation of the lumen. However, there are no randomized trials showing an improved patient outcome by using EUS-FNA instead of EUS-B-FNA. There are obvious practical and logistical advantages in performing both tracheal and esophageal US with the sequential use of one endoscope. Therefore, the combination of EBUS-TBNA and EUS-B-FNA in a single setting has quickly gained ground. This dual and complementary approach allows an extended assessment of the mediastinum, with access to nearly all relevant lymph nodes for lung cancer staging and permits the diagnosis of paratracheal, parabronchial and para-esophageal lung and mediastinal lesions.

EBUS and EUS-B procedure

These are minimally invasive outpatient procedures, frequently performed under moderate sedation or general anesthesia to allow better patient's tolerance, and operator's control through image collection, puncture, and aspiration. The typical length of the combined approach ranges from 15 to 50 minutes.[6,7]

The echoendoscope is inserted by oral route (e.g., mouth protector, laryngeal mask, orotracheal tube), or by nasal route in some centers, and advanced through the airway guided by endoscopic visualization under careful maneuvering. It is worth mention that a tracheal tube prevents US visualization of structures in the area where it is placed (e.g., 2L and 2R stations).

Direct contact of the transducer with the tracheobronchial wall is a precondition for optimal ultrasonic visualization. When this is a challenge, a saline-filled balloon may be attached to the EBUS bronchoscope tip to improve contact with the mucosa and diminish artifacts. Airway anatomy and vascular ultrasound imaging landmarks are used to identify lymph node stations and/or other mediastinal structures. These are systematically assessed by B-mode (Fig. 1) and documented regarding their shape, echogenicity, size, margins, hilar structure, and presence or absence of necrotic sign, since these characteristics are important for the probability of malignancy.[8] Doppler mode permits the evaluation of intranodal and mediastinal vessels providing complementary information. When elastography is available, is can be of help to discriminate between elastic (e.g., normal, inflammatory) versus rigid tissues (e.g., malignancy, fibrosis) in the lymph node, allowing a better selection of the puncture spot, or choosing among various lymph nodes in one nodal station.[8] Nevertheless, for staging, all lymph nodes above 5mm should be sampled starting from the contralateral hilar and mediastinal structures (N3) of the primary lesion, followed by ipsilateral mediastinum (N2) and finally ipsilateral hilar lymph nodes (N1). For diagnosis,

if not previously done, the main tumor(T) is punctured after finalizing staging, to avoid unintended needle contamination that ultimately could lead to false cancer upstage.

As stated, EUS-B can be performed with the same equipment as an individual or sequential procedure, in the same setting.[9] The scope is inserted through the mouth or, less commonly, through the nose into the esophagus and advanced in gently screw movements until the gastric fundus. Normally, the endoscopic view is not useful and US scanning guides the procedure. Once in the stomach the operator can identify several abdominal organs, namely the left liver lobe and left adrenal gland (LAG), that can be biopsied, if lung metastasis is suspected. Retracting the scope to the esophagus-allows the visualization of adjoining lymph node stations and lung tumors.[10]

Sampling is achieved by a dedicated needle – commonly 21G or 22G, but there are also 19G and 25G –that is gently pushed into the target structure under real-time US visualization. Compared to TBNA, esophageal FNA is frequently easier due to tissue softness and absence of cartilage. An inner stylet, designed to avoid contamination by bronchial or esophageal cells, is then completely removed. Suction may be applied, by attaching a syringe to the proximal part of the needle, and 8-12 movements are done inside the aimed structure. Suction is stopped and the needle is removed from the working channel of the EBUS bronchoscope for sample collection (e.g., slide smears, liquid container for cell block). By EBUS-TBNA is possible to puncture stations 1R, 1L, 2R, 2L, 4R, 4L, 7, 10R, 10L, 11R, 11L and by EUS-B-FNA stations 2L, 4L, 7, 8, and 9. In very specific situations, EUS-B may allow sampling from station 5 (sub-aortic) or station 6(para-aortic) lymph nodes11 but a trans-vascular approach, although possible, is seldom recommended in clinical practice.

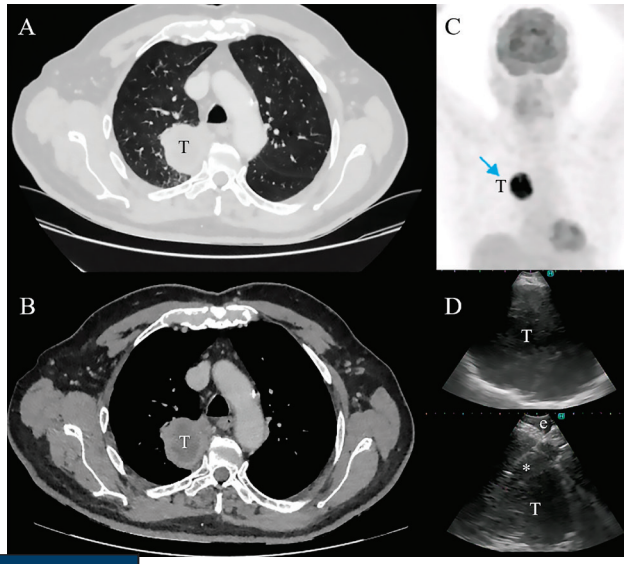

Figure 3

72 year-old male, heavy ex-smoker, with a right upper lobe 46mm solid lung lesion on CT (A), adjacent to the trachea and esophagus (B). PET-CT (C) showed increased FDG captation only in the primary tumor (T). EBUS-TBNA and EUS-B-FNA were performed for systematic staging and diagnosis (D). A small 4R lymph node station (6mm) was positive for malignant cells. The main lesion was punctured with a 21G needle (*) throught the esophagus (e) and the final diagnosis was a lung squamous cell carcinoma (T2bN2).

EBUS/EUS-B 19G needles are also available and may further enhance the diagnostic yield in lung cancer[12] but their increased size can make it harder to penetrate the airway wall and the sample may also have more blood or epithelial contamination. An alternative modality to acquire histological specimens is the use of EBUS-guided intranodal forceps biopsy. The airway is punctured first with a 21/22G needle, and a small track is created between the mucosa and the lymph node, enabling the transtracheal or transbronchial introduction of mini forceps under sonographic guidance. This adapted technique proved to be safe and with an increased diagnostic yield for sarcoidosis and lymphoma[13] but it should be performed only by trained and skillful bronchoscopists. More recently, an adaptation of this mediastinal EBUS biopsy technique, using miniature cryoprobes instead of the classical forceps biopsy, has been described in small case series[14] and one randomized clinical trial[15] with promising results that, nevertheless, require deeper investigation prior to an attempt at standardization and routine clinical application.

In some thoracic departments and interventional pulmonology units there is the possibility of performing rapid on-site examination (ROSE) by an attending physician or a cytopathologist. The sample is immediately assessed regarding its quality and quantity. A meta-analysis proved that ROSE does not significantly improve the diagnostic yield during TBNA but is associated with fewer needle passes and a requirement of additional procedures to make a definitive diagnosis.[16] Besides, some studies showed that the success rate for obtaining suitable tissue does not seem to be related to ROSE or needle size, suggesting that technical details may be less important than adequate sampling with more needle passes for acquiring tumor cells.[17] Scientific data is conflicting, and further prospective trials are needed to clarify the precise role of ROSE in lung cancer staging.

Lung cancer diagnosis

If lung cancer is suspected, tissue or cells should be obtained to establish a definite diagnosis. The initial approach may be quite variable but clinical guidelines recommend sampling the best accessible lesion that provides the most advanced stage with the lowest risk, if possible, with simultaneous diagnosis and staging.[18]

Traditionally, imaging tests are followed by invasive procedures such as flexible bronchoscopy or CT-guided transthoracic needle aspiration (CT-TTNA). Flexible bronchoscopy has a high diagnostic yield for endobronchial tumors but for peripheral and extraluminal lesions its sensitivity is low. CT-TTNA holds a significant risk of complications in central and small pulmonary le-

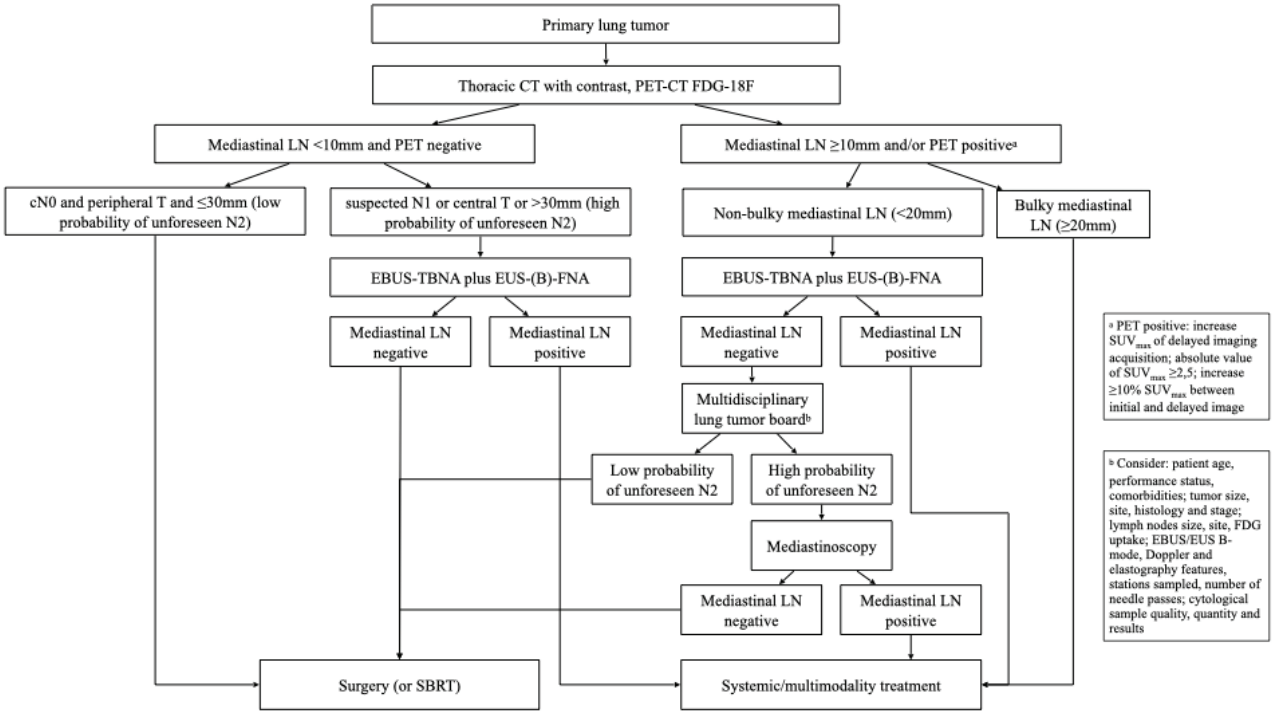

Figure 4

Proposed algorithm for mediastinal lymph node staging in NSCLC patients. LN – lymph node; FDG – fluorodeoxyglucose; SBRT – stereotactic body radiotherapy

sions, especially in patients with pulmonary architectural disruption, such as emphysema.

EBUS-TBNA and EUS-B-FNA are an important option to diagnose lung cancer in patients with centrally located tumors, close to the tracheobronchial tree or the esophagus. The selection between EBUS and EUS depends on the operator expertise and the location of the suspicious lesion. In an observational study, combined EBUS-TBNA with EUS-B-FNA provided a definitive diagnosis in 87.6% of cases, after failure of CT-TTNA and/or flexible bronchoscopy.[19] Trained bronchoscopists have shown that it is feasible and safe to perform diagnostic endosonography in lesions that are at least 19mm apart for the central airway or the esophagus.[10,20] Furthermore, newer EBUS scopes have a smaller US transducer that enables to reach deeper into the lobar bronchus, upper lobe bronchus and sometimes segmental bronchi, expanding the possibility of diagnosis of lung tumors (Fig. 2).

By using EBUS/EUS-B there is always the potential of providing diagnosis and mediastinal staging in a single procedure, as stated before. In these cases, it is crucial that all lymph nodes are punctured first, and the primary tumor is sampled afterwards, to avoid needle contamination and upstaging. In some patients, if the primary lesion cannot be easily assessed, tissue still may be acquired from highly suspicious metastatic lymph nodes to diagnose lung cancer.

A randomized controlled trial published in 2015 showed that EBUS-TBNA performed as the initial procedure to diagnose suspicious pulmonary lesions reduced the time to treatment decision, when compared with flexible bronchoscopy or CT-TTNA.[21] However, it should be emphasized that EBUS-TBNA is not aimed to substitute those conventional techniques since its size and angulation does not allow an accurate and complete inspection of the airway lumen. Most physicians still start the procedure with a flexible bronchoscope – to evaluate the airways and clear secretions – and then execute endosonography. A systematic review and meta-analysis comprising 14 studies, EBUS-TBNA had an average yield of 89% for diagnosing centrally located lung tumors and average sensitivity for diagnosing malignancy was 91%.[22] Of course, these studies have a bias regarding patient selection, that is also seen in CT-TTNA publications.

Clinical guidelines for NSCLC recommend the acquisition of adequate volume of specimens for molecular profiling.[23] EBUS-TBNA can provide sufficient cells for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) genetic analysis in more than 94% of cases.[24] To detect multiple genes mutation, next generation sequencing (NGS) platforms, can be applied to EBUS samples, although the success rate is highly variable[25]but taking≥4 good quality samples is a predictor of success.[26] It is also feasible to evaluate the expression of PD-L1 on tumor cells in endosonography samples for selection of NSCLC patients for immunotherapy. One study

compared EBUS-TBNA aspirates with resected specimens and found a high correlation at PD-L1 ≥1% and but less at ≥50%, probably related to low-tumor cellularity.[27] The intra-tumoral heterogeneity of PD-L1 expression may offer an important barrier for cytology and small biopsies. ROSE may allow for a qualitative and quantitative assessment of these samples improving lung cancer genotyping and preventing the need for additional biopsies or procedures.[28] Standardized specimen collection, processing and staining protocols are needed to compare the outcomes in future studies.

Lung cancer staging

The correct evaluation of the mediastinal and hilar compartment is of extreme importance to choose the best treatment and for prognosis in NSCLC patients. When international staging guidelines are followed, lung cancer patients are submitted to fewer procedures with less morbidity and mortality.[29]

Imaging studies such as contrast chest CT and PET-CT are used as initial methods for staging. Commonly, CT is the first diagnostic and staging exam that assesses the primary tumor (T), nodal stations (N), and possible chest and high-abdominal metastasis (M). Regarding the N discriminator, thorax CT defines the anatomical margins, nodal zones and allows the measure of lymph node short axis – ≥10mm is considered a predictor of malignant involvement. It is worth mention that this cut-off is insufficient to confirm or exclude lymph node metastasis, due to its low sensitivity for malignancy[3,4]. Indeed, in 20% of cases there are metastasis in lymph nodes with less that 10mm short axis.[30] Also, morphologic characteristics, such as capsule disruption or central necrosis, are not satisfactory to confirm malignancy.

PET-CT scan provides a metabolic map with increased staging sensitivity (79-85%) and specificity (89-95%) compared to thoracic CT sensitivity (57-61%) and specificity (77-82%) for detecting malignant lymph nodes in NSCLC patients.[31,32] A recent meta-analysis, including 3535 patients, confirmed a moderate sensitivity (79%) and specificity (65%) of PET in predicting occult lymph node metastasis.[33] Also, its negative predictive value (NPV) for regional lymph node staging is moderate and decreases for lymph nodes <10mm or when the nodal station is abutting central primary lesions.[34,35] Another concern is the rate of PET-CT false-positive cases, that can reach up to 25%, due to inflammatory, infectious, and granulomatous diseases.[34] Thus, in clinical practice physicians cannot be completely reassured about mediastinal lymph node status based only on imaging tests.

Guidelines recommend that minimally invasive mediastinal staging should be performed in all potential candidates for curative surgery, to exclude metastasis with the maximum degree of confidence but there are exceptions. Further staging procedures may be omitted in patients with peripheral tumors less than 3 cm – especially non-adenocarcinoma histological type – when previous imaging techniques are not suspicious for lymph node involvement, since the rate of unforeseen N2 disease is lower compared with central and bigger tumoral lesions.[36–38] In patients with cT1 tumors PET-CT NPV is 93-97% but for cT2 or cT3 it drops significantly.[39]

The concept of minimally invasive cytological or histological sampling may be different according to local clinical practice, resources, and expertise but always implies the exclusion of N2/N3 disease prior to treatment. Non-guided TBNA is not considerate a staging procedure, because is not able to secure an accurate and systematic lymph node sampling. The most common worldwide use for EBUS and EUS-B is lung cancer staging and it is consensual that is safe, reliable, and effective when performed by trained and experienced operators, compliant with scientifically validated standards.[2]A large database study assessing mediastinal staging costs proved that endosonography is also associated with lower costs compared to mediastinoscopy.[40]

International guidelines first advised that at least three different mediastinal nodal stations (4 R, 4L, 7) should be sampled in NSCLC patients with an abnormal mediastinum by CT or PET-CT.[2] For NSCLC mediastinal staging an initial meta-analysis included 9 studies and showed an EBUS-TBNA pooled sensitivity of 90%, specificity of 99%, accuracy of 96%, negative and positive predictive value of 93% and 99%, respectively.[41] The first EBUS-TBNA studies had patient selection bias and design problems. Following work confirmed endosonography value when the results were positive for malignancy but showed limitations regarding the technique's sensitivity and NPV. For example, Dooms C. et al demonstrated that endosonography had a low sensitivity in cN1 NSCLC (38%) which was increased to 73% when mediastinoscopy was added.[42]

An important randomized controlled trial proved that staging NSCLC should begin with EBUS/EUS followed by surgical staging if sonographic findings were negative because this was able to improve the detection of nodal metastases and reduce pointless thoracotomies.[43]

Hence, guidelines and systematic reviews recommend endosonography as the initial sampling method for mediastinal lymph node staging and stated that a negative result should be further confirmed by other invasive methods.[2,37,41,44,45]

As knowledge progressed, evidence indicated that not every NSCLC patient with a negative EBUS/EUS staging result needed to undergo further invasive tests. El-Osta et al evaluate the role of EBUS-TBNA in detecting occult mediastinal disease in NSCLC without radiologic mediastinal involvement.[46] Pooled sensitivity was low (49.5%), but the NPV was 93%, implying that only 7% of cases with a radiologically plus EBUS-TBNA negative mediastinum would have occult mediastinal nodal involve-

ment, and could proceed to curative treatment without further confirmatory biopsy. In 2016, a systematic review and meta-analysis reinforced the earlier findings: combined EBUS and EUS achieved a mean sensitive of 86% and a mean NPV of 92%, were the mean prevalence of N2/N3 disease was 34%.[47] On average, addition of EUS to EBUS increased sensitivity by 12% and addition of EBUS to EUS increased sensitivity by 22%. In 2019, a study by Crombag L. et al reinforced the notion that physicians should do a complete mediastinal endosonography staging and go beyond the concept of assessment of three nodal stations 4L, 4R and 7.[48] Systematic EBUS-TBNA followed by EUS-B-FNA increased sensitivity for the detection of N2/N3 disease when compared to PET-CT targeted EBUS alone. The overall sensitivity for the combined approach was 82% with a NPV of 87%. Finally, in another meta-analysis, the rate of unforeseen N2 after a negative endosonography (9.6%) was similar in NSCLC patients who underwent surgical resection with or without preceding mediastinoscopy.[49]

These outcomes lead to the conclusion that a dual endosonography approach to lymph node staging significantly increases the sensitivity and NPV, reducing the need for surgical staging procedures in all patients. One should bear in mind that this systematic staging is essential but increases procedure length, needs prolonged sedation, adds complexity, and requires skills and training. EBUS-TBNA should be undertaken first, followed by EUS-B.[50] If subsequent lymph node punctures performed by the esophageal route entails a risk of upstaging the patient, a new needle should be used when proceeding to other structures.

In real-life practice, the pre-test probability has to be assessed since specific groups of patients are at higher risk of false-negative results such as in the presence of a centrally located lung tumor (i.e. a tumor located within the inner third of the lung lobe) (Fig. 3); a pulmonary lesion ≥3cm diameter; suspected N2 disease by PET-CT; confirmed N1 disease; restaging following chemotherapy; unsatisfactory or low sampling during EBUS-TBNA and or EUS-B-FNA; and if nodal stations are unreachable by EBUS and/or EUS, especially in tumors located in the left upper lobe.[2,51] Each negative EBUS along with EUS cytological results should be discussed in a multidisciplinary lung tumor board. If there is a concern for false-negative results, the next staging steps should be planned and the patient undergo surgical techniques, such as cervical mediastinoscopy or more extensive procedures. If not, they may be omitted. New trials are underway to further study and cast some light regarding the value of mediastinoscopy in EBUS/EUS negative NSCLC patients.[52]

There are other possible indications for EBUS/EUS-B in lung cancer staging, although less frequent and with limited evidence. EUS-B can assess and puncture the LAG and some trials demonstrated that adequate tissue sampling is feasible in 87-89 % of patients with suspected metastasis.[53,54] In other situations, experienced operators were able to sample abdominal metastases and malignant pericardial effusions for NSCLC staging[55,56] but we need to emphasize that this does not represent a general recommendation.

Lung cancer restaging and recurrency

To downstage stage III disease, NSCLC patients may be submitted to neoadjuvant chemotherapy. It is very important to identify the responders since they may be able to profit from subsequent surgery.

Recommendations for restaging after induction chemotherapy are difficult to define due to the rate of false-negative and false-positive cases by non-invasive and minimally invasive procedures.[57] In 2008 it was published the first EBUS-TBNA restaging study in lung cancer with an overall sensitivity of 76% and NPV of 20%.[58] SzlubowskiA. et al combined EBUS and EUS for NSCLC restaging an accomplished an overall sensitivity, accuracy and NPV of 67%, 81% and 73%, respectively.[59]

In 2020, a systematic review where patients were restaged by EBUS, EUS or both demonstrated a pooled sensitivity of EBUS-TBNA of 65% and EUS-FNA of 73% (combined 65%).[60] The negative likelihood ratio was 35% for EBUS-TBNA and 27% for EUS-FNA. The main problem is that induction treatment with chemotherapy or chemoradiation may led to necrosis and fibrosis in metastatic lymph nodes. Identification and sampling of these lymph nodes is sometimes difficult with less cellular material and more challenging for pathology evaluation.

Surgical approaches such as mediastinoscopy for restaging may be technically difficult due to adhesions and fibrosis caused by the previous treatments and may not be feasible in frail patients. Guidelines suggest that initial NSCLC restaging may be performed by EBUS-TBNA and EUS-B-FNA for detection of persistent nodal disease but, if negative, the patient should undergo subsequent surgical staging before radical surgery is attempted[2]. As formerly stated, the best possible approach in these cases should be defined by the multidisciplinary committee.

Another important issue concerns the risk for tumor recurrency or progression. In lung cancer, therapeutic outcomes are constantly monitored, especially by non-invasive exams, but as the primary lesion and/or metastasis becomes resistant to treatment, rebiopsy may be necessary to redirect second and third-line treatments. EBUS and EUS/EUS-B may also be used to confirm disease relapse or for molecular subtyping, although current data relies on scarce clinical cases and retrospective studies.[61–63] Endosonography sensitivity is reported to be lower in patients submitted to radiotherapy compared to previous surgical treatments. As new lung cancer treatment strategies and targeted therapies are tested and coming out of the pipeline of pharmaceutical compa-

nies, it is expected an increasing need for accurate and high-quality evaluation of tumor biology and molecular profiling by minimally invasive methods, such as endosonography.

Learning EBUS-TBNA and EUS-B-FNA

Structured training, competence maintenance and adherence to guideline recommendations are mandatory to obtain optimal results.

Evidence-based simulator training and assessment of skills in EBUS-TBNA followed by clinical supervised training is the suggested method to acquire proficiency.[2,64] A comprehensive program on EBUS is offered by the European Respiratory Society.[65] For the moment, an EUS-B-FNA simulator training is not available, but a validated assessment tool for competences in EUS-FNA exists.[64]

CONCLUSIONS

EBUS-TBNA and EUS-B-FNA are mandatory techniques for the diagnosis and staging of patients suspected of lung cancer. Based on the above data, mediastinal staging guidelines will have to be revised and new algorithms proposed (Fig. 4).

In addition, EBUS and EUS-B have a significant clinical impact for lung cancer restaging.

The success of EBUS and EUS-B is based on multiple factors such as patient selection, available equipment, management of specimens (acquisition, processing, and interpretation) and proficiency of the entire team. As every technique, there is a learning curve not only for the bronchoscopist but also for the pathologist and everyone involved. This leads to procedural safety and efficacy. Structured learning and educational EBUS/EUS programs are essential to appropriately implement and disseminate these low-invasive exams and offer lung cancer patients the best standard of care in an era of personalized medicine.

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