—Review Article—

Endoscopic ultrasound in the diagnosis and staging of lung cancer

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ABSTRACT

We reviewed the role of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and esophageal ultrasound guided fine needle aspiration (EUS-FNA) in the pretherapeutic assessment of patients with proven or suspected lung cancer. EUS-FNA and EBUS-TBNA have been shown to have a good diagnostic accuracy in the diagnosis and staging of lung cancer. In the future, these techniques in combination with positron emission tomography/computed tomographic may replace surgical staging in patients with suspected and proven lung cancer, but until then surgical staging remains the gold standard for adequate preoperative evaluation.

Key words: Cancer, diagnosis, endobronchial ultrasound, endosonography, esophageal ultrasound, lung, staging

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality in the western countries, and the prognosis is poor[1-4] since the survival rate for non-small cell lung cancer (NSCLC) varies from 73% for stage IA to 25% for stage IIIA.[4]

Accurate staging of NSCLC is mandatory for allocation to surgical treatment, which is curative only in cases of localized disease.

In general, surgical treatment cannot be recommended in patients with NSCLC and T4 and/or N2–N3 disease and/or M1-disease, and the recommended treatment is chemotherapy and radiation therapy.

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The aim of the present review was to go through the literature on the role of Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), and esophageal ultrasound guided fine-needle aspiration (EUS-FNA) in the pretherapeutic assessment of patients with proven or suspected lung cancer.

WHAT IS THE DIAGNOSTIC APPROACH?

The diagnostic approach in patients suspected of lung cancer can be divided into two phases.

1. Imaging techniques: Computed tomographic (CT) and positron emission tomographic (PET) are cornerstones, but in some cases magnetic resonance imaging and ultrasound examination can be of value
2. Techniques that allow a pathological diagnosis: Bronchoscopy, trans-thoracic needle aspiration lung biopsy, endosonography ([EBUS-TBNA] and [EUS-FNA]), thoracocenteses, medical thoracoscopy and other techniques (mediastinoscopy, video-assisted thoracic surgery and thoracotomy) [Figure 1].

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The role of endosonography

Among the invasive techniques, EBUS-TBNA and EUS-FNA are gaining ground fast, mainly because they can be an alternative to surgical staging (mediastinoscopy).[5,6]

Current guidelines suggest that endosonography could be used as first-line approach both for diagnosis and for staging of suspected and proven lung cancer,[7,8] since it has a high accuracy for demonstrating lymph node (LN) metastases. Surgical staging procedures can be avoided in a considerable proportion of patients. However, in general, negative findings by EUS-FNA or EBUS-TBNA should be confirmed by surgical techniques, for example mediastinoscopy.

Instruments and procedure

Endosonography procedures can be performed in an outpatient setting under local analgesia with mild sedation. A range of instruments with linear transducers suitable for monitoring of the biopsy needle are available. These endoscopes use frequencies between 5 and 10 MHz with a penetration at 5 MHz of around 6-8 cm. The instruments provide an endoscopic and an ultrasonic picture at the same time. It is recommended using 7.5 MHz as a routine and change the frequency, if necessary.

The procedure is performed with a dedicated needle assembly which consists of a long steel needle, a sheath and a handle for manipulation of the needle.[5] The needle is attached to the working channel of the endoscope. When the lesion has been outlined, the needle is advanced under real-time ultrasonic guidance.

What structures can be reached by esophageal ultrasound and endobronchial ultrasound?

In short, EUS is excellent for the left and lower paraoesophageal structures as well as structures below the diaphragm, while EBUS provides access to structures close to the large airways on both sides.

Lung and pleural tumors close to the esophagus, mediastinal LN in station 2 L, 4 L (high and lower left paratracheal nodes), 7 (the subcarinal node), 8, 9 (nodes located in the lower mediastinum) and structures below the diaphragm (i.e. retroperitoneal LNs close to the aorta and the celiac trunk, tumors in the left liver lobe and the left adrenal gland) are reached with EUS. EBUS can reach lung tumors and LNs located in the hilar regions such as stations 10, 11 and 12 (right and left sided). It must be noted that EBUS is also useful in station 2R, 4R, 2 L, 4 L and 7.

As shown in Figure 2, the most important structures that can be reached by EBUS and EUS are shown and they are also summarized in Table 1.

Comparison of the techniques

Various randomized clinical trials (RCTs) compared the diagnostic yield of EBUS and EUS with others techniques (conventional TBNA (cTBNA), PET-CT, surgical techniques).

Yasufuku *et al.*[11] compared the diagnostic accuracy of EBUS-TBNA versus invasive surgical staging techniques. The sensitivity for mediastinal LN staging for EBUS-TBNA and mediastinoscopy was 81% and 79% respectively, but this difference was not significant.

The multicentre RCT of Annema *et al.*[6] (the ASTER study) compared mediastinoscopy with combined

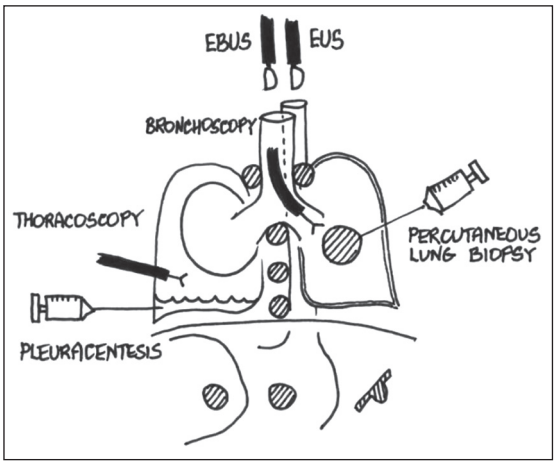

Figure 1. Invasive procedures

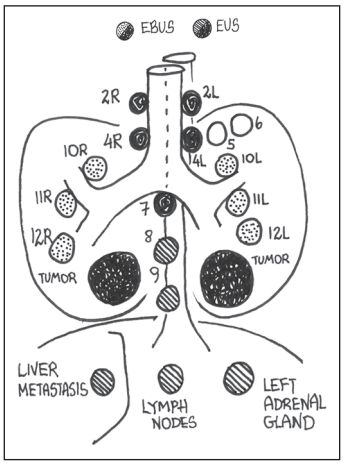

Figure 2. Structures that can be reached by EBUS and EUS

Table 1. Location, detection and biopsy of the structures that can be reached by EBUS and EUS

Structures	Location	EBUS		EUS		Comment
		Detection	Biopsy	Detection	Biopsy	
Lung tumor	Left and right	+++	+++	+++	+++	Possible to reach from both trachea and esophagus
2R, 4R	Paratracheally to the right	+++	+++	+	+	The trachea lies between the transducer and the LNs, limiting visualization of this area
2L, 4L	Paratracheally to the left	+++	+++	+++	+++	Routine
5	Laterally to station 4L in the aortopulmonary window with the (invisible) ligamentum arteriosum as anatomical border	–	–	++	(+)	Easy to detect, but difficult to biopsy due to the intervening pulmonary artery. In EUS-FNA the elevator can help in controlling the needle
6	Lateral to the ascending aorta and the aortic arch	–	–	++	(+)	Biopsy is not a routine: The needle may be passed through the aorta[9] or by a high esophageal approach using 7-8 cm of the needle length[10]
7	Under the carina	+++	+++	+++	+++	Routine
8, 9	Situated inferior to station 7	–	–	+++	+++	Close to esophagus, no relation with the trachea
10, 11, 12	LNs in the hilar regions	+++	+++	–	–	Close to trachea and main bronchi, no relation with the esophagus
Spleen		–	–	+++	+	Seldom relevant
Left liver lobe		–	–	+++	+++	Routine
Left adrenal gland		–	–	+++	+++	Routine
Right adrenal gland		–	–	+	+	Not routine
Pleural effusion	Left and right sided	–	–	+++	++	Not routine since it in most cases can be sampled with thoracocentesis

EBUS: Endobronchial ultrasound, EUS: Esophageal ultrasound, LNs: Lymph node, FNA: Fine-needle aspiration, R: Right, L: Left

EUS-FNA and EBUS-TBNA. Two hundred forty-one patients with potentially operable NSCLC were randomized, 118 to surgical staging and 123 to endosonography, of whom 65 also underwent surgical staging. The primary outcome was sensitivity for mediastinal nodal (N2/N3) metastases. This was 80% for surgical staging and 94% for endosonography, followed by surgical staging ($P = 0.04$).

Moreover, a staging strategy combining endosonography and surgical staging compared with surgical staging alone resulted in fewer unnecessary thoracotomies.

Endobronchial ultrasound-guided transbronchial needle aspiration was also compared with cTBNA in two RCTs.[12,13] EBUS guidance significantly increased the yield of TBNA in all stations except in the subcarinal region in both studies. In one study,[12] the overall diagnostic yield was 71% for TBNA and 80% for EBUS ($P < 0.05$). In the other study,[13] the overall diagnostic yield was 33.3% for TBNA and 66.7% for EBUS ($P = 0.01$).

Tournoy *et al.*[14] compared EUS-FNA and surgical mediastinal staging. Forty patients were randomized, 19 received EUS-FNA and 21 surgical staging. The primary outcome was the rate of surgical intervention: EUS-FNA resulted in a reduction of 68% in surgical staging. The sensitivity for LN metastases was 73% for the surgical staging group and 93% for the EUS group. The complication rate was 5% for the surgical staging group and 0% for EUS group. The length of hospital stay was 2 days in the surgical staging group and 0 days in the EUS group.

A RCT published in 2011[15] described faults and benefits of PET-CT in multimodality mediastinal staging. One hundred and eighty-nine patients were enrolled; 98 were assigned to receive mediastinal staging with PET-CT, followed by invasive staging (mediastinoscopy and/or EUS-FNA) and 91 to receive invasive staging without prior PET-CT. In an intention-to-treat analysis, the overall accuracy of the consensus N stage was not significantly higher in the PET-CT group than in the other group (90% *vs.* 85%). Excluding the patients in whom PET-CT was not performed ($n = 14$) the difference was significant (95% *vs.* 85%). Thus, PET-CT was shown to improve discrimination between N0-1 and N2-3.

Indications

The main indications for endosonography in a patient with suspected or proven lung cancer are:

1. Diagnosis
2. Mediastinal LN staging
3. Evaluation of tumor invasion (T4)
4. Pleural fluid evaluation (M1a)
5. Assessment of M1b disease
6. Re-staging after chemotherapy and radiation therapy.

Diagnosis

With endosonography, it is possible to biopsy centrally located lung tumors and peripheral lung tumors close to the esophagus. The role of EBUS-TBNA and EUS-FNA in the diagnosis of central located lung tumor was assessed in various studies. For EUS, the sensitivity varied from 88% to 100%,[16-19] while for EBUS the sensitivity was reported 91% in a cohort of 37 patients.[20] Moreover, Tournoy *et al.*[21] evaluated EBUS-TBNA after a nondiagnostic bronchoscopy in 60 patients: Lung cancer was diagnosed in 46 patients and the overall sensitivity was 82% with an NPV of 23%. Moreover, the sensitivity for lung tumor <25 mm was 78% whilst the sensitivity for lung tumor >25 mm was 86%.

Mediastinal lymph node staging

Fourmeta-analyses reported the sensitivity of EBUS-TBNA for diagnosis of mediastinal LNs in patients with lung cancer. Adams *et al.*[22] reported a sensitivity of 88%. Chandra *et al.*[23] have reported a pooled sensitivity of 92%. Dong *et al.*[24] reported a sensitivity of 90%. Gu *et al.* reported a sensitivity of 93%.[25] Concerning EUS-FNA, the pooled sensitivity was 88% in the meta-analysis of Micames *et al.* and Puli *et al.*[26,27] reported a pooled sensitivity of 88%.

Imaging abnormal mediastinum: Suspected mediastinal lymph nodes metastases at imaging techniques, that means peripheral positron emission tomography/computed tomographic positive lung tumor with enlarged and/or positron emission tomography/computed tomographic activity in the mediastinal lymph nodes.

In patients with abnormal mediastinum on imaging techniques the probability of having nodal metastases ranges from 50% to 80%.[28] In the meta-analyses already mentioned[22-25] no data were provided about the sensitivity in this group of patients. In the pooled calculations, two studies were included in which there were no abnormalities in the mediastinal LN at the imaging investigations.[29,30]

In the RCT of Annema *et al.*,[6] the sensitivity of endosonography alone for detecting mediastinal metastases in patients with abnormal mediastinal LNs was 86%. In this group of patients when the surgical staging was associated with endosonography the sensitivity increased to 97%. For the surgical staging alone, the sensitivity was 83%.

Two large prospective studies investigated the sensitivity of EBUS in patients with abnormal mediastinal LNs on imaging techniques. Herth *et al.*[31] found a sensitivity of 94%. Ernst *et al.*[32] found a sensitivity of 91%.

In recent years, a prospective case series[33] considered 259 patients with mediastinal or hilar abnormalities in patients with suspected or confirmed lung cancer. The overall sensitivity of EBUS-TBNA was 87%.

A part from the studies already mentioned when abnormal radiological mediastinal LNs are considered, the sensitivity of EBUS — ranges from 85% to 97%.[34-45]

The sensitivity of EUS-FNA was 83% in patients with positive mediastinal LNs.[25] In this clinical scenario, several other prospective studies have demonstrated sensitivity ranges from 83% to 97%.[18,46-60]

Consequently, in patients with imaging abnormalities of the mediastinum and negative endosonography there is still a risk of mediastinal LN metastases that should lead to mediastinoscopy or other surgical staging procedures.

Imaging negative mediastinum: Mediastinal lymph nodes are normal at imaging techniques, but the possibility of nodal metastases is still present in the following cases:

- Peripheral PET positive lung tumor with enlarged and/or PET activity in the hilar LNs
- Lung tumor without any PET activity
- Centrally located lung tumor.

In these situations, the probability to have nodal metastases ranges from 6% to 30%.[28]

The meta-analysis of Micames *et al.*[26] reported in this subgroup of patients a pooled sensitivity for detecting N2 disease of EUS-FNA of 58%.

A recent study[61] compared the overall rate of noncurative lung resection performed in NSCLC patients with occult N2 disease staged with PET/CT only or with PET/CT and EBUS-TBNA. In the EBUS-group, there was a lower rate of noncurative noncurative lung resection (8.1% *vs.* 12.5%).

Herth *et al.*[31] showed that potentially operable patients (T1-T4) with no signs of mediastinal involvement on CT may benefit from pre-surgical staging by means of EBUS-TBNA and. One hundred patients underwent EBUS and surgical staging. Malignancy was detected in 19 patients, but missed in two. The sensitivity of EBUS-TBNA for detecting malignancy was 92.3%.

In a similar trial,[30] despite negative CT and PET, EBUS-TBNA showed mediastinal LNs metastases in eight out of one hundred patients.

A prospective, controlled comparison study[57] assessed the role of EUS and EUS-FNA in 80 patients with lung cancer and negative mediastinal LNs at CT scan. EUS-FNA identified two patients as N3 disease in 56 patients without mediastinal LN involvement on CT.

Similar results have been published in another prospective trial[62] comparing CT and EUS-FNA in 47 patients with NSCLC. EUS-FNA demonstrated N2 disease in five patients. The remaining 42 patients underwent thoracotomy. LN metastases were identified in 16 patients: 11 had only peribronchial or hilar LN involvement that could not be detected by EUS, and the remaining 5 had N2 disease. Thus, five patients were understaged by EUS-FNA.

Thus, further studies are needed to assess the reliability of negative endosonography results in patients with negative imaging of the mediastinum.

In the ASTER study,[6] the posttest probability for nodal metastases after a negative endosonography was 20% for the subgroup of patient with imaging positive mediastinum and 9% in the subgroup of patients with imaging negative mediastinum. With the addition of a confirmatory mediastinoscopy the posttest probability for missed nodal metastases dropped only for abnormal mediastinum by imaging, from 20% to 5%, but remained unaffected for normal mediastinum by imaging.[6]

In conclusion irrespectively of the presence of abnormalities at imaging in the mediastinal LNs, when the suspicion for metastases is high, the preferred initial technique for mediastinal staging should be endosonography.[7,8] Identification of one malignant LN does not mean that mediastinal staging is optimal. At least, three stations (subcarinal, left paratracheal and right paratracheal stations) should be assessed.[7,8]

Evaluation of tumor invasion (T4)

Endosonography allows visualization of the possible invasion of the large vessels and the heart. Hence, if T4 disease is assessed surgery in general will be contraindicated. In a cohort of 424 patients with suspected lung cancer, EUS had a relatively low sensitivity of 39% in assessing T4 tumors.[51]

Pleural fluid evaluation (M1a)

In patients with lung cancer, malignant pleural effusion is synonymous of M1a disease that excludes curative intended operation. EUS provides visualization of the pleura on both sides, and pleural fluid aspiration is feasible,[63] which may be useful in selected cases. However, transthoracic ultrasound guided thoracocentesis is the standard way to perform pleural fluid analysis.

Assessment of M1b disease

Esophageal ultrasound guided fine needle aspiration has been described for the diagnosis of unknown lesions in the spleen,[64] but were very seldom relevant in connection with staging of lung cancer.

The left adrenal gland is reached as a routine by EUS. Several reports have demonstrated a high diagnostic yield and accuracy and significant impact on treatment modality.[65,66]

Until recently only the left adrenal gland was considered to be routinely visualized by EUS by a transgastric approach. In a series of 150 consecutive patients, in addition to demonstrate the left adrenal gland, the right adrenal gland was imaged in 87% of patients by transduodenal approach.[66] The latter has earlier only been reported in selected cases.[67]

Esophageal ultrasound can detect liver lesions and can confirm the diagnosis of liver metastasis establishing a definitive diagnosis.[68]

Re-staging after chemotherapy and radiation therapy

Patients with NSCLC at stage III (N2/N3) who are downstage to N0 by chemoradiation therapy might benefit from subsequent surgical resection of the tumor. How mediastinal LNs can best be re-evaluated is still under discussion.

Repeated mediastinoscopy performed in a restaging setting resulted in a sensitivity ranging from 50% to 74% and a false negative (FN) rate between 9% and 38%. Technical difficulties arise in up to 40% of

patients because of mediastinal adhesions and fibrotic changes induced by the initial mediastinoscopy and the neoadjuvant chemoradiation therapy.[69]

In the study of von Bartheld *et al.*[69] 58 consecutive patients with stage III NSCLC underwent EUS-FNA for restaging purposes after chemoradiation therapy. EUS-FNA had a sensitivity of 44% and an FN rate of 58% for mediastinal nodal involvement. These findings are lower compared with several smaller studies (sensitivity: 75-92%; FN rate: 8-33%).[70-72]

The sensitivity of EBUS-TBNA for restaging NSCLC was evaluated in two studies: Herth *et al.*[73] showed a sensitivity of 76% and an FN rate of 80%. Szlubowski *et al.*[74] found a sensitivity and FN rate of 67 and 23%, respectively.

Thus, there seems to be a lack of agreement concerning the role of endosonography in restaging since the mentioned studies have obtained results pointing in different directions.[69,73,74]

Contraindications

Contraindications of EBUS-TBNA are similar to contraindications of flexible bronchoscopy.[75] These contraindications should also be considered for EUS-FNA. Moreover, it is contraindicated to puncture cystic lesions in the mediastinum due to the risk of mediastinitis.[76]

Staging of lung cancer with endosonography

It is recommended to start taking biopsies from M1-structures and then proceed to N1 to N2 to N3 LNs and thereafter to the lung tumor [Figure 3] to avoid the spread of malignant cells to LNs that could bring the patient in an inoperable stage. We recommend using a new needle when going from M1b (for example the left adrenal) to the mediastinum, although there is no evidence that it harms the patient not to do so.

Endosonography with one or two endoscopes?

The benefits of performing EUS and EBUS with two different endoscopes instead of one are mainly motivated by benefits of the EUS endoscope. EUS is better tolerated (no cough) by the patients, the ultrasonic window angle is larger (150-180 *vs.* 50-60° with EBUS), the ultrasonic picture is better due to a higher resolution, small structures are better-visualized, there are no cartilage rings that have to be penetrated by the biopsy needle, the maneuverability of the needle is better due to an "elevator," and histological biopsies

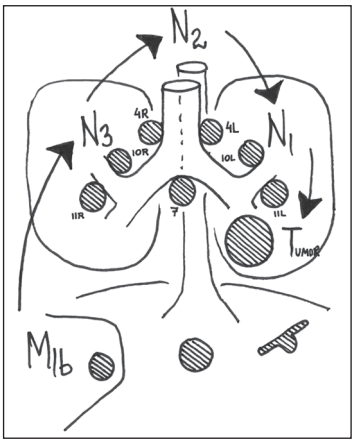

Figure 3. The correct order of taking biopsies

can be obtained with a true cut 19 G needle, However the EUS endoscope is too big to introduce into the trachea and bronchi and here the EBUS endoscope must be used.

Currently, there is no single endoscope that offers the benefits of both.

However, it is increasingly accepted to perform EUS with the small EBUS — endoscope, the so-called EUS-B procedure.[77,78] First the EBUS endoscope is used in the trachea as usual (EBUS-TBNA) and thereafter it is inserted in the esophagus (EUS-B-FNA).

Hwangbo *et al.*[77] in 150 patients evaluated EUS-B-FNA for LNs that were inaccessible or difficult to access by EBUS-TBNA. The sensitivity of EBUS-TBNA in the detection of mediastinal metastasis was 84.4%. This value for the combined approach of EBUS-TBNA and EUS-B-FNA increased to 91.1%, although the differences were not statistically significant.

Herth *et al.*[78] analyzed 139 patients who underwent endoscopic staging with EBUS-TBNA first, and then the same endoscope was used to perform EUS-FNA. Sensitivity was 89% for EUS-FNA and 92% for EBUS-TBNA. The combined approach had a sensitivity of 96% and a negative predictive value of 95%, values higher than either approach alone. Thus, the combined procedure with one single scope seems promising.

CONCLUSION

Esophageal ultrasound guided fine-needle aspiration, and EBUS-TBNA have been shown to have a good diagnostic accuracy in the diagnosis and staging of lung

cancer. In the future, these techniques in combination with PET/CT may replace surgical staging in patients with suspected and proven lung cancer, but until then surgical staging remains the gold standard for adequate preoperative evaluation.

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