Added value of endoscopic ultrasound to endobronchial ultrasound in non-small cell lung cancer staging

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Abstract: Combining endoscopic ultrasound (EUS/EUS-B) and endobronchial ultrasound (EBUS) can improve diagnosis and accurate staging of non-small cell lung cancer (NSCLC). Guidelines recommend endoscopic techniques to sample suspicious nodules and masses. While EBUS is the preferred initial procedure of choice, EUS/EUS-B has been shown to have high sensitivity in sampling mediastinal and subdiaphragmatic disease. Each procedure has unique implications but when combined, offers an additive benefit in the staging of malignant disease. Following EBUS with EUS/EUS-B during a diagnostic procedure increases overall sensitivity and negative predictive value, leading to improvement in time to diagnosis and staging, decreased health care costs, and improved patient comfort. The combined diagnostic sensitivity and yield are significantly increased compared to outcomes from a single procedure alone. Between EBUS and EUS/EUS-B, the mediastinum can technically be completely staged by minimally invasive techniques alone, reducing the need for surgical sampling. These endoscopic measures also have lower complication rates when compared to traditional surgical mediastinoscopy. In this paper, we will introduce EUS/EUS-B and describe the advantages of adding these procedures to EBUS. We will also describe biopsy techniques, comparison of these procedures, identification of lymph node landmarks, staging and restaging of the mediastinum, limitations, and future directions in endosonography.

Keywords: Lung cancer; staging; endobronchial ultrasound (EBUS); endoscopic ultrasound (EUS)

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Introduction

Lung cancer remains the leading global cause of cancer-related deaths and disability in both men and women (1,2). Because of its high morbidity and mortality, rapid diagnosis and accurate staging is essential in determination of treatment and identification of potential surgical candidates.

Advancements in radiographic imaging and biopsy methods have improved lung cancer staging over the years. Radiographic techniques such as computed tomography (CT) and positron emission tomography-computed tomography (PET-CT) have helped identify suspicious nodules as well as distant metastases. However, tissue sampling is still required for confirmation of malignancy and staging due to high false positive results with imaging alone (3-11).

Historically, the test of choice in sampling mediastinal disease was surgical mediastinoscopy. However, this invasive method requires general anesthesia and has complications including hemorrhage, tracheal injury, pneumothorax, recurrent laryngeal nerve palsy, and a mortality rate of 0.08% (12).

Current guidelines for lung cancer diagnosis and staging

recommend endoscopic methods as the first procedure for acquiring tissue (13,14). Since its development, a growing body of literature has shown endobronchial ultrasound (EBUS) to be superior to surgical methods in sampling mediastinal disease including mediastinal masses, lymphadenopathy, and metastatic disease (13,15-18). This minimally invasive technique does not require anesthesia, offers better patient comfort, costs less, and has overall lower risks (19). EBUS has since been utilized as the first procedure in accessing hilar and mediastinal lesions as well as central parenchymal and intrabronchial lesions (19,20). The EBUS scope can be used for transesophageal biopsies (EUS-B), mirroring the endoscopic ultrasound (EUS) technique that is more commonly utilized by gastroenterologists in the United States.

Endoscopic procedures can also expedite time to staging. When combined with the use of rapid on site evaluation (ROSE), providers can obtain rapid confirmation of accurate sampling and receive preliminary pathology results to expedite time to diagnosis (21).

Here, we describe the benefit of combining two minimally invasive ultrasound-guided techniques through endobronchial route (EBUS) and transesophageal route (EUS/EUS-B) in the diagnosis and staging of lung cancers.

Lung cancer staging guidelines

Accurate lung cancer staging is essential in the determination of therapy options and overall prognosis for the patient.

The European Society of Gastrointestinal Endoscopy (ESGE), European Respiratory Society (ERS), European Society of Thoracic Surgeons (ESTS), American College of Chest Physicians (ACCP), and National Comprehensive Cancer Network (NCCN) guidelines outline the different scenarios where tumors and lymph nodes should be sampled (13,14). All central tumors, peripheral tumors >3 cm or lymph nodes >1 cm on CT, N1 lymph node involvement on PET-CT, and any PET positive mediastinal lymph nodes with standardized uptake value (SUV) >2 regardless of node size on PET should be staged. Invasive mediastinal staging is not required in patients with peripheral tumor size <3 cm and without lymph node involvement on CT or PET-CT.

The ACCP currently recommends endoscopic methods as the best first step in evaluating and staging potentially resectable non-small cell lung cancer (NSCLC) (13). These techniques are also recommended for suspected N2 or N3 lymph node involvement. Patients with poor lung function should be staged to identify N1 lymph node metastases prior to planning for stereotactic body radiation therapy (SBRT) or sub-lobar resection (15). Early identification of N2/N3 lymph nodes and distant metastases can prevent futile surgery while identifying those who could benefit from neoadjuvant therapy. The technique used to sample the mediastinum is selected at the discretion of the operator and their skill level (13). In the event that endoscopic biopsies of suspicious nodes are nondiagnostic, the ACCP does recommend surgical sampling.

The endoscopic procedures

The three procedures to be discussed in this paper are EBUS, EUS, and the passage of an ultrasound bronchoscope (EBUS scope) through the esophagus to acquire samples which is called EUS-B. We will collectively refer to the transesophageal approach as EUS/EUS-B. Distinctions will be made when citing references that have studied EUS and/or EUS-B separately.

Background on EBUS and EUS/EUS-B

EBUS is currently the first diagnostic technique used in evaluating centrally located lesions including hilar, mediastinal, central parenchymal, and intrabronchial lesions (19,20). Its diagnostic accuracy and safety profile make EBUS the ideal diagnostic modality (13,14,22).

While not standard practice, an experienced pulmonologist may pass instruments through the esophagus for additional sampling of lesions. EUS-B refers to the technique of passing a linear ultrasound bronchoscope probe through the esophagus to access nearby structures. EUS is a longer probe that is passed through the esophagus to obtain samples most typically within and near the gastrointestinal tract. The EUS and EBUS scopes have differences in their structure that offer advantages. The EUS scope is longer than the EBUS scope and therefore covers more distance and range. However, unlike the EBUS scope, the larger diameter of the EUS scope does not permit its use within the airways. When moderate sedation is used, the smaller EUS-B may be more comfortable and better tolerated than the EUS scope. The linear convex EUS scope has a 180° view that is parallel to the endoscope shaft and can obtain images at a depth of 3 to 8 cm. In comparison, the convex EBUS scope has a 50° to 80° view parallel to the endoscope shaft and obtains images between 2 to 5 cm in depth though this can vary depending on scope type.

Sampling technique

Both EBUS and EUS/EUS-B obtain samples through either fine needle aspirations (FNA) or fine needle biopsies (FNB). Although the 180° view by EUS offers a better imaging quality and range, there has been no statistically significant difference in mediastinal lymph node or left adrenal gland sampling between EUS and EUS-B (23,24). Mangiavillano *et al.* found that in sampling parenchymal lesions of the lung, FNB was superior in diagnostic accuracy and sensitivity when compared to FNA (25). Both EUS and EUS-B can be performed during the second half of a staging session, allowing more time for the patient to ease out of the sedation from the first half of their procedure. Typically, the sedation requirements are much less with EUS/EUS-B compared to EBUS due to less cough reflex during EUS.

There are a range of FNA and FNB needles produced by medical device companies that are compatible with the working channels of the EBUS or EUS scopes. The EBUS compatible needles have a similar gauge range at 19, 21, 22, and 25 and a working length of 0–5 cm. The more commonly sized needles for use with EUS include 19, 22, and 25 gauge needles with a length ranging from 0–8 cm. The longer needles used with EUS permits sampling of deeper structures.

The techniques for needle aspiration are similar in both EUS/EUS-B and EBUS. The needle is quickly advanced to puncture the lymph node. Once the needle is positioned, quick agitations inside the lymph node acquire sample. During this process, needle movement must be visualized within the lymph node to ensure proper sampling of the target. Poor contact between the ultrasound probe and esophageal wall can be overcome with saline filled balloons with a latex-free option for patients with a latex allergy (26). Despite the improvement in image quality with use of balloons, there are no studies suggesting correlation with improvement in diagnostic yield.

While EUS and EUS-B may appear similar, there are situations where one may be preferred over the other. Due to the increased length of the scope, EUS is better for biopsies of certain sub-diaphragmatic lesions such as the right adrenal gland or right lobe of the liver. In situations where decreased sedation is required or there are higher O_2 requirements, the patient may tolerate EUS-B more than EUS, possibly because of the smaller diameter in scope size (27-33).

The order of procedures in combining EBUS and EUS makes a difference on outcomes. Korevaar *et al.* found that the addition of EBUS to EUS/EUS-B increased sensitivity by 22% while EUS/EUS-B to EBUS increased sensitivity by 12% (34). Hwangbo *et al.* found that EUS added small additional value to EBUS. When EUS was performed first, more lesions were missed and EBUS had an increased additive value (35). EUS still remained important in upstaging the cancer and diagnosing metastases that were missed by EBUS, specifically with lymph nodes at station 4L and also posteriorly and inferiorly located station 7 (36). Interestingly, the lesions missed by EBUS and picked up by EUS were not located in the inferior mediastinum but in station 4L and 7.

Practical use of EUS/EUS-B

Mediastinal lymph nodes

EUS/EUS-B provides access to para-esophageal lymph nodes that have limited or no accessibility by traditional EBUS. *Table 1* provides a comparison of sites accessible by EUS/EUS-B and EBUS. Sites better reached by EUS/EUS-B include lesions closer to the esophagus such as lymph nodes in the inferior mediastinum including stations 1, 2R, 2L, 3P, 4L, 5, 6, 7, 8, 9, and 10L (27,39). There are techniques to sample para-aortic station 6 both with and without traversing the aorta (37,38,40). Inferior mediastinal and sub-diaphragmatic nodes and structures that can be sampled by EUS/EUS-B include lymph nodes in station 8 and 9, the celiac axis, left lobe of the liver, bilateral adrenal glands, and the spleen (41). *Figure 1* shows a liver mass as seen using EUS.

The ease of biopsy can vary depending on the laterality of the lesion. EUS/EUS-B can sample stations 2L and 4L (paratracheal stations), station 7 (subcarinal station), and stations 8 and 9 (inferior mediastinal stations). *Figure 2* shows visualization of station 7 by EUS. In their evaluation of patients who underwent combined EBUS and EUS, Wallace *et al.* found that EUS was superior to EBUS in detecting malignant disease in stations 5, 6, and 7 (42). Assisi *et al.* found that in patients suspected to have NSCLC, sampling of stations 7–9 had a sensitivity of 90.5% which was higher than that of station 4L (75%) and station 5 (87.5%) (43). Typically, due to interference by the trachea, lymph nodes in station 2R and 4R have limited accessibility. However, if large enough (≥2 cm), lymph nodes in station 4R can also be reached.

Rarely, as many as one in 30 patients with NSCLC may have inferior mediastinal lymph node involvement without

Table 1 Accessibility by EBUS, EUS-B, and EUS

Lymph nodes/structures	EBUS	EUS-B	EUS
1: supraclavicular nodes	X	X*	X*
2R: upper paratracheal nodes, right	X	X**	X**
2L: upper paratracheal nodes, left	X	X	X
3A: prevascular nodes	X***	–	–
3P: retrotracheal nodes	X	X	X
4R: lower paratracheal nodes, right	X	X*	X*
4L: lower paratracheal nodes, left	X	X	X
5: subaortic (AP window) nodes	–	X	X
6: para-aortic nodes	–	X****	X****
7: subcarinal nodes	X	X	X
8: paraesophageal nodes	–	X	X
9: pulmonary ligament nodes	–	X	X
10: hilar nodes	X	–	–
11: interlobar nodes	X	–	–
Gastrohepatic ligament nodes	–	X	X
Celiac axis lymph nodes	–	X	X
Left lobe of liver	–	X	X
Right lobe of liver	–	–	X
Left adrenal gland	–	X	X
Right adrenal gland	–	–	X

"X" indicates that the lymph node station or structure is usually accessible with the specified diagnostic technique. "–" indicates that the lesion is not accessible by the specified technique. *, depending on its location, station 1 may be reached by either EBUS or EUS/EUS-B. **, stations 2R and 4R may be accessible by EUS or EUS-B if the target is large enough. Lymph nodes smaller than 1 cm are usually difficult to access due to the trachea. ***, station 3A is typically inaccessible by EBUS unless using a transvascular approach. ****, station 6 can be accessed with techniques both with and without traversing the aorta. These techniques are described by Liberman *et al.* (37,38). EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; EUS-B, endoscopic ultrasound through the esophagus using an ultrasound bronchoscope.

involving upper mediastinal lymph nodes (15). Sampling of CT and PET negative lymph nodes and adrenal glands can be upstaged by endoscopy with 8% having skipped adrenal metastases identified by EUS only (44). The expanded range of EUS/EUS-B allows for biopsy of extra-nodal lesions.

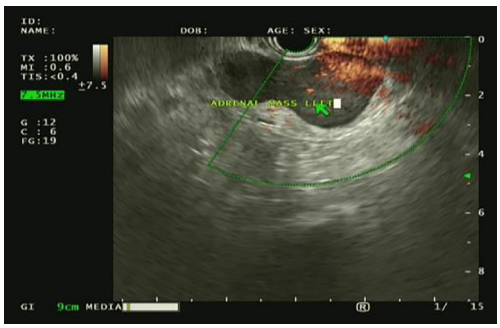

Figure 1 Liver mass identified on EUS. The green arrow points at a hypoechoic, rounded structure consistent with a mass within the liver. EUS, endoscopic ultrasound.

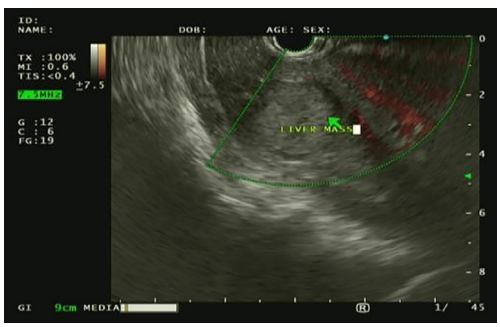

Figure 2 Station 7 as seen on EUS. While station 7 can be accessed by EBUS, it is sometimes easier to sample the lymph nodes through a transesophageal approach using EUS/EUS-B. EUS, endoscopic ultrasound; EBUS, endobronchial ultrasound; EUS-B, endoscopic ultrasound through the esophagus using an ultrasound bronchoscope.

Biopsies near major vessels

Frequently, lymph nodes of interest are located near major vessels. Aspirations of airway adjacent lymph nodes sampled through or behind vessels such as the aorta, pulmonary artery, and portal vein are not associated with an increased rate of adverse events (45). Para-aortic station 5 and 6 lymph nodes can also be biopsied by EUS/EUS-B with or without traversing the aorta (37-39). A meta-analysis of 17 studies looked at the safety of EBUS/EUS/EUS-B needle aspiration of thoracic and abdominal lesions behind major vessels including the aorta, pulmonary artery, and portal vein. The authors found a pooled sampling accuracy for EBUS/EUS-B/EUS of 85% with a bleeding risk of 1.4%, all of which were mild and self-resolved (45). A

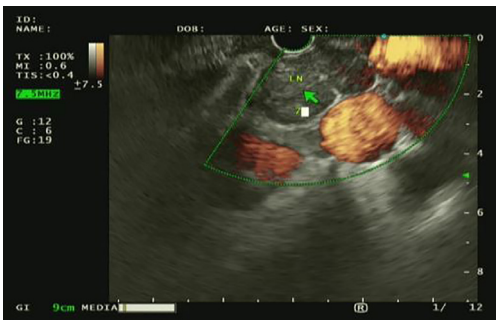

Figure 3 Enlarged, left adrenal gland seen on EUS. EUS, endoscopic ultrasound.

retrospective study evaluated 33 consecutive patients who underwent mediastinal staging through the pulmonary artery or aorta and found an overall yield of 73% with no complications in the immediate post-procedural or 12-month follow-up period (46). In a larger retrospective study of 100 patients, transvascular biopsies were obtained by EUS and EBUS through the aorta and pulmonary artery with a median of 2 passes (47). There were no operative or immediate postoperative complications and only one patient had a delayed complication of aortic pseudoaneurysm which was conservatively managed in the median 12 month follow-up period. The overall sensitivity of the samples from this study was 71.5% with a diagnostic accuracy of 74.5%. Another study by von Bartheld *et al.* reviewed outcomes in biopsies through the aorta in 14 patients and found a sensitivity of 64–75% with specificity of 100% (48). The lower sensitivity may be due to the lower number of passes and targets biopsied (49,50).

Methods for sampling lymph nodes at station 6 without traversing the aorta have also been described (15,23). In a case series of 12 consecutive patients, station 6 was accessed by passing the needle through the proximal esophagus towards the para-aortic area (51). Successful diagnosis by cytology was made without any immediate or 30-day post-procedural morbidity.

Adrenal glands

A unique addition of EUS/EUS-B is biopsy of the adrenal glands, a common and sometimes isolated metastatic site of lung cancer (52-54). Both the left and right adrenal glands when visualized by ultrasound are described as having a characteristic "seagull sign" (55). The techniques to sample the left and right adrenal glands are different. To access the left adrenal gland, the EUS/EUS-B scope is passed through the stomach. The back left side is viewed to locate the left kidney and identify the left adrenal gland by its bird-like appearance. Both EUS and EUS-B can be used to biopsy the left adrenal gland. In contrast, the right adrenal gland is accessible only by EUS using a transduodenal approach. The right kidney is identified and the scope withdrawn anterior to and above the right kidney while slowly scanning for the right adrenal gland. In our practice, the left adrenal gland is easier to identify than the right but both are accessible with user experience. *Figure 3* shows a mass in the left adrenal gland as identified by EUS.

EUS/EUS-B can be used to sample both the adrenal glands and lung lesions in the same session, providing accurate and expedited staging. Our practice has experience in sampling adrenal glands using EUS. In a case series of 13 patients, the presence or absence of metastatic disease was established in all patients with a diagnostic yield of 100% (56). This is consistent with prior reports (57,58). Our institution also looked at 113 patients who underwent adrenal gland sampling with EUS and showed upstaging in 24% of patients to stage 4 due to presence of metastatic disease in the adrenal glands. Diagnosis by combined procedure can precede abnormal diagnostic imaging as 14% of patients in our study had normal or no PET scan uptake in the adrenal glands but found pathology on endosonography with malignancy on biopsy. In another study, EUS identified skip metastases to the adrenal gland that were not detected on CT and PET imaging (44).

Central and parenchymal tumors

EUS/EUS-B can be used to accurately sample central and parenchymal tumors. In a retrospective study of 55 patients, EUS-FNA had both an accuracy and sensitivity of 94.5% without immediate or 30-day morbidity (59). Another retrospective study based in Italy found that parenchymal lesions difficult to access by EBUS were able to be biopsied by EUS-FNA/FNB with an overall diagnostic accuracy of 88.9% (25). Our facility has had success in obtaining transesophageal lung biopsies of central tumors close to the esophagus. In a sample of 20 patients, adequate tissue sample led to definitive diagnosis in 19 patients with a 95% diagnostic yield with no major procedural complications noted in the immediate 30-day period (56). This is similar to the diagnostic yield reported in previous studies at 95–100% (30,31,59,60).

Patient factors

EUS/EUS-B also provides an option for biopsy in patients who are otherwise poor candidates for a standard bronchoscopy (28). Some patients may not be amenable to bronchoscopy secondary to airway stenosis or respiratory failure (17). EUS-B may have an advantage over EUS in these cases. In a series of 10 patients investigated by Khoury *et al.*, awake EUS-B was performed in patients with higher risk of complications from sedation (29). Scenarios included advanced chronic obstructive pulmonary disease (COPD) with severe hypoxemia, uncontrolled congestive heart failure, severe pulmonary hypertension, severe obstructive sleep apnea, mandibular deformity leading to difficult intubation, and refusal of sedation. Through EUS-B, mediastinal lymph nodes in these patients were safely and successfully sampled without complications. Another study found that EUS-B was tolerated better with a shorter procedure time, fewer oxygen desaturations during the procedure, better operator experience, and required fewer sedatives without compromising on diagnostic accuracy (59).

Efficacy of EUS/EUS-B

EUS/EUS-B has been found to be efficacious in detecting and staging NSCLC. In a study evaluating EUS-FNA of cancers in the mediastinum, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were reported at 92%, 100%, 100% and 80% respectively (61). The pooled sensitivities in two meta-analyses of EUS-FNA in nodal staging of NSCLC were 83% and 89% (13,62).

EUS/EUS-B has demonstrated advantages over surgical approaches for biopsy. In a randomized control trial comparing EUS-FNA with surgical mediastinoscopy in 40 patients, there was no difference in the diagnostic results of the two procedures (63). EUS can also access lesions that are inaccessible by a conventional surgical approach. Without EUS, the AP window and para-aortic area would require surgical sampling not by standard mediastinoscopy but through video-assisted thoracoscopic surgery (VATS), Chamberlain procedure (left anterior mediastinoscopy), or extended cervical mediastinoscopy. Thus, EUS offers the additional advantage of being minimally invasive while acquiring biopsies in areas inaccessible by EBUS and standard mediastinoscopy.

Occult metastases in a radiographically normal mediastinum are detected by EUS-FNA with a sensitivity of 58% (62). In a prospective study evaluating patients with a radiographically normal mediastinum, 2 out of 56 patients were identified with N3 disease using EUS-FNA (64). Similarly, another trial identified 5 out of 47 patients as having N2 disease (65). The additional benefits of EUS/EUS-B in detecting occult malignancy are further detailed in the following section.

Combined EBUS/EUS/EUS-B

Combining EBUS with EUS/EUS-B offers advantages when compared to single procedure alone. Multiple studies have shown additive benefits leading to rapid diagnosis of malignancy and improved staging accuracy.

Combined procedure compared to single procedure

Due to the broadened accessibility of lymph nodes, combined EBUS with EUS/EUS-B can completely stage the mediastinum and include sub-diaphragmatic structures often affected by metastatic disease. Multiple studies have shown that the combination of EBUS with EUS/EUS-B has an increased diagnostic accuracy and sensitivity compared to EBUS alone in patients with proven or suspected lung cancer (14,34,66).

Combined EBUS/EUS/EUS-B has a high sensitivity in detecting mediastinal lymph node metastasis. Liberman *et al.* described a combined sensitivity of 91% while another study reports a sensitivity of 93%, similar to that reported elsewhere in medical literature (17,18,41,67). One study found combined procedure increased sensitivity by 21% when compared to EUS alone and 13% when compared to EBUS alone (14). A meta-analysis of 13 studies found that the combined approach had a mean sensitivity of 86% and NPV of 92% (34). Another meta-analysis of 10 studies showed that combined EBUS/EUS had a significantly higher sensitivity in staging lung cancer when compared to EBUS-TBNA alone with the additional benefit of diagnosing mediastinal adenopathy (68). In an analysis of 276 patients, Torii *et al.* found that adding EUS-B-FNA to EBUS-TBNA increased the diagnostic yield from 72.6% to 75.9% (28).

Occult metastases in radiographically normal mediastinum appear to occur more frequently in patients with central, solid, and adenocarcinomatous tumors (69). However, adenocarcinomatous histology was also associated with a higher prevalence of false negative results when examined by endosonography (70). Despite this, combined

EBUS with EUS/EUS-B has a role in detecting occult disease. Our institution evaluated 161 patients with CT and PET scans showing normal lymph nodes in the mediastinum, hilum, lobar, and sublobar regions (44). After endoscopic staging using EBUS and EUS, 13% of patients were found to have nodal disease. Of those with positive nodal disease, 28% of patients had occult N1 disease, 61% had occult N2 disease, and 9% had adrenal involvement. A retrospective study of 279 patients by Kim *et al.* found a 29.7% prevalence of occult metastases with 38.6% of those cases being detected by EBUS with EUS-B (69). Shin *et al.* found a sensitivity of 47% using EBUS with or without EUS-B to detect occult malignancy (70). In a recent study, EUS when performed after EBUS was found to be more useful in upstaging disease from N1 to multilevel N2/N3 disease rather than from N0 to N1/N2 (71). Because combined endoscopy can detect N3 disease that may otherwise be missed on surgical mediastinoscopy, there is an important role for endosonography in staging of occult disease.

Despite being a combination of two procedures, depending on user familiarity and technique, combining EBUS/EUS only slightly increases the procedure time (27,36).

Combined procedure compared to surgical approach

The combined approach has better results compared to surgical mediastinoscopy. A prospective controlled trial comparing combined EBUS/EUS with mediastinoscopy showed sensitivity, negative predictive value, and diagnostic accuracy of 91%, 96%, and 97% respectively in EBUS/EUS as compared to 79%, 90%, and 93% in mediastinoscopy (18). Another prospective trial designed by Liberman *et al.* found that combined EBUS/EUS diagnosed N2/N3/M1 disease in 14% of patients who had negative findings using standard mediastinoscopy (67). These findings are supported by a multicenter randomized study that found the sensitivity of endosonographic staging of N2/N3 disease superior to that of surgical staging (72).

Through the cumulative benefits of a combined procedure, surgery can be avoided. Hwangbo *et al.* showed increased diagnostic accuracy and overall sensitivity when EUS-B-FNA was added to EBUS (36). While EBUS had a sensitivity of 84.4% with diagnostic accuracy of 95.1%, adding EUS-B-FNA increased the overall sensitivity to 91.1% and diagnostic accuracy to 97.2%. By combining the two procedures, mediastinoscopy was avoidable in 41 of 150 patients.

Current guidelines recommend surgical staging if there is a high index of suspicion of metastases despite negative endosonography. However, there is newer data that suggests that endoscopy may replace the need of surgical confirmation. A recently published study by Bousema *et al.* evaluated the outcomes of lung tumor resection following systematic endosonography with or without confirmatory mediastinoscopy (73). While there was an unforeseen N2 rate that was detected by mediastinoscopy, it did not exceed the study's noninferiority boundary, suggesting that confirmatory mediastinoscopy can be omitted in the event of a negative systemic endosonographic evaluation of the patient. In a patient with a radiographically normal mediastinum, when biopsies obtained with combined endoscopic procedure are negative, there is a trend towards omission of surgical exploration of the mediastinum (24,44). Through its wide range of access from mediastinal lymph nodes to subdiaphragmatic structures, EBUS/EUS/EUS-B can potentially replace surgical staging with NSCLC.

Limitations

Despite the wide range of nodes expected to be covered by EUS/EUS-B, not all lesions can be biopsied due to technical reasons. Authors Hwangbo *et al.* found that there was difficulty in accessing station 5, possibly due to the narrow sonographic angle of the linear probe with EUS-B (36). Other limitations to EUS-B when compared to EUS include fixed needle angle, and limited push against the esophageal wall (27,36). Both EUS/EUS-B have limited access to the anterior nodes and structures when compared to standard EBUS.

In patients who have already received chemo-radiotherapy, samples obtained by EUS/EUS-B may not be as reliable. In a study by von Bartheld *et al.*, restaging the mediastinum with EUS-FNA alone after chemo-radiation had a sensitivity of 44% and a false negative rate of 58% (74). Combined EBUS/EUS has a better sensitivity of 76% and specificity of 100% in restaging after neoadjuvant treatment (75,76). However, in a study evaluating combined EUS/EUS-B in restaging the mediastinum, 17% of patients with negative biopsy by endoscopy had metastatic disease when re-examined by transcervical extended mediastinal lymphadenectomy (TEMLA) (76,77). These differences in re-staging by endoscopy may be due to post-inflammatory changes such as adhesions and fibrosis (78). The current ESGE/ERS/ESTS guidelines suggest that restaging

after neoadjuvant chemo-radiation may be performed by either endoscopic method. However, if there is no detection of persistent disease, surgical mediastinal staging may be indicated prior to radical surgery (grade C recommendation) (14).

Physician familiarity and experience with EUS/EUS-B limits extensive use of this procedure. Diagnostic yield is dependent on the operator's level of skill. There is currently no standardized training for pulmonologists interested in using EUS/EUS-B. Ng *et al.* found that with supervision and training, experienced bronchoscopists can perform EBUS/EUS-B with relative ease (79). After 3 consecutive cases with an Endoscopic Ultrasound Assessment Tool (EUSAT) score of 50 or higher, the provider was determined competent in performing EUS-B-FNA as part of their usual practice without added supervision. American Thoracic Society (ATS), ERS, and ACCP recommend 40 procedures for initial competency and afterwards, 20 procedures to maintain competency. Though gastrointestinal guidelines require 150 EUS-FNA of the pancreas before achieving competency, this number may be lower in EUS-B-FNA due to easier maneuverability of the bronchoscope as well as easier accessibility of the mediastinal lymph nodes (67,79-82).

Conclusions

The development of endosonographic techniques including EBUS and EUS/EUS-B have led to the replacement of mediastinoscopy as the initial test in staging of NSCLC. Though each procedure has proven useful in identifying malignancy, they have limitations in target accessibility. Combining EBUS and EUS/EUS-B provides thorough coverage of the mediastinum and even includes structures inferior to the diaphragm. There is an additive value and the resulting sensitivity and negative predictive value are higher than that of a single procedure. EUS has played a large role in decreasing the need for surgical interventions for diagnostic sampling. The selection of EUS or EUS-B in conjunction with EBUS would depend on the user's familiarity and comfort level with the techniques. For the average bronchoscopist, the EUS-B offers the advantage of shorter endoscope length as it is the same device used for EBUS. However, in the hands of an experienced provider, EUS can provide better visualization of the lesion due to differences in probe ultrasound and access to more distal structures such as the right adrenal gland and right lobe of the liver. Regardless of which procedure is added to EBUS, these combined techniques have repeatedly shown a benefit in complete staging, time to diagnosis, patient comfort, and overall cost.

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