Endobronchial Ultrasound–guided Transbronchial Needle Aspiration for Non–Small Cell Lung Cancer Staging

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Abstract

Real-time endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) is an established technique for invasive mediastinal staging of non–small cell lung cancer (NSCLC). Needle-based techniques are now recommended as a first-line diagnostic modality for mediastinal staging. Accurate performance of systematic staging with EBUS-TBNA requires a detailed knowledge of mediastinal anatomy. This examination begins at the N3 lymph nodes, progressing through the N2 and N1 lymph node stations, unless a higher station lymph node is positive for malignant cells by rapid on-site cytologic examination. Objective methods of identifying EBUS-TBNA targets include sampling any lymph node station with a visible lymph node or with a lymph node greater than 5 mm in short axis. Three passes per station or the use of rapid on-site cytologic examination with identification of diagnostic material (tumor or lymphocytes) up to five passes are well-established techniques. Obtaining sufficient tissue for molecular profiling may require performing more than three passes. The operating characteristics of EBUS-TBNA are similar to mediastinoscopy. However, mediastinoscopy should be considered in the setting of a negative EBUS-TBNA and a high posterior probability of N2 or N3 involvement.

Keywords: endobronchial ultrasound–guided transbronchial needle aspiration; non–small cell lung cancer; staging

The practice of real-time endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA, also referred to as curvilinear probe EBUS-TBNA or linear EBUS-TBNA) has increased dramatically over the last decade. More than 85% of pulmonary and critical care programs participating via survey now have EBUS-TBNA equipment (1). With increasing prevalence of EBUS-TBNA systems, applications of the technology have increased.

The American Thoracic Society, European Respiratory Society, European Society of Medical Oncology, and American College of Chest Physicians (ACCP) have all issued specific recommendations for invasive sampling of mediastinal lymph nodes for non–small cell lung cancer (NSCLC) staging (2–4). Recently, the third edition of the ACCP Guidelines for Lung Cancer recommended needle-based methods as first-line approaches for invasive mediastinal staging of NSCLC (5). The goal of this review is to outline the approach and techniques necessary to effectively use EBUS-TBNA to perform invasive mediastinal staging for NSCLC.

Advancing NSCLC stage is invariably associated with dramatic decreases in survival (6). Accurate staging of NSCLC is paramount to ensure that patients receive appropriate treatment. The aggregate sensitivity of integrated positron emission tomography–computed tomography (PET-CT) for detection of mediastinal spread of NSCLC is only 62% (7). Similarly, positive PET-CT findings must be verified to ensure that a false-positive result does not preclude potentially curative therapy. Despite these considerations and recommendations to perform invasive mediastinal staging, mediastinoscopy has traditionally been underused (8). The widespread availability of EBUS-TBNA may allow for more patients to undergo indicated invasive mediastinal staging.

A large systematic review including more than 1,500 patients identified no serious complications of EBUS-TBNA and only agitation, cough, and blood at the puncture site as minor complications (9). Prospective databases report rates of complication of EBUS-TBNA of approximately 1%, although complications including mediastinitis, pericarditis, and death have been reported (10, 11). Given the safety record of EBUS-TBNA, incorrect pathologic staging may be the greatest risk of the procedure. Thus, an understanding

(Received in original form November 14, 2013; accepted in final form January 19, 2014)

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CME will be available for this article at www.atsjournals.org

Am J Respir Crit Care Med Vol 189, Iss 6, pp 640–649, Mar 15, 2014

Originally Published in Press as DOI: 10.1164/rccm.201311-2007CI on January 31, 2014
Internet address: www.atsjournals.org

of the appropriate anatomic landmarks and lymph node stations is paramount. This requires strict adherence to the changes outlined in the International Association for the Study of Lung Cancer 7th edition lymph node map and subsequently published by the Union for International Cancer Control (12, 13). For instance, a station 10R lymph node located on the medial aspect of the airway in the Mountain-Dresler system is considered a station 7 lymph node under the seventh edition of TNM. This is the difference between N1 and N2 disease and could possibly determine surgical candidacy, depending on local practice.

Detterbeck and coworkers have classified the thoroughness of mediastinal staging for needle-based techniques (14). Level A staging (complete sampling) is defined as sampling of each visible lymph node in each station (1, 2R, 2L, 3, 4R, 4L, and 7) using at least three passes per node or rapid on-site cytologic examination (ROSE). If using ROSE, either malignant cells or lymphatic tissue must be documented. To our knowledge, no study has evaluated the yield of complete mediastinal staging aspirating all EBUS-TBNA–accessible stations (including 3p). Station 3A cannot be reached via EBUS-TBNA due to the interposition of large mediastinal vessels on either side (15). Level B staging (systematic assessment) requires sampling nodes in each station using at least three passes per node or ROSE at stations 2R, 2L, 4R, 4L, and 7. It should be noted that both complete (Level A) and systematic (Level B) staging require sampling stations 5 and 6 if a left upper lobe tumor is present. These stations are largely inaccessible to EBUS-TBNA. The noted exception is aspiration of station 5 through the pulmonary artery, which has only been performed in extenuating circumstances (16). Endoscopic ultrasound-guided fine-needle aspiration has been used to inconsistently aspirate station 5 (17, 18). Others have questioned whether the sampled lymph nodes in these series are actually lateral to the ligamentum arteriosum (19). Invasive staging of stations 5 and 6 may require transthoracic needle aspiration or a surgical approach. Level C staging (selective assessment) is defined by aspiration of at least one abnormal lymph node ($\geq$1 cm by CT or ultrasound) or fewer than three passes and no ROSE. Studies performed to date have focused on systematic (Level B) or selective (Level C) staging. Further investigations may determine if complete (Level A) sampling of all accessible lymph nodes in all accessible stations (including 1 and 3p) is superior to systematic (Level B) or selective (Level C) staging.

Systematic surgical mediastinal staging has a superior accuracy when compared with selective approaches, although the effect on overall survival is less clear (20, 21). Systematic and selective mediastinal staging with EBUS-TBNA have not been directly compared. Considering the limited sensitivity of CT and PET-CT and the data from surgical approaches, systematic sampling of mediastinal lymph nodes via EBUS-TBNA may be superior to selective sampling. In certain circumstances, selective staging of the mediastinum may be appropriate. Aspiration of an enlarged N3 lymph node with ROSE confirmation of malignant cells may obviate the need for further nodal sampling. A procedure performed only to obtain tissue for diagnosis and/or molecular profiling in the setting of known M1 disease would not require a systematic staging examination. On the contrary, the presence of a large central tumor with no enlarged lymph nodes on CT scan is still associated with a significant risk of N2 or N3 involvement, and systematic staging would be indicated. An approach to estimating the pretest probability of mediastinal lymph node involvement based on the radiographic presentation has been well described (7, 20). In this review, we focus on systematic approaches to invasive mediastinal staging.

The Staging Examination

The technique of EBUS-TBNA has been described previously (22, 23). Briefly, the lymph node to be aspirated is visualized under ultrasound, generally using a 7.5 MHz transducer. A saline-filled balloon may be used to enhance the ultrasound image, although some practitioners do not find this helpful. Images may be frozen and measurement of a lymph node performed. Verification of the presence of vasculature within the ultrasound field may be confirmed using Doppler mode. The sheath is advanced under visualization. The needle may then be safely inserted into the lymph node (accounting for the 20-degree angle between the needle and transducer, Figure 1). The stylet is used to remove bronchial epithelial cells. Suction may be applied (although there is no evidence to support this practice) (24) and the needle oscillated within the lymph node (Figure 2). Aspirated material is then smeared onto glass slides for fixation and evaluation. Additionally, material for creation of cell block, microbiologic evaluation, and flow cytometry may be collected and may be helpful when evaluating for alternative or concurrent diagnoses. Details regarding pathologic handling and processing have been published previously (25, 26).

EBUS-TBNA is commonly used for both diagnosis and staging during the same procedure. A well–thought-out plan for the procedure is crucial to accomplishing both goals. The general approach to the staging examination is to sample the highest station lymph nodes first. This requires first evaluating the N3 level nodal stations, followed by those of the N2 level, and finally the N1 level (as demonstrated in Figure 3). Each nodal station should be considered for possible needle aspiration, regardless of PET avidity. Herth and colleagues evaluated the yield of EBUS-TBNA for mediastinal staging of NSCLC in patients with no lymph nodes greater than 1 cm in short axis on CT and without evidence of abnormal tracer uptake on PET imaging (27). Sampling all lymph nodes greater than 5 mm in short axis identified previously unsuspected malignancy in 9 of 97 patients (27). Similarly, Yasufuku and colleagues identified pathologic N2 disease in 4 of 102 patients with negative CT and PET scans (28). These findings are consistent with the reported sensitivity of PET and PET-CT (7) and the well-described occurrence of "skip" metastases in NSCLC (29, 30).

A single EBUS-TBNA needle may be used to perform the staging procedure if the N3 nodes are sampled first, followed by the N2 lymph node stations and the N1 lymph node stations (31). Alternatively, a different needle may be used for each station, although this approach increases the cost of the procedure (28). If a single needle is used, it is paramount that the needle not be contaminated with tumor from a prior aspiration of a lower N stage lymph node station. For example, if an ipsilateral 11R lymph node (N1) involved by tumor is sampled before a station 7 lymph node (N2) that is not involved, the sample from the N2 station may include

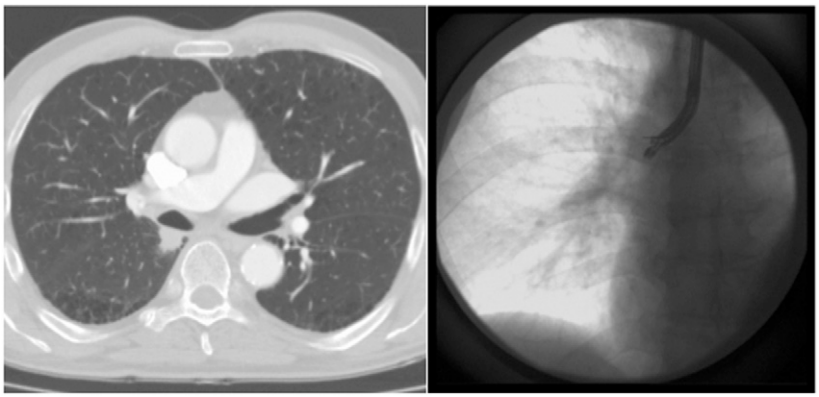

Figure 1. Axial computed tomography (CT) image from a 69-year-old man incidentally found to have a lesion of the superior segment of the right lower lobe. This lesion was accessible via the right main stem bronchus with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). There were no enlarged (>1 cm in short axis) mediastinal or hilar lymph nodes on CT. Fluoroscopy was used in this case to verify the location of the mass, but it is generally not needed for diagnosis or staging. An image has been included to highlight the 20-degree angle of the needle to the transducer. A separate 21-gauge EBUS-TBNA needle was used to perform the staging examination.

tumor cells. This error would result in artificially upstaging the disease. Similar considerations exist when attempting to establish a diagnosis and perform invasive mediastinal staging in the same examination. In the example shown in Figure 1, one needle was first used to access the lesion for diagnosis and a different needle used to complete mediastinal staging, beginning at the N3 stations.

Given that a larger number of stations need to be sampled during systematic EBUS-TBNA staging, debate has arisen as to whether this procedure is best performed under moderate or deep sedation. In one of the largest initial studies of EBUS-TBNA for NSCLC staging (502 patients), there was no difference in yield based on the use of moderate sedation or general anesthesia, although patients were selected by the need for additional procedures (e.g., rigid bronchoscopy or ablative techniques) (32). No study has randomized patients to moderate or deep sedation. Yield was compared between two different institutions using different methods of sedation in unselected patients undergoing EBUS-TBNA (less than half had NSCLC).

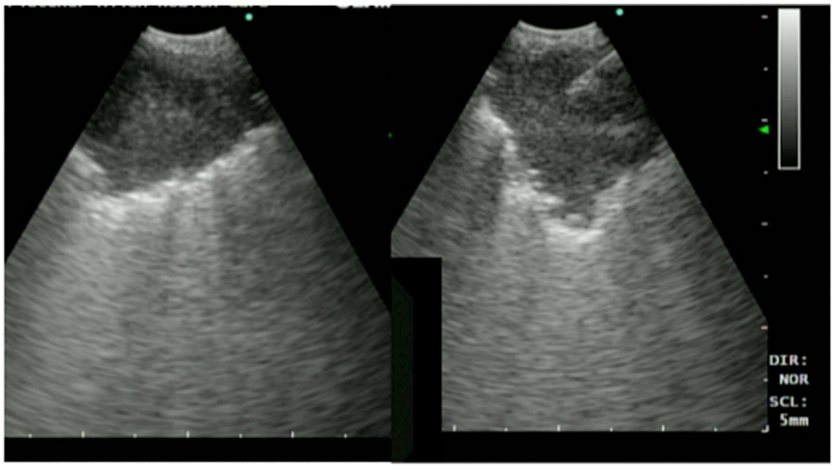

Figure 2. Endobronchial ultrasound views of the mass lesion depicted in Figure 1. The second image demonstrates the endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) needle within the lesion. EBUS-TBNA was used first to diagnose the lesion and then to complete the staging examination.

A higher yield was reported for procedures performed under deep sedation, although there are multiple possible confounders of these data (33). Systematic EBUS-TBNA staging of the mediastinum under moderate sedation is well described (Table 1) (28, 34–42). Patient satisfaction after EBUS-TBNA performed under moderate sedation appears to be quite high (43). Further studies are needed to clarify if yield differs between procedures performed under moderate or deep sedation. Yield is likely dependent on a number of factors, including the skill and speed of the operator, availability and efficiency of ROSE (if used), and familiarity and capabilities of the assisting staff. The need to perform additional procedures, such as navigational bronchoscopy or endobronchial debridement, may also dictate sedation choice.

Evaluation and Sampling of Lymph Nodes

Increasing lymph node size on CT scan has long been considered a risk factor for malignant involvement. Most studies evaluating the usefulness of CT scanning for mediastinal staging have used a cutoff of 1 cm in short axis to define an abnormal lymph node. The short axis is identified by locating the largest diameter of the lymph node and then measuring the longest perpendicular diameter to that line. Using this cutoff, the operating characteristics of the test result in an aggregate median sensitivity and specificity of 55 and 81%, respectively (7).

EBUS-TBNA allows sampling of lymph nodes much smaller than 1 cm in short axis. Objective criteria for identifying stations to be aspirated include obtaining needle aspirates from all accessible lymph nodes or from lymph nodes greater than 5 mm in short axis (Table 1). The average size of lymph nodes sampled in the two studies specifically evaluating the CT- and PET-negative mediastinum were 7.9 mm and 6.9 mm (27, 44), highlighting that lymph nodes less than 1 cm in short axis may be consistently aspirated.

Several studies have retrospectively examined the ultrasound characteristics of lymph nodes (37, 45). In the largest of these, Fujiwara and colleagues reported a high negative predictive value for metastases if the following signs were not present: round shape, distinct margin,

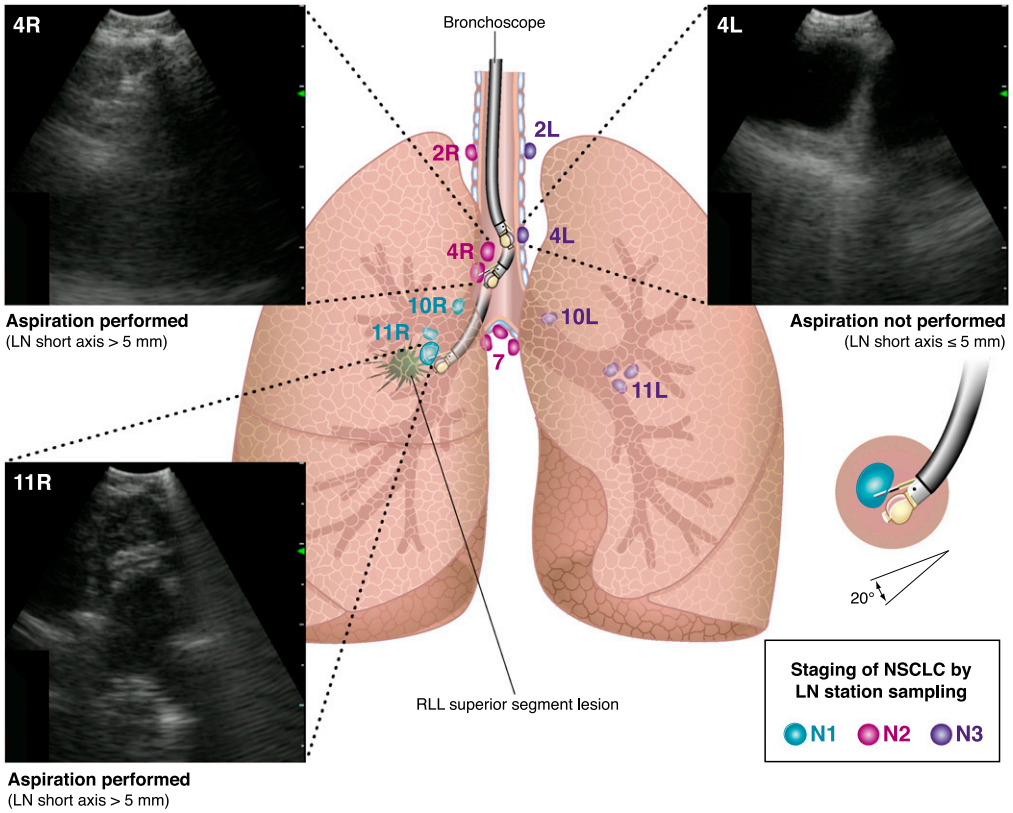

Figure 3. Depiction of the staging examination. The endobronchial ultrasound is first used to evaluate all N3 lymph node stations, followed by the N2 lymph node stations and the N1 lymph node stations. Representative ultrasound images are shown from three stations. At station 4R, both lymph nodes were aspirated. For clarity, the primary lesion of the right lower lobe is depicted inferior to the actual location. LN = lymph node; NSCLC = non–small cell lung cancer.

heterogeneous echogenicity, and the coagulation necrosis sign (45). Increasing size and round or oval shape were confirmed as risk factors for malignancy in a separate investigation (37). Vascular patterns have also been evaluated retrospectively as markers of malignancy. Increasing vascularity in specific patterns (beyond a few main vessels running toward the center of the lymph node) may be useful in identifying malignant lymph nodes (46). The absence of a central nodal vessel on ultrasound may also be predictive of malignant involvement (47). Larger prospective studies are needed to validate these findings. The importance of correct staging of NSCLC and the safety of EBUS-TBNA currently dictate that the prudent practitioner perform aspirates at least from all stations with lymph nodes greater than or equal to 5 mm in short axis when performing a systematic evaluation. Different size criteria for determining EBUS-TBNA targets (e.g., lymph nodes $\geqslant$ 7 mm) have not been systematically evaluated. Morphologic features on ultrasound may be helpful in deciding which lymph nodes in a given station to aspirate, if performing Level B thoroughness of staging (44).

The number of passes to perform when aspirating a lymph node station is an area of considerable interest. Evidence suggests that diagnostic yield for detection of malignant cells does not increase above three passes (48). If ROSE is used, a well-validated approach would be to perform repeat aspirations until adequate cell material (e.g., sufficient for a specific diagnosis or lymphocytes) is obtained or five passes are completed (35, 44).

As in the case illustrated in Figure 1, EBUS-TBNA is commonly used as both a diagnostic and staging modality. Thus, adequate diagnosis and staging of NSCLC requires obtaining sufficient material not merely for identification of malignant cells but also for subtyping and molecular testing. EBUS-TBNA has been shown to be effective in identifying mutations associated with NSCLC, including those in the Kirsten rat sarcoma (KRAS), epidermal growth factor receptor (EGFR), and echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase (EML4-ALK) fusion genes (49–52). In a single-center study, Folch and coworkers demonstrated that EBUS-TBNA yield for molecular profiling of KRAS, EGFR, and EML4-ALK was not inferior to mediastinoscopy or bronchoscopic forceps biopsy but was superior to transthoracic needle sampling (53). A recent prospective multicenter analysis of EBUS-TBNA samples from 774 patients with NSCLC reported that polymerase chain reaction–based EGFR analysis could be performed in 90% of specimens when indicated (54). However, there was no standardized approach to the procedure.

EBUS-TBNA yield for molecular testing (in this case, initial testing for KRAS followed by EGFR and EML4-ALK testing if negative) was evaluated when a median of four passes was performed (range, 3–5).

Table 1: Real-Time Endobronchial Ultrasound-guided Transbronchial Needle Aspiration for Systematic Mediastinal Staging of Non–Small Cell Lung Cancer

First Author	Year	N	cStage	Sedation	Site Selection	Sites Sampled	Technique	ROSE	Complications	Sensitivity (%)
Yasufuku (35)	2005	105	cN1-3	Moderate	>5 mm SA	1.6	Up to 5 passes	Yes	None	95*,†,‡,§
Szlubowski (41)	2009	226	cN0-3	Moderate	>5 mm SA	1.4	3-5 Passes	No	None	89*,‖
Lee (84)	2012	73	cN0-3	GA	All accessible	2.6¶	Minimum 1 pass	No	Atrial fibrillation	95†,‡,§
Bauwens (42)	2008	106	cN1-3	Moderate	All accessible	1.8	NR	No	Pneumothorax	95†,‡,§
Memoli (37)	2011	100	cN1-3	Moderate	All visible	2.3	Up to 3 passes	Yes	None	87†,‡
Yasufuku (44)	2011	153	cN0-3	GA	>5 mm SA	2.8	Up to 5 passes	Yes	None	81‡,§
Wallace (63)	2008	138	cN2-3	Moderate	Visible LNs	1.4	Minimum 3 passes	No	None	69*,†,‡,§
Yasufuku (28)	2006	102	cN0-3	Moderate	>5 mm SA	2.0	Up to 5 passes	Yes	None	92*,†,‡
Herth (32)	2006	100	cN0	Moderate	>5 mm SA	1.2	4 Passes**	No	None	92‡,§
Nakajima (40)	2010	49	cN1-3	Moderate	>5 mm SA	2.6	Up to 5 passes**	Yes	None	94†,††
Herth (27)	2008	97	cN0	GA	>5 mm SA	1.6	2 Passes	No	None	89‡,§

Definition of abbreviations: cStage = clinical stage before procedure; EBUS-TBNA endobronchial ultrasound–guided transbronchial needle aspiration; GA = general anesthesia (not differentiated from deep sedation); LN = lymph node; NR = not reported; SA = short axis.
Sensitivity presented is per patient.
*Sensitivity includes metastases to sites not accessible by EBUS-TBNA.
†If EBUS-TBNA negative, sensitivity is compared to clinical follow up ⩾ 6 months.
‡If EBUS-TBNA negative, sensitivity is compared to LN dissection at resection.
§If EBUS-TBNA negative, sensitivity is compared to mediastinoscopy.
‖If EBUS-TBNA negative, sensitivity is compared to transcervical extended mediastinal lymphadenectomy.
¶Sites sampled during staging of possible surgical disease.
**Personal communication with corresponding author.
††If EBUS-TBNA negative, sensitivity is compared to restaging EBUS-TBNA.

In 81 of 85 cases, sufficient material was available to complete the required molecular testing. ROSE was used to guide sampling. These authors conclude that four passes is likely the minimum number required to complete molecular testing using the described algorithm (55). EBUS-TBNA has been used to obtain tissue for simultaneous multiplexed genetic testing from more than 15 different genes (56). Tissue requirements for this type of extensive molecular testing remain unknown.

Both 21-gauge and 22-gauge needles are available for EBUS-TBNA. A multicenter retrospective comparison of yield by needle size did not report significant differences, although use of the 21-gauge needle was associated with fewer passes when ROSE was used (57). In a well-designed prospective analysis, the two different needles were each used to sample the same lymph nodes from 33 patients (58). There were no differences in diagnostic yield; however, the 21-gauge needle resulted in better preservation of histologic structure.

Acquiring adequate tissue for subtyping and molecular profiling requires ongoing communication between those performing bronchoscopy and cytopathologists or technicians preparing and interpreting the specimens. Specimen handling and the types of tests performed vary and can affect tissue use. Please refer to the excellent review of Bulman and colleagues regarding these aspects (26). Indeed, interpretation of EBUS-TBNA results can vary greatly with pathologist experience (59). In the absence of more robust data, we concur with the recommendation of Bulman and colleagues (26) that ROSE may be useful to assist in assessing diagnostic quality and tissue quantity during EBUS-TBNA performed for diagnosis and staging.

Yield for Systematic Staging

Based on aggregate evidence profiles, the overall diagnostic yield of EBUS-TBNA appears to be similar to that of mediastinoscopy (7). There are conflicting data regarding yield at specific stations between the two modalities (19, 60), but prospective trials evaluating all stations from the same group of patients have documented good agreement (44).

Not all studies have used a systematic (Level B) approach to staging. An aggregate evidence profile limited to studies that performed systematic sampling and included objective criteria for determining EBUS-TBNA targets is presented in Table 1. Although negative predictive value is the most clinically relevant measure when discussing EBUS-TBNA, sensitivity is preferred when directly comparing test performance. Systematic mediastinal staging using EBUS-TBNA resulted in a median per-patient sensitivity of 92% (Table 1). Parenthetically, this value is similar to the overall sensitivity of 89% reported in the complete ACCP evidence profile (7). Multiple studies have documented a higher sensitivity per lymph node station (compared with per patient) due to exclusion of lymph node stations not accessible by EBUS-TBNA in the per lymph node analysis (37, 44). This sensitivity may be as high as 98% and is useful when considering the performance of the test at a single accessible lymph node station.

Level B (systematic) thoroughness requires sampling lymph nodes that are less than 1 cm in short axis. Importantly, there does not seem to be a dramatic fall in aggregate sensitivity when aspirating small lymph nodes. Individual reports have documented stable sensitivity for detection of malignancy down to lymph node sizes of 5 mm (28). There were only two reported procedure-related complications from the studies included in Table 1, resulting in an

overall complication rate of 0.14%. In the hands of experienced practitioners, systematic and thorough EBUS-TBNA lymph node sampling does not appear to result in decreased sensitivity or an increase in the risk of complications.

Combined EBUS-TBNA and Endoscopic Ultrasound Needle Aspiration

Combining endoscopic ultrasound needle aspiration (EUS-NA) and EBUS-TBNA results in a similar aggregate sensitivity to that of EBUS-TBNA alone (7). The sensitivity of combined staging is generally higher than either technique alone within single trials, although these differences have not been statistically significant (18, 61–65). However, the number of passes performed is not consistently reported, and only two studies either completed three needle passes per station or used ROSE (62). The small increase in sensitivity within these trials has not resulted from identification of malignant disease from stations 8 and 9 (not accessible by EBUS-TBNA) but from sampling of stations accessible by both techniques. Further studies will be required to understand if there is a statistically significant advantage to accessing mediastinal lymph node stations via different anatomic approaches or if the use of ROSE and/or strict sampling techniques (e.g., number of passes) with EBUS-TBNA alone is sufficient. EUS-NA may be performed using the standard EBUS bronchoscope, with the caveat that the left adrenal gland and the left hepatic lobe cannot be examined. There does not appear to be a difference in yield if the EBUS bronchoscope is used for both the endobronchial and esophageal examinations (66).

Role of Mediastinoscopy

EBUS-TBNA and mediastinoscopy are complementary diagnostic modalities. The best strategy to incorporate these two techniques for optimal patient care is undefined. The ASTER study (Assessment of Surgical Staging vs Endosonographic Ultrasound in Lung Cancer: A Randomized Clinical Trial) randomized 241 patients from multiple centers to either mediastinoscopy or combined EUS-NA and EBUS-TBNA followed by mediastinoscopy. Initial mediastinal staging with combined endosonography, followed by mediastinoscopy if endosonography was negative, resulted in a greater sensitivity for detection of metastases and a significant reduction in unnecessary thoracotomies (17). Based on this trial, a cost-effectiveness analysis including three European countries concluded that the initial needle-based approach to staging would result in lower costs and greater quality-adjusted life years compared with surgical staging (67). Extrapolating these data, an argument could be made to perform mediastinoscopy in all patients undergoing mediastinal staging with a negative EBUS-TBNA examination. However, this approach may be unnecessary and has the potential to lead to increased costs, patient discomfort, and complications.

More recently, Yasufuku and colleagues performed systematic NSCLC staging with EBUS-TBNA and mediastinoscopy in a cohort of 153 patients with confirmed or suspected NSCLC being considered for surgical resection. The sensitivity of EBUS-TBNA and mediastinoscopy were 81 and 79%, respectively (44). The six patients who were understaged by EBUS-TBNA included two in whom station 2R was not sampled. Four patients with micrometastases were not detected, highlighting the problem of heterogeneous malignant involvement of the lymph node. Three patients had metastases noted in station 5 or 6, which could not be sampled by either technique, implying a greater sensitivity for these techniques when considered by station. There were no complications of EBUS-TBNA. Mediastinoscopy was associated with a 2.6% rate of minor complications such as hematoma and wound infection. Despite similar operating characteristics in this trial, the limitations of EBUS-TBNA and mediastinoscopy differ.

False-negative EBUS-TBNA samples (e.g., lymphoid tissue is obtained by EBUS-TBNA but the lymph node actually contains malignancy) may be due to factors such as operator experience, difficulty accessing specific locations, tissue handling, and cytopathologist experience. There is also evidence that false-negative EBUS-TBNA staging may be at least partially accounted for by heterogeneous involvement of the lymph node (28). In contrast, discovery of N2 disease after negative mediastinoscopy is commonly secondary to areas inaccessible during the procedure, such as the posterior subcarinal region (station 7) (68). Understanding of the limitations of each procedure can assist in guiding procedural selection and interpretation of results during lung cancer staging.

Consensus guidelines recommend needle-based techniques as the initial invasive staging modality, with the following proviso: "in cases where the clinical suspicion of mediastinal node involvement remains high after a negative result using a needle technique, surgical staging (mediastinoscopy, VATS [video-assisted thorascopic surgery], etc.) should be considered" (7). Factors associated with a higher risk of mediastinal lymph node involvement include tumor characteristics (larger size, central location), N1 lymph node enlargement, mediastinal lymph node size (7), and endobronchial ultrasound characteristics (37, 45, 47). Although endobronchial ultrasound characteristics are not well validated as selection criteria of EBUS-TBNA targets, knowledge of the several carefully performed studies evaluating the risk of malignancy in mediastinal lymph nodes may prove useful. Larger, round or oval lymph nodes on ultrasound have been identified as higher risk for malignancy by multiple studies. Other factors, such as upper lobe tumor location and PET avidity, may be helpful (69, 70).

Use of an evidence-based approach to address serial testing is important. This approach is guided by the posterior probability of metastatic disease. For example, a patient with a large central tumor and a mediastinal station that is both enlarged on CT and PET positive, but has a negative EBUS needle aspiration of that station, still has a high posterior probability of disease. Based on further evaluation and extrapolation of the data from the ASTER trial, the posttest probability of mediastinal disease in patients with a radiographically abnormal mediastinum by CT or PET and negative endosonography was 20% (71). Addition of mediastinoscopy would decrease the posttest probability to 5%. However, if the mediastinal lymph nodes were not enlarged, fluorodeoxyglucose negative, and without endosonographic evidence of malignancy, a subsequent mediastinoscopy would not alter the posttest probability of disease (9% in this

case). It should be noted that this specific approach is based on calculations from a single trial and has not been rigorously studied in a prospective manner.

Minimizing the number of procedures a patient is exposed to is also important. EBUS-TBNA should be the first invasive test in patients with a peripheral lesion and enlarged or fluorodeoxyglucose-avid mediastinal lymph nodes being considered for curative intent therapies, allowing diagnosis and staging in the same examination. One approach to minimizing unnecessary procedures in this setting is initial EBUS-TBNA for diagnosis and staging, followed by navigational or radial EBUS-guided biopsy of the peripheral lesion if EBUS-TBNA is negative. All of these considerations must be viewed with regard to available expertise in these procedures and, ultimately, patient preference.

Training and Competency

The most recent European Respiratory Society/American Thoracic Society statement on interventional pulmonology was published in 2002 and recommends completion of 40 supervised procedures for achievement of initial competency in EBUS (72). Similarly, guidelines from the ACCP on interventional pulmonology recommend completion of 50 supervised procedures for initial competency (73). These recommendations refer to the ability of operators to interpret radial ultrasound images and do not reflect a minimum competency standard for the use of real-time EBUS-TBNA, which was introduced into the market after their publication (22). To our knowledge, there are no specific initial competency recommendations specifically for real-time EBUS-TBNA.

The number of procedures required to competently perform EBUS-TBNA is unknown. Rates of sample adequacy similar to that reported in the literature have been reported from institutions adopting the procedure. The number of procedures needed to reach this level of proficiency ranged from at least 10 to greater than 50 procedures (74–76). However, operator skills may increase up to 120 procedures, and there is evidence that operators acquire competency at different rates (77, 78). Using EBUS-TBNA for systematic mediastinal staging usually requires successful aspiration of a larger number of lymph nodes of smaller size. A more developed cognitive and technical skill set is likely required to accurately perform systematic mediastinal staging with EBUS-TBNA. Based on these considerations, it has been argued that 50 supervised procedures should be performed before independently performing EBUS-TBNA for mediastinal staging, although opinions vary (79, 80).

EBUS-TBNA skills are increasingly acquired during fellowship training (1). This has led to the development of combined cognitive and skills assessments (81, 82). These tools may assist in the development and measurement of the detailed anatomic knowledge and procedural skills required to complete EBUS-TBNA mediastinal staging. Certainly in the absence of clear guidelines, practitioners must carefully monitor their own yield and that of the institution within which they practice. Factors such as sample handling and cytopathologic interpretation may dramatically affect yield (59, 83). A low threshold for considering confirmatory mediastinoscopy must be maintained when practitioners begin applying EBUS-TBNA for mediastinal staging.

Conclusions

EBUS-TBNA has evolved to become a recommended technique for mediastinal staging of NSCLC. A considered approach to the procedure includes planning for both diagnosis and staging. The staging portion of the examination requires beginning with a new EBUS-TBNA needle and proceeding from the higher lymph node stations to the lower (e.g., N3 followed by N2) or changing needles at each station. Systematic staging requires prespecified objective criteria for identifying EBUS-TBNA targets to be aspirated. A low threshold for considering confirmatory mediastinoscopy should be maintained. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Drs. Gerard Silvestri and Frank C. Detterbeck for their input and comments during development of the manuscript.

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