CHEST

Technical Aspects of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

CHEST Guideline and Expert Panel Report

Momen M. Wahidi, MD, MBA, FCCP; Felix Herth, MD, FCCP; Kazuhiro Yasufuku, MD, PhD, FCCP; Ray Wesley Shepherd, MD, FCCP; Lonny Yarmus, DO, FCCP; Mohit Chawla, MD, FCCP; Carla Lamb, MD, FCCP; Kenneth R. Casey, MD, MPH, FCCP; Sheena Patel, MPH; Gerard A. Silvestri, MD, MS, FCCP; and David J. Feller-Kopman, MD, FCCP

BACKGROUND: Endobronchial ultrasound (EBUS) was introduced in the last decade, enabling real-time guidance of transbronchial needle aspiration (TBNA) of mediastinal and hilar structures and parabronchial lung masses. The many publications produced about EBUS-TBNA have led to a better understanding of the performance characteristics of this procedure. The goal of this document was to examine the current literature on the technical aspects of EBUS-TBNA as they relate to patient, technology, and proceduralist factors to provide evidence-based and expert guidance to clinicians.

METHODS: Rigorous methodology has been applied to provide a trustworthy evidence-based guideline and expert panel report. A group of approved panelists developed key clinical questions by using the PICO (population, intervention, comparator, and outcome) format that addressed specific topics on the technical aspects of EBUS-TBNA. MEDLINE (via PubMed) and the Cochrane Library were systematically searched for relevant literature, which was supplemented by manual searches. References were screened for inclusion, and well-recognized document evaluation tools were used to assess the quality of included studies, to extract meaningful data, and to grade the level of evidence to support each recommendation or suggestion.

RESULTS: Our systematic review and critical analysis of the literature on 15 PICO questions related to the technical aspects of EBUS-TBNA resulted in 12 statements: 7 evidence-based graded recommendations and 5 ungraded consensus-based statements. Three questions did not have sufficient evidence to generate a statement.

CONCLUSIONS: Evidence on the technical aspects of EBUS-TBNA varies in strength but is satisfactory in certain areas to guide clinicians on the best conditions to perform EBUS-guided tissue sampling. Additional research is needed to enhance our knowledge regarding the optimal performance of this effective procedure. CHEST 2016; 149(3):816-835

KEY WORDS: endobronchial ultrasound; evidence-based medicine; guidelines; transbronchial needle aspiration

ABBREVIATIONS: AQuIRE = Quality Improvement Registry, Evaluation and Education; CHEST = American College of Chest Physicians; EBB = endobronchial biopsy; EBUS = endobronchial ultrasound; EBUS-STAT = Endobronchial Ultrasound Skills and Tasks Assessment Tool; GOC = Guidelines Oversight Committee; PICO = population, intervention, comparator, and outcome; ROSE = rapid on-site evaluation; TBLB = transbronchial lung biopsy; TBNA = transbronchial needle aspiration; TBNCS = transbronchial needle capillary samplings

Summary of Recommendations

1. In patients undergoing EBUS-TBNA, we suggest that either moderate or deep sedation is an acceptable approach (Grade 2C).

2. In patients undergoing EBUS-TBNA, we suggest that ultrasonographic features can be used to predict malignant and benign diagnoses, but tissue samples should still be obtained to confirm a diagnosis (Ungraded Consensus-Based Statement).

3. In patients undergoing EBUS-TBNA, we suggest that tissue sampling may be performed either with or without suction (Ungraded Consensus-Based Statement).

4. In patients undergoing EBUS-TBNA, we recommend that the use of either a 21- or 22-gauge needle is an acceptable option (Grade 1C).

5. In the absence of rapid on-site evaluation (ROSE) in patients suspected of having lung cancer and undergoing EBUS-TBNA for diagnosis, we suggest that a minimum of 3 separate needle passes be performed per sampling site (Ungraded Consensus-Based Statement).

6. In patients undergoing EBUS-TBNA for diagnostic evaluation, we recommend that tissue sampling can be performed with or without rapid on-site evaluation (Grade 1C).

7. In patients undergoing EBUS-TBNA for the diagnosis and/or staging of suspected or known non-small cell lung cancer, we recommend that additional samples, beyond those needed to establish the diagnosis, be obtained for molecular analysis (Grade 1C).

8. In training EBUS-TBNA operators, we suggest that low- or high-fidelity simulation be incorporated in training (Grade 2C).

9. In evaluating EBUS-TBNA operators, we suggest that validated EBUS skills assessment tests be used to objectively assess skill level (Ungraded Consensus-Based Statement).

10. In patients with suspected sarcoidosis with mediastinal and/or hilar adenopathy, we recommend that EBUS-TBNA be used for diagnosis (Grade 1C).

11. In patients with suspected tuberculosis with mediastinal and/or hilar adenopathy who require lymph node sampling, we recommend that EBUS-TBNA be used for diagnosis (Grade 1C).

12. In patients with suspected lymphoma, we suggest that EBUS-TBNA is an acceptable initial, minimally invasive diagnostic test (Ungraded Consensus-Based Statement).

Endobronchial ultrasound (EBUS) is a technology that allows real-time visualization of structures adjacent to the airways during bronchoscopy. Linear EBUS incorporates an ultrasound transducer into the tip of a standard bronchoscope and guides transbronchial needle aspiration (TBNA) of lymph nodes and parabronchial masses. Radial EBUS integrates a miniature ultrasound transducer into a freestanding probe that can be advanced through the bronchoscope's working channel into the periphery of the lung to guide sampling of peripheral lung nodules and masses. EBUS was introduced into bronchoscopy almost a decade ago and has transformed the diagnostic approach to mediastinal and hilar diseases, particularly in lung cancer.

The American College of Chest Physicians' (CHEST) lung cancer guidelines (third edition) summarized the data on EBUS-TBNA in the mediastinal staging of lung cancer and reported an overall median sensitivity of 89% and a median negative predictive of 91%.[1] Based on these findings, the

AFFILIATIONS: From the Duke University Medical Center (Dr Wahidi), Division of Pulmonary and Critical Care Medicine, Durham, NC; Division of Pulmonary and Critical Care Medicine (Dr Herth), University of Heidelberg, Heidelberg, Germany; Division of Thoracic Surgery (Dr Yasufuku), Toronto General Hospital, University of Toronto, Toronto, ON, Canada; Virginia Commonwealth University Medical Center (Dr Shepherd), Richmond, VA; Division of Pulmonary and Critical Care Medicine (Drs Yarmus and Feller-Kopman), Johns Hopkins University, Baltimore, MD; Division of Medicine (Dr Chawla), Memorial Sloan Kettering Cancer Center, New York, NY; Division of Pulmonary and Critical Care Medicine (Dr Lamb), Lahey Clinic Hospital, Burlington, MA; Division of Pulmonary and Critical Care (Dr Casey), University of Wisconsin School of Medicine and Public Health, Madison, WI; CHEST (Ms Patel), Glenview, IL; and Division of Pulmonary and Critical Care Medicine (Dr Silvestri), Medical University of South Carolina, Charleston, SC.

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ENDORSEMENTS: This guideline has been endorsed by the American Association of Bronchology and Interventional Pulmonology, American Association for Thoracic Surgery, Canadian Thoracic Society, European Association for Bronchology and Interventional Pulmonology, and Society of Thoracic Surgeons.

CORRESPONDENCE TO: Momen Wahidi, MD, MBA, FCCP, Duke University Medical Center, Box 102356, Durham, NC 27710; e-mail: momen.wahidi@duke.edu

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guidelines recommended ultrasound-guided, needle-based sampling techniques over surgical staging as the first step in the mediastinal staging of lung cancer.

As EBUS-TBNA became more available and adopted by clinicians, questions emerged about the optimal performance of the procedure and best conditions for a maximal diagnostic yield. The overall objective of the present CHEST guideline and expert panel report was to examine the current knowledge of the technical aspects of linear EBUS-TBNA, including patient factors (sedation), procedural aspects (ultrasonographic features of lymph nodes, needle size, number of needle passes, use of suction, and presence of rapid on-site cytologic evaluation), and proceduralists' aptitude (training). We specifically did not address the diagnostic yield of EBUS-TBNA in the diagnosis and staging of lung cancer because this topic was addressed in the third edition of the CHEST lung cancer guidelines.[1] We did believe, however, that the diagnostic yield of EBUS-TBNA in other mediastinal diseases, such as TB, sarcoidosis, and lymphoma, has not been not well studied and opted to include these questions in our report.

Methods

Expert Panel Composition

The chair of the panel was approved by CHEST's Guidelines Oversight Committee (GOC), and additional members who were interested in serving on the guideline panel were asked to submit their curriculum vitae, a statement of interest, and conflict of interest disclosure forms to the GOC for review. The GOC then reviewed each panelist for possible conflicts of interest as well as their credentials. The final panel consisted of the guideline chair and eight panelists, who were divided among 15 topic groups as content specialists for their particular area of expertise, as well as one additional member serving as a liaison to the GOC.

Conflicts of Interest

All panel nominees were reviewed for their conflicts of interest by the GOC. After review, nominees who were found to have no substantial conflicts of interest were approved, while nominees with potential conflicts of interest that were considered to be manageable were "approved with management." Panelists who were approved with management were prohibited from voting on recommendations. A grid to track the conflicts of interest for each recommendation or suggestion was created for each PICO (population, intervention, comparator, outcome) question at the time of voting (e-Table 1).

Formulation of Key Questions and Systematic Literature Searches

The expert panel drafted a total of 15 key questions in a PICO format (Table 1). All panelists reviewed the PICO questions and, with the help of the methodologist (S. P.), finalized the search terms, inclusion and exclusion criteria, and databases that would be searched.

The methodologist performed a systematic search of the literature for individual studies for PICO questions 1 through 12 in July 2014 and for PICO questions 13 through 15 in October 2014 by using MEDLINE (via PubMed) and the Cochrane Library. A combination of the National Library of Medicine's medical subject headings and other key words specific to each topic were used to identify studies. Reference lists from relevant retrievals were also searched, and additional papers were manually added to the search results. To account for all of the literature pertaining to each topic, searches were not limited by language, study design, or publication date. Additional details on literature searches and the selection of studies are available (e-Appendix 1).

Study Selection and Data Extraction

After completion of the literature searches, studies were reviewed for relevance through two rounds of screening. Panel members were paired and assigned to specific topics, and each topic group screened the identified studies by using specific inclusion criteria based on the PICO components of each key question. In the first round of screening, panel members reviewed the titles and abstracts of identified records for potential eligibility. Records deemed eligible then underwent a second round of full-text screening for final inclusion. For both rounds of screening, recommendations for inclusion were made independently in parallel and then compared. Disagreements were resolved through discussion. Important data from each study that passed the second round of screening were then extracted into structured data tables. Panelists were divided into pairs for extraction, with one panelist performing the data extraction and the other panelist independently reviewing the extracted data. Completed evidence tables for each topic are available (e-Table 2).

Quality Assessment

The methodologist assessed the quality of all included studies. Randomized controlled trials were assessed by using the Cochrane Risk of Bias Tool.[2] Observational studies were assessed by using the Cochrane Bias Methods Group Tool to Assess Risk of Bias in Cohort Studies.[3,4] In cases in which existing systematic reviews were available, the Documentation and Appraisal Review Tool[5] was used to assess the methodologic quality.

Meta-analysis and Evidence Profiles

Upon completion of quality assessment and the development of evidence tables, a computer software program (Review Manager, Version 5.1; The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) was used to create meta-analyses on topics for which the data were homogeneous and poolable based on predefined outcomes. When possible, meta-analyses included studies from published systematic reviews as well as new studies identified through updated searches. Heterogeneity of the pooled results was assessed by using the χ^2 test and Higgins' I^2 value, and a forest plot was examined for the consistency of results. A Higgins' I^2 value $\geq$ 50% and P values $<$ .05 were considered to be significant for heterogeneity. Results from the meta-analyses are available (e-Table 3).

Grading the Evidence

Evidence profiles were created by using the GRADEpro software (GRADE Working Group). This software was used to rank the quality of the body of evidence according to four categories: high, moderate, low, and very low (Table 2).[6] The quality of the evidence was then used to determine the strength of the supporting evidence that informs a recommendation. Additional information on grading the body of evidence can be found in the "Methodologies for the Development of CHEST Guidelines and Expert Panel Reports."[7] Evidence profiles for each PICO question are available (e-Table 4).

TABLE 1] PICO Questions

Study Characteristic	Inclusion Criteria	Exclusion Criteria
KQ 1: Sedation		
Populations	Patients undergoing EBUS-TBNA procedures	None
Interventions	Deep sedation/general anesthesia	None
Comparators	Moderate sedation	None
Outcomes	Diagnostic yield of the procedure, patient comfort	None
Study design	RCT, cohort, case-control, case series, prospective studies, retrospective studies	None
KQ 2: Artificial airways		
Populations	Patients undergoing EBUS-TBNA procedures	None
Interventions	Use of artificial airways (endotracheal tube, laryngeal mask)	None
Comparators	No artificial airways	None
Outcomes	Diagnostic yield of the procedure	None
Study design	RCT, cohort, case-control, case series, prospective studies, retrospective studies	None
KQ 3: Ultrasonographic features of lymph nodes		
Populations	Patients undergoing EBUS-TBNA procedures	None
Interventions	Ultrasonographic features of lymph nodes	None
Comparators	No specific ultrasonographic features	None
Outcomes	Determination of benignity or malignancy of lymph nodes	None
Study design	RCT, cohort, case-control, case series, prospective studies, retrospective studies	None
KQ 4: Use of suction		
Populations	Patients undergoing EBUS-TBNA procedures	None
Interventions	Suction	None
Comparators	No suction	None
Outcomes	Diagnostic yield of the procedure	None
Study design	RCT, cohort, case-control, case series, prospective studies, retrospective studies	None
KQ 5: Needle size		
Populations	Patients undergoing EBUS-TBNA procedures	None
Interventions	Needle size, 22-gauge	None
Comparators	Needle size, 21-gauge	None
Outcomes	Diagnostic yield of the procedure	None
Study design	RCT, cohort, case-control, case series, prospective studies, retrospective studies	None
KQ 6: Number of needle passes		
Populations	Patients undergoing EBUS-TBNA procedures	None
Interventions	$\geq$ 3 needle passes	None
Comparators	$<$ 3 needle passes	None
Outcomes	Diagnostic yield of the procedure	None
Study design	RCT, cohort, case-control, case series, prospective studies, retrospective studies	
KQ 7: Use of ROSE		
Populations	Patients undergoing EBUS-TBNA procedures	None
Interventions	ROSE	None
Comparators	No ROSE	None

(Continued)

TABLE 1] *(Continued)*

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Outcomes	Diagnostic yield of the procedure	None
Study design	RCT, cohort, case-control, case series, prospective studies, retrospective studies	None
KQ 8: Molecular marker testing		
Populations	Patients undergoing EBUS-TBNA procedures	None
Interventions	Testing for molecular markers	None
Comparators	Surgical specimens, radiographic specimens	None
Outcomes	Success of molecular marker testing	None
Study design	RCT, cohort, case-control, case series, prospective studies, retrospective studies	None
KQ 9: Scope insertion		
Populations	Patients undergoing EBUS-TBNA procedures	None
Interventions	Scope insertion via mouth	None
Comparators	Scope insertion via nose	None
Outcomes	Diagnostic yield of the procedure	None
Study design	RCT, cohort, case-control, case series, prospective studies, retrospective studies	None
KQ 10: Use of balloon		
Populations	Patients undergoing EBUS-TBNA procedures	None
Interventions	Routine use of the balloon	None
Comparators	No balloon use	None
Outcomes	Diagnostic yield of the procedure	None
Study design	RCT, cohort, case-control, case series, prospective studies, retrospective studies	None
KQ 11: Simulation training		
Populations	Operators of EBUS-TBNA	None
Interventions	Simulation-based training	None
Comparators	Conventional training with no simulation	None
Outcomes	Successful performance of EBUS TBNA on either simulators or patients	None
Study design	RCT, cohort, case-control, case series, prospective studies, retrospective studies	None
KQ 12: Performance metrics		
Populations	Operators of EBUS-TBNA	None
Interventions	Testing of performance metrics	None
Comparators	No performance test	None
Outcomes	Discriminatory ability of the test (novice, intermediate, and advanced operators)	None
Study design	RCT, cohort, case-control, case series, prospective studies, retrospective studies	None
KQ 13: Diagnostic accuracy of EBUS-TBNA		
Populations	Patients undergoing EBUS-TBNA	None
Interventions	EBUS-TBNA for sarcoidosis	None
Comparators	No comparator	None
Outcomes	Diagnostic accuracy and/or diagnostic yield of EBUS-TBNA	None
Study design	RCT, cohort, case-control, case series, prospective studies, retrospective studies	None

(Continued)

TABLE 1] *(Continued)*

Study Characteristic	Inclusion Criteria	Exclusion Criteria
KQ 14: Diagnostic accuracy of EBUS-TBNA		
Populations	Patients undergoing EBUS-TBNA	None
Interventions	EBUS-TBNA for tuberculosis	None
Comparators	No comparator	None
Outcomes	Diagnostic accuracy and/or diagnostic yield of EBUS-TBNA	None
Study design	RCT, cohort, case-control, case series, prospective studies, retrospective studies	None
KQ 15: Diagnostic accuracy of EBUS-TBNA		
Populations	Patients undergoing EBUS-TBNA	None
Interventions	EBUS-TBNA for lymphoma	None
Comparators	No comparator	None
Outcomes	Diagnostic accuracy and/or diagnostic yield of EBUS-TBNA	None
Study design	RCT, cohort, case-control, case series, prospective studies, retrospective studies	None

EBUS-TBNA = endobronchial ultrasound-transbronchial needle aspiration; EBUS-STAT = Endobronchial Ultrasound Skills and Tasks Assessment Tool; KQ = key question; PICO = population, intervention, comparator, and outcome; RCT = randomized controlled trial; ROSE = rapid on-site evaluation.

Recommendations

The panel as a whole worked together to draft statements for each PICO question that had sufficient evidence. Evidence tables, meta-analyses, evidence profiles, and all of the included studies were used to formulate recommendations and their associated grades.

Recommendations were graded by using the CHEST grading system (Table 3).[7] In instances in which there was insufficient evidence, but a recommendation was still warranted, a weak suggestion was developed and "Ungraded Consensus-Based Statement" replaced the grade.

All drafted recommendations and suggestions were presented to the panel in an online anonymous voting survey. Panelists were requested to indicate their level of agreement on each statement, based on a 5-point Likert scale derived from the Grading of Recommendations Assessment, Development and Evaluation grid.[7,8] Panelists also had the option to provide open-ended feedback on each statement with suggested edits or general remarks. The conflict of interest grids were forwarded along with the voting survey, and panelists were instructed to refrain from voting on any recommendations in which they had a potential conflict of interest. Based on CHEST policy, each statement required 75% participation and at least 80% consensus to pass. Any recommendations or suggestions that did not pass were revised by the panel based on the feedback provided, and a new survey was sent out that incorporated those changes.

Peer Review Process

Identified reviewers from the GOC, the CHEST Board of Regents, and the *CHEST* journal reviewed the content of the manuscript. All reviewers assessed both content and methods, including consistency, accuracy, and completeness. The manuscript was revised according to feedback from peer review, and it was subsequently approved by the GOC and Board of Regents prior to submission to the *CHEST* journal.

TABLE 2] Rating the Confidence in the Estimate of the Effect

Quality of the Evidence	Level of Confidence in the Estimate of the Effect
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect

Wording of definitions from Balshem H et al.[6]

TABLE 3] CHEST Grading System

Grade of Recommendation	Balance of Benefit Vs Risk and Burdens (Strength of the Recommendation: Level 1 or 2)	Methodologic Strength of Supporting Evidence (Quality of Body of Evidence: A, B, C, or Consensus-Based)	Implications
Graded evidence-based guideline recommendations			
Strong recommendation, high-quality evidence (1A)	Benefits clearly outweigh risks and burdens, or vice versa	Consistent evidence from randomized controlled trials with no important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect
Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risks and burdens, or vice versa	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies	Recommendations can apply to most patients in most circumstances. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Strong recommendation, low- or very low-quality evidence (1C)	Benefits clearly outweigh risks and burdens, or vice versa	Evidence for at least one critical outcome from observational studies, case series, or from randomized controlled trials with serious flaws or indirect evidence	Recommendations can apply to most patients in most circumstances. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Weak recommendation, high-quality evidence (2A)	Benefits closely balanced with risks and burdens	Consistent evidence from randomized controlled trials with no important limitations or exceptionally strong evidence from observational studies	Best action may differ depending on circumstances or patients' or societal values. Further research is very unlikely to change our confidence in the estimate of effect
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balanced with risks and burdens	Evidence from randomized controlled trials with important limitations (eg, inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies	Best action may differ depending on circumstances or patients' or societal values. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Weak recommendation, low- or very low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burdens; benefits, risks, and burdens may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or from randomized controlled trials with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Ungraded consensus-based suggestions			
Consensus-based (Ungraded Consensus-Based Statement)	Uncertainty due to lack of evidence but expert opinion that benefits outweigh risks and burdens or vice versa	Insufficient evidence for a graded recommendation	Future research may well have an important impact on our confidence in the estimate of effect and may change the estimate

Results

Sedation

Sedation is defined as a continuum of altered consciousness levels, including minimal sedation (anxiolysis), moderate sedation (conscious sedation), deep sedation, and general anesthesia. Moderate sedation is defined as a drug-induced depression in consciousness wherein patients can respond purposefully to verbal commands while maintaining a functional airway, spontaneous ventilation, and cardiovascular function. Deep sedation causes a deeper state of depressed consciousness in which patients cannot be easily aroused but respond purposefully to repeated or painful stimulation and may have compromised airway function and spontaneous ventilation; cardiovascular function is usually maintained.[9]

The ideal type of sedation in EBUS procedures is an important question for bronchoscopists as they seek the best conditions to optimize their diagnostic yield, enhance patients' comfort, and avoid complications. Sedation also represents a significant contributory element in the economics of EBUS-TBNA as it relates to cost of care, work flow, and health-care resources utilization in terms of anesthesia services and medications.

Three studies met the inclusion criteria and compared moderate and deep sedation during EBUS bronchoscopy. The primary outcomes of these studies included diagnostic yield, procedural complications, and patient satisfaction. The two studies that reported on diagnostic yield between patients undergoing deep or moderate sedation had conflicting results. The retrospective study by Yarmus et al[10] assessed 309 patients from two separate institutions and multiple proceduralists performing EBUS with moderate or deep sedation. The authors found a statistically significant benefit of deep sedation use on diagnostic yield in a multivariable analysis. The trial by Casal et al,[11] a prospective randomized controlled study of 149 patients, found no difference in the diagnostic yield in a single-center/single-operator setup. However, fewer patients in the moderate sedation group were able to complete the procedure compared with the deep sedation group ($P = .028$). The studies by Dal et al[12] and Casal et al[11] also assessed patient comfort and satisfaction, and no differences were found overall between sedation groups. There were no major complications or escalation of care in either sedation group reported in any of the studies included in this analysis.

The level of evidence, size, and quality of the existing studies affected our grading and conclusion regarding the choice of sedation used for EBUS bronchoscopy. The study by Yarmus et al[10] was limited by its retrospective design and comparison of two different institutions with inherent, and potentially confounding, differences in practice and patients. Although the study by Casal et al[11] was prospective and randomized, their results must be viewed with caution because the sample size was small and the procedures were performed at one institution and by a single experienced physician. The study by Dal et al[12] did investigate patient comfort, but the outcomes with regard to diagnostic yield were not addressed in the study. No study addressed the difference in cost of care between the two choices of sedation.

1. In patients undergoing EBUS-TBNA, we suggest that either moderate or deep sedation is an acceptable approach (Grade 2C).

Artificial Airways

When performing EBUS bronchoscopy procedures, the bronchoscopist has the option of inserting the scope through natural orifices (nose or mouth), a laryngeal mask airway, or an endotracheal tube.

The literature search found insufficient evidence to recommend for or against an artificial airway for insertion of the EBUS bronchoscope in terms of diagnostic yield of EBUS-TBNA. Because of the lack of data regarding PICO Question 2 (Table 1), we are unable to make a formal recommendation regarding placement of an artificial airway during EBUS-TBNA bronchoscopy. The suggestion regarding sedation in EBUS-TBNA bronchoscopy and the discussion of PICO Question 9 regarding route of scope insertion in EBUS-TBNA bronchoscopy offers further details.

Clearly, the level of sedation plays a critical role in determining the need for an artificial airway; however, PICO Question 2 specifically assessed the impact on diagnostic yield if an artificial airway is used during EBUS-TBNA bronchoscopy. One prospective study[13] looked at the use of a modified laryngeal mask airway during EBUS-TBNA but did not assess diagnostic yield as an outcome. This study compared 70 patients who underwent EBUS-TBNA with intravenous anesthesia, muscle relaxation, and modified laryngeal mask airway ($n = 46$) or topical aerosolized 2% lidocaine only ($n = 24$). The laryngeal mask airway group was found to have higher oxygen saturation during EBUS probe insertion and significantly lower heart rate, systolic

blood pressure, and diastolic blood pressure during the procedure. In addition, reduced body movement, absence of choking or suffocation episodes, and no procedural termination were noted in the laryngeal mask airway group.

One institution[14] reported their anesthesia practice for EBUS-TBNA as safe, using general anesthesia, muscle paralysis as needed, and a laryngeal mask airway. An endotracheal tube was used in the setting of difficult laryngeal mask airway placement, obesity, or severe untreated gastroesophageal reflux disease. No specific data on diagnostic yield were reported. Earlier studies of EBUS-TBNA[15-17] reported on the use of either combined rigid and flexible bronchoscopy with general anesthesia, flexible bronchoscopy alone with moderate sedation with no specified route, or local anesthesia with an oral route.

CHEST Quality Improvement Registry, Evaluation and Education (AQuIRE) bronchoscopy module captured comprehensive data on TBNA.[18] Over a 12-month period, 891 patients were enrolled to undergo TBNA procedures at six institutions, including 853 EBUS-TBNA procedures (95.7%) and 38 conventional TBNA procedures (4.3%). Laryngeal mask airway was used in 433 procedures (48.6%), endotracheal tube in 59 (6.6%), and tracheostomy tube in 4 (0.4%); the remainder were conducted via the nasal route in 109 (12.2%) or the oral route in 295 (33.1%) with no artificial airway. Data for diagnostic yield by use of an artificial airway were not reported.

It is important to recognize that the placement of the endotracheal tube may block the ultrasonographic view of the higher paratracheal lymph nodes (lymph node stations 1, 2R, 2L, and 3P) and should be avoided if one of these lymph nodes is the sampling target of the procedure.

If using a transoral artificial airway, a bite block should be considered to protect the bronchoscope from bite damage. This approach is recommended independent of the depth of sedation. A minimum size of 8.0 should be used if placing an endotracheal tube for EBUS-TBNA to accommodate the scope diameter and leave room for gas exchange.

In conclusion, there is insufficient quality of evidence to recommend for or against artificial airways for EBUS-TBNA. Reported practice is scattered and is largely based on expert opinion, operator comfort, sedation type, and institutional standards.

Ultrasonographic Features

EBUS can distinguish lymph nodes and lung masses from vessels, and it can also display ultrasonographic features of the examined structures such as size, shape, border, heterogeneity, central hilar structure, and necrosis. Just as with CT and MRI scanning, bronchoscopists are interested in identifying imaging features that would predict certain diseases to help them guide the sampling process.

Nine studies met the inclusion criteria and provided analysis of the characteristics of lymph nodes that predict malignancy during EBUS.[19-27] Outcomes from the studies could not be combined because of the heterogeneity of the data and the fact that the ultrasonographic features assessed were not the same in each study or they had varying definitions of what constituted "abnormal."

Fujiwara et al[20] published the largest series to date assessing endoscopic lymph node features that could help distinguish benign from malignant disease by evaluating > 1,000 lymph nodes in nearly 500 patients. In addition, they provided a standard classification system to define ultrasound features that were then variably assessed by others. The predefined features they assessed were: (1) size (short-axis < 1 cm, > 1 cm), (2) shape (oval, round), (3) margin (indistinct or distinct), (4) echogenicity (homogeneous or heterogeneous), (5) presence or absence of central hilar structure, and (6) presence or absence of a central necrosis sign. In multivariate analysis, they found that a round shape, distinct margins, heterogeneous echogenicity, and a central necrosis sign were independently predictive of malignancy. Furthermore, when all four factors were absent, 96% of the lymph nodes were benign.

Three additional studies also assessed size criteria as a predictor; however, the results are conflicting. Although Fujiwara et al[20] found that size was not a reliable indicator, others have found that larger lymph nodes are more likely to harbor metastases.[21,24,26] These inconsistencies are possibly due to differences in how size was defined. Fujiwara et al[20] and Satterwhite et al[26] used a dichotomous variable (< 1 cm or > 1 cm in the short-axis) and had similar findings, whereas Garcia-Olivé et al[21] used a 2-cm cutoff and Memoli et al[24] used 5-mm increases in size > 1 cm. In the latter two studies, a statistically significant increase in presence of malignancy in a lymph node occurred as the size increased. These studies also confirmed that round-shaped lymph nodes were more likely malignant than

triangular or draping lymph nodes. Memoli et al[24] could not confirm that a distinct border conferred a higher risk for malignancy, a finding previously noted by Fujiwara et al.[20] They also assessed PET avidity and, after adjusting for lymph node size, hypermetabolic lymph nodes on PET scans did not confer an increased risk of malignancy.

Nakajima et al[25] assessed vascular image patterns within lymph nodes as a way to predict malignancy. They developed a classification system by using grades (0-3) predefined as increasing vascular involvement from no blood flow (grade 0) and single central vessel (grade I) and considered those benign. As vessel involvement increased in the node to rich flow with $>$ 4 vessels (grades 2 and 3), the nodes were considered malignant. The sensitivity and specificity for malignancy in patients with grade 2 or 3 blood flow in a lymph node were 87.7% and 69.6%, respectively, suggesting that increased vascularity assessed by using power/color Doppler mode ultrasound is useful in predicting malignancy. Satterwhite et al[26] confirmed the benign findings in those patients with a central intranodal vessel (Nakajima class 1).

Two studies have assessed ultrasound features of lymph nodes in patients with sarcoidosis. Imai et al[22] compared ultrasound features of patients with sarcoidosis and lung cancer. Lymph nodes with homogeneous echogenicity and a germinal center were more likely to indicate sarcoidosis than lung cancer. Dhooria et al[19] attempted to use ultrasound features within lymph nodes to distinguish sarcoidosis from TB. They found that coagulation necrosis and heterogeneous echogenicity within lymph nodes were more likely to be present in TB as opposed to sarcoidosis.

In conclusion, the ultrasonographic predictors of malignancy in lymph nodes are not reliable enough to forgo biopsy to obtain a definitive tissue diagnosis. However, it is reasonable for experienced practitioners to use ultrasound features to guide sampling such that they obtain the highest yield from lymph nodes likely to be malignant. Future research should attempt to replicate the findings from these studies in a prospective manner by using standardized criteria in consecutive patients with both benign and malignant disease. In addition, technologies that take advantage of automated measurements within the EBUS processor, as well as other novel approaches to aid in distinguishing benignity from malignancy, should be tested on a larger scale.[23,27]

2. In patients undergoing EBUS-TBNA, we suggest that ultrasonographic features can be used to predict malignant and benign diagnoses, but tissue samples should still be obtained to confirm a diagnosis (Ungraded Consensus-Based Statement).

Suction

The application of suction to needles during tissue aspiration has been a standard practice for many decades in numerous medical specialties, including in the use of conventional TBNA. Some theorize that suction may increase tissue trauma in the biopsy site and result in more bleeding and lower yields. Others argue that suction is beneficial and produces a higher number of aspirated cells. Although this question has been studied in other anatomical sites, limited evaluation of the use of suction has been performed in EBUS-TBNA.

Only one study was found to address this question. Casal et al[28] performed a randomized prospective trial comparing EBUS-TBNA with suction vs EBUS-TBNA without the use of suction, referred to as transbronchial needle capillary sampling (EBUS-TBNCS). Subjects were randomized either to undergo TBNCS in passes 1 and 3 or TBNA with suction in passes 2 and 4 or the opposite order. Separate needles were used for passes 1 and 3 vs those used with passes 2 and 4. Only the initial four passes were included in the analysis. The primary end point was the concordance between suction TBNA and TBNCS for diagnostic yield and the adequacy of samples. There were no significant differences between the two groups in specimen adequacy, diagnosis rate, or specimen quality regardless of node size. Concordance rates between the techniques were high, ranging from 83.3% to 95.8% for adequacy, diagnostic yield, and specimen quality.

Other issues relating to the use of suction during EBUS-TBNA that remain unknown include whether differing amounts of negative suction have an effect on acquisition of material or whether the effect of suction interacts with the various sizes of the needle. These questions require further study.

In cases in which EBUS-TBNA is being performed with suction and the samples obtained are bloody, operators should consider switching to the use of no suction at the same sampling site. If intranodal blood vessels are visualized on EBUS imaging with or without Doppler imaging, operators should also consider obtaining samples without suction.

3. In patients undergoing EBUS-TBNA, we suggest that tissue sampling may be performed either with or without suction (Ungraded Consensus-Based Statement).

Needle Size

Several needles are available to obtain specimens via EBUS-TBNA, including those of variable sizes (25-, 22-, or 21-gauge) and materials (stainless steel or nitinol). The size of the needle may affect the quantity of tissue obtained, degree of tissue trauma, and amount of aspirated blood—each of which can affect the quality of the specimen and the diagnostic yield.

Five trials comparing needle sizes met our criteria for review, including three retrospective studies,[29-31] one prospective study,[32] and one randomized trial.[33] Of note, these trials compared only 21- and 22-gauge needles; no data are available on 25-gauge needles.

Nakajima et al[29] reviewed 45 EBUS-TBNA specimens in 33 patients in whom both 21- and 22-gauge needles were used. There was no statistically significant difference in diagnostic yield, although two patients with adenocarcinoma were only diagnosed with the 21-gauge needle. The authors also found that the 21-gauge needle provided better "histologic structure" with an increased number of tumor cells present, but it was also associated with more blood contamination. The 22-gauge needle, however, tended to have improved preservation of nonnecrotizing granuloma compared with the 21-gauge needle ($P = .695$).

Yarmus et al[30] used the CHEST AQuIRE to review 1,235 procedures and found no significant difference in sample adequacy or diagnostic yield. The use of the 21-gauge needle, when combined with the presence of rapid cytologic on-site evaluation, was associated with fewer needle passes per lymph node (3.5 vs 4.2; $P < .01$), potentially suggesting improved quality of specimen.

Jeyabalan et al[31] reviewed 303 patients referred for EBUS-TBNA over $2^1/_2$ years. Needle size was selected at the discretion of the operator, and samples were assessed by histopathologists blinded to the needle used. No significant difference in diagnostic yield for malignancy was seen. The major limitation of this study was the retrospective, single-center study design. It is also noteworthy that specimen analysis was performed by experienced histopathologists; thus, these data may not be extrapolated to centers using cytopathologic interpretation.

Saji et al[32] prospectively evaluated 56 consecutive patients undergoing EBUS-TBNA for the evaluation of mediastinal lesions. Use of the 21-gauge needle produced a higher cytologic sensitivity and overall diagnostic yield (cytologic + histologic sensitivity), but there was no difference in histologic sensitivity. This study differs from the others in that it assessed results on a per-patient basis as opposed to a per-lymph node basis.

The only randomized trial comparing 21- vs 22-gauge needles was performed by Oki et al[33] in 60 patients with hilar/mediastinal adenopathy or tumor adjacent to a central airway. Patients were randomly assigned to have the first two needle passes with either the 21- or 22-gauge needle, and specimens were assessed for adequacy and diagnostic yield. There were no differences between groups in terms of target size, lymph node station, or prevalence of disease. Likewise, there was no difference between needle gauges in either outcome measure, although there was a trend of more inadequate samples with the 21-gauge needles.

At this time, needle choice should be determined by the operator. Some factors influencing needle size choice may include location and vascularity of the node. Future studies should investigate if a smaller or more flexible needle would improve sampling at station 4L (known for its slightly angulated location) or if smaller needles would result in less blood contamination when sampling more vascular nodes. Studies should also examine if a particular needle size should be used depending on how the specimens are being processed (histopathology vs cytopathology) and if needle size can affect the diagnosis of diseases that are more difficult to diagnose by EBUS-TBNA, such as lymphoma.

4. In patients undergoing EBUS-TBNA, we recommend that the use of either a 21- or 22-gauge needle is an acceptable option (Grade 1C).

Number of Needle Passes

The number of needle passes per sampling site has implications on procedural efficiency (time spent on sampling by the proceduralist and interpretation of tissue samples by the pathologist, particularly when sampling multiple sites) balanced by the desire to achieve maximum diagnostic yield. For this discussion, a "pass" is a distinct entry and exit of the needle through the airway wall, and each pass typically includes five to 15 agitations of the needle within the target site.

Lee et al[34] conducted the only study that addressed this issue. EBUS-TBNA was performed on 163 stations in

102 patients with potentially operable non-small cell lung cancer and mediastinal adenopathy. Every target node was punctured four times. Sample adequacy was 90.1% after the first pass, 98.1% after two passes, and reached 100% after three passes. The sensitivity for differentiating malignant from benign lymph node stations was 69.8%, 83.7%, 95.3%, and 95.3% for one, two, three, and four passes, respectively.

Based on this study, it seems that optimal diagnostic values with EBUS-TBNA can be obtained after a minimum of three passes with the caveat that this suggestion pertains to lung cancer diagnosis and staging. No data exist regarding the number of needle passes required to obtain a sufficient diagnostic yield for lymphoma or other nonmalignant diseases of the mediastinum. The sampling of tissue for molecular marker testing is discussed in Statement 7.

5. In the absence of rapid on-site evaluation (ROSE) in patients suspected of having lung cancer and undergoing EBUS-TBNA for diagnosis, we suggest that a minimum of 3 separate needle passes be performed per sampling site (Ungraded Consensus-Based Statement).

Rapid On-Site Evaluation

Since the development of TBNA through a flexible bronchoscope in the late 1960s, rapid on-site evaluation (ROSE) has been used with conventional TBNA to improve the diagnostic yield, decrease the number of needle passes, and reduce the need for additional diagnostic procedures.[35] With the advent of EBUS, it was unclear if the same benefits would be realized by using ROSE because EBUS provides real-time confirmation that the needle is in the target and may obviate the need for a concurrent pathologic confirmation of tissue adequacy.

We identified three trials that fulfilled the inclusion criteria and addressed this issue.[36-38] Oki et al[36] conducted the only prospective randomized clinical trial on this question. They randomized 120 patients with mediastinal adenopathy and high suspicion of lung cancer to undergo EBUS-TBNA with or without ROSE. The collected material was blown by air with a syringe onto a glass slide. In patients assigned to the ROSE group, one glass slide was used for ROSE and another was submitted for Papanicolaou-stained cytologic examination. For ROSE, a cytotechnologist evaluated the cell material of the air-dried smears on-site (Diff-Quik staining method). The decision regarding termination or additional sampling was made by the examiner on the basis of the ROSE results. Mean puncture number was significantly lower in the ROSE group (2.2 vs 3.1 punctures; $P < .001$), but mean bronchoscopy time was similar between groups (22.3 vs 22.1 min; $P = .95$). The sensitivity and accuracy for diagnosing lung cancer were 88% and 89%, respectively, in the ROSE group, and 86% and 89% in the non-ROSE group. Additional procedures including EBUS-TBNA for lesions other than the main target lesion and/or transbronchial biopsy in the same setting were performed in 11% of patients in the ROSE group and 57% in the non-ROSE group ($P < .001$). This study showed that ROSE can decrease the number of punctures and reduce the need for additional staging and diagnostic procedures.

Two other trials retrospectively reviewed the value of ROSE. Griffin et al[37] conducted a retrospective analysis of 294 EBUS-TBNA specimens; 48% had been performed with ROSE. There was no significant difference in diagnostic yield, number of sites sampled per patient, or clinical decision-making between specimens collected with or without ROSE.

Murakami et al[38] analyzed the records of 780 patients by using EBUS-TBNA. The results of 100 EBUS-TBNA procedures, with or without ROSE, in 98 patients with a definitive diagnosis of a small cell lung cancer were reported. ROSE did not have any impact on the diagnostic yield (99% with ROSE vs 90% without ROSE; $P < .1$), but it reduced the number of aspirates per procedure (mean 2.3 with ROSE vs 4.0 without ROSE; $P < .01$).

In conclusion, the current data suggest that ROSE does not affect the diagnostic yield in EBUS-TBNA procedures, but it may reduce the number of needed aspirations as well as the number of other procedures (ie, TBLB) required. It is noteworthy that ROSE may be beneficial in judging the quantity of available malignant cells when testing for molecular markers is planned in patients with advanced adenocarcinoma of the lung.

6. In patients undergoing EBUS-TBNA for diagnostic evaluation, we recommend that tissue sampling can be performed with or without rapid on-site evaluation (Grade 1C).

Molecular Markers

Molecular marker testing in advanced adenocarcinoma or undifferentiated non-small cell lung cancer of the

lung is now considered standard of care and necessary for tailoring the best chemotherapy to the cancer characteristics of each individual patient. Because EBUS-TBNA is increasingly used to diagnose lung cancer, it is imperative to understand whether this modality provides adequate tissue for molecular markers and the optimal number of aspirations to do so.

Fourteen studies met the inclusion criteria and addressed the utility of EBUS-TBNA sample acquisition for molecular analysis testing. The primary outcome was the success of EBUS-TBNA to acquire samples that were sufficient to be tested for molecular markers. A total of 684 cases were included. The studies by Lee et al,[39] Bugalho et al,[40] and Schmid-Bindert et al[41] were prospective trials assessing the feasibility of molecular marker testing in patients with non-small cell lung cancer. They found that mutational testing was feasible and reproducible. The remainder of these studies were retrospective[42-52]; however, all displayed a very high adequacy rate for obtaining tissue that was sufficient to test for mutational markers, leading to the strength of our recommendation.

Only one retrospective study addressed the number of passes required to have adequate tissue for molecular testing. In 85 patients with adenocarcinoma or non-small cell lung cancer, Yarmus et al[52] found that 93.5% of EBUS-TBNA specimens were adequate for molecular profiling. A median of four EBUS-TBNA passes, in conjunction with ROSE, were needed to establish this adequacy rate. The current data are insufficient to identify the number of passes needed to obtain adequate tissue for molecular marker testing, but it is strongly suggested that additional samples, over the proposed diagnostic threshold of three passes (as discussed in the earlier section on Needle Passes), are recommended.

7. In patients undergoing EBUS-TBNA for the diagnosis and/or staging of suspected or known non-small cell lung cancer, we recommend that additional samples, beyond those needed to establish the diagnosis, be obtained for molecular analysis (Grade 1C).

Scope Insertion Site

Conventional flexible bronchoscopy has been performed via a variety of entry sites, including nasal, oral, or artificial airways. The choice of access depends on several variables such as type of sedation, anatomy, scope size, and institutional or practitioner preferences. Traditionally, the transnasal approach has been popular for conventional flexible bronchoscopy due to improved patient comfort, reduced gag, decreased lidocaine dosing, and enhanced bronchoscope stability. Limitations can be due to nasal anatomy, scope size, thrombocytopenia, or coagulopathy.[53-55] In a prospective cohort survey study of conventional bronchoscopy, 74% of patients who underwent nasal bronchoscopy (385 of 461 [83.5%]) compared with 57.1% (70 of 461 [15.2%]) via the oral route stated they would "definitely return" for repeat flexible bronchoscopy if indicated.[56] However, preferences for the oral route prevailed based on patient comfort and less insertion site bleeding in one prospective study,[57] and the transoral route was noted as the predominant insertion site in a Japanese national survey of bronchoscopists.[58]

PICO Question 9 looked at the transnasal vs transoral approach when performing EBUS-TBNA independent of an artificial airway. The importance of this issue compared with traditional flexible bronchoscopy rests on the larger diameter, more rigid distal end, and the recessed forward oblique bronchoscopic view of an EBUS scope. The latter is of varying degrees depending on the manufacturer. Although diagnostic yield is the main primary end point in assessing procedural technology, feasibility, safety, and patient comfort are equally important end points. Beaudoin et al[59] analyzed 196 consecutive patients at their institution who underwent EBUS-TBNA by six different attending physicians, with or without trainees. This retrospective review was an indirect comparison of nasal vs oral approaches, and it reported a diagnostic yield of 22 of 52 (42.3%) in the oral route group vs 74 of 155 (51.4%) in the nasal route group ($P = .26$). This is the only published study looking at diagnostic yield based on insertion site of a dedicated linear EBUS bronchoscope. An early study[17] of EBUS-TBNA reported only use of the oral route with local anesthesia and an accuracy of 97.1%.

The CHEST AQuIRE captured comprehensive data on TBNA.[17] During a 12-month period at six US institutions, 891 TBNA procedures were performed. EBUS-TBNA was used in 853 procedures (95.7%), and the remaining 38 (4.3%) used conventional TBNA. Nasal bronchoscope insertion was completed in 109 (12.2%) procedures. Data for scope insertion route specifically by scope type, by mode of TBNA, and diagnostic yield by bronchoscopy route were not reported.

In conclusion, there is insufficient quality of evidence to support any route of bronchoscope insertion for EBUS-TBNA over another. Translating the experience and literature from conventional flexible bronchoscopy given the size and rigidity of the EBUS bronchoscope distal tip, as well as the limited bronchoscopic view, is difficult.

Balloon Use

The currently available EBUS scopes can be fitted with disposable balloons over their distal ultrasound tips. The balloons can be filled with saline to overcome poor contact between the ultrasound probe and the bronchial wall and assist in obtaining a clear ultrasound image. Although the saline-filled balloon can enhance image acquisition, it is unclear if that translates into a better diagnostic yield. It is worth remembering that the balloons come at an additional, albeit small, cost and are made of latex and thus cannot be used in patients with latex allergies.

No studies were found addressing this issue, and therefore no recommendations or suggestions can be made. From a practical perspective, balloons are commonly used when the target lymph nodes are located in the paratracheal areas (2R, 2L, 4R, and 4L), particularly for the slightly challenging angle of the left paratracheal lymph node (4L), and hilar stations (10R and 10L). Balloons may or may not be needed in lymph node stations 7 and 11.

Simulation Training

There is growing interest in moving away from conventional training on patients and relying on simulation-based training for procedures.[60] Simulation technology in EBUS bronchoscopy is available in two forms: low-fidelity inanimate mechanical airway models and high-fidelity computer-based electronic simulation.

Three studies met the inclusion criteria comparing conventional EBUS-TBNA training vs simulation-based training incorporating either a low- or high-fidelity simulation tool.[61-63] Two of the included studies assessed EBUS-TBNA skill acquisition in pulmonary medicine and thoracic surgery trainees. Outcomes such as the percentage of correctly identified lymph nodes, acquisition of lymphocytes, and procedural time were assessed either by the simulator[63] or by experienced observers in clinical training involving actual patients.[62] Although a meta-analysis regarding the percentage of correctly identified lymph nodes and acquisition of lymphocytes found that there was no difference between the two groups, results of these two studies did find that simulation training leads to rapid acquisition of EBUS-TBNA skills, similar to that of conventional training. The remaining study[61] was a randomized controlled trial comparing wet laboratory training vs computer EBUS-TBNA simulation. There was no significant difference between the groups in the primary outcome measure of procedure time or successful nodal aspirates. However, accurate lymph node identification was superior in the computer-based simulation group. Results of all three studies highlight that the same level of training can be acquired via conventional or simulation-based training; however, the latter minimizes novice operators' practice on patients.

8. In training EBUS-TBNA operators, we suggest that low- or high-fidelity simulation be incorporated into training (Grade 2C).

Assessing EBUS-TBNA Operator Skill

Measurement of competency and procedural skill in bronchoscopy and numerous other medical procedures has been the subject of increased focus and research in the last several years. The limitations of procedural competency measurements based solely on number of procedures performed are well recognized; researchers have thus sought other methods to measure bronchoscopy skills, including simulation skill assessments and other performance-based metrics. A study in general bronchoscopy by Wahidi et al[64] showed that performance-based competency metrics could be used as a tool to assess bronchoscopy skills. Skill levels were assessed by using the Bronchoscopy Skills and Tasks Assessment Tool in cohorts of new pulmonary fellows performing basic bronchoscopy.

For EBUS bronchoscopy, a study by Davoudi et al[65] evaluated the validity and reliability of a similar tool, the Endobronchial Ultrasound Skills and Tasks Assessment Tool (EBUS-STAT). The EBUS-STAT scores bronchoscope introduction, navigation, image acquisition, vascular imaging, nodal imaging, sampling of one station, and image modification. It also includes a 25-slide test of CT and EBUS imaging knowledge. The tool was administered to eight operators each in a beginner (< 20 EBUS procedures performed), intermediate (20-50 EBUS procedures), and experienced (> 50 EBUS procedures) category of bronchoscopists. The EBUS-STAT was able to statistically significantly distinguish the categories of beginner, intermediate, and experienced broncoscopy operators. The mean EBUS-STAT scores for the beginner, intermediate, and experienced groups were 31.1, 74.9, and 93.6,

respectively, from a 100-point scale ($P < .001$). The two testers had detailed knowledge and experience with the assessment tool, resulting in a very high inter-rater reliability ($r = 0.9991$, $P < .00005$), which may not be true for testers who are not as familiar with the tool. It was also noted that the significant difference in scores among the three groups was in the technical portion of the scores and not the test portion, suggesting that the skills portion may be the more important part of the EBUS-STAT tool.

Another small prospective study used virtual reality simulation to assess EBUS performance. Konge et al[66] examined simulator metrics with discriminatory ability in experienced EBUS operators (n = 6), untrained novices (n = 8), and simulator-trained novices (n = 8). Each operator performed two simulated EBUS-TBNA procedures on the GI-BRONCH Mentor (Simbionix Products). Of eight metrics examined, the simulator metrics that demonstrated statistically significant differences among experienced and novice EBUS operators were the number of successfully sampled lymph nodes ($P = .047$) and procedure time ($P = .002$). These two metrics were combined into a quality score that demonstrated a median quality score for the experienced group of 0.24 and 0.098 for the novice group ($P = .001$). This study showed that not all EBUS-TBNA metrics have discriminatory ability but that virtual reality EBUS simulators may have a role in assessing operator ability prior to performing the procedure in patients.

A third study examined four cohorts of EBUS users to validate a different EBUS simulator, the AccuTouch Flexible Bronchoscopy Simulator (CAE Healthcare).[67] Twenty-two bronchoscopists were divided into the following groups: novice bronchoscopists, experts without EBUS experience, basic clinical EBUS training (pulmonary trainees or recent graduates), and EBUS experts. Significant differences among groups were found by the simulator for the metrics of total procedure time, percentage of successful biopsies, and percentage of lymph nodes correctly identified ($P = .05$). The findings suggest that this simulator can accurately discriminate among various skill levels of EBUS operators.

These three studies are heterogeneous and thus preclude the pooling of data.[65-68] Although the overall sample size of these three studies is small, they support the use of a validated EBUS skills assessment tool in performing EBUS-TBNA in human subjects as well as the use of simulators to distinguish between the skill levels of EBUS operators. It is important to recognize that none of the included simulation studies examined whether the skills demonstrated on a simulation assessment are transferred to an improvement in clinical skills as performed in patients. These types of tools may prove useful in determining physicians' hospital procedural privileges or in other types of training programs.

Although not included in the final analysis, several other studies examined related aspects of EBUS performance metrics. Three studies used cumulative sum analysis techniques to evaluate the learning curve of EBUS operators and reported how many procedures are needed to attain competency.[68-70] These studies included a very small number of operators and demonstrated significant variability in learning EBUS-TBNA. Wahidi et al[71] examined the learning curve of general pulmonary fellows with EBUS-TBNA and found an average of 13 procedures were required to perform the first successful independent procedure. Another study assessed the EBUS learning curve among nine interventional pulmonary fellows; it found very variable learning rates and noted improvement in some performance metrics even after 200 clinical cases.[72] These additional studies did not specifically examine the strength, discriminatory ability, or reliability of EBUS performance metrics tools as was done in the three primary studies included in the analysis.

9. In evaluating EBUS-TBNA operators, we suggest that validated EBUS skills assessment tests be used to objectively assess skill level (Ungraded Consensus-Based Statement).

Diagnosis of Sarcoidosis

The diagnosis of sarcoidosis is based on the presence of a compatible clinical scenario, radiographic findings, and histologic confirmation of noncaseating granulomatous inflammation. Transbronchial lung biopsy (TBLB), endobronchial biopsy (EBB), and TBNA are commonly used bronchoscopic techniques for determining granulomas. EBUS-TBNA was initially introduced as a minimally invasive modality for lymph node staging in lung cancer. However, the use of EBUS-TBNA has been expanded for the evaluation of patients with mediastinal and hilar adenopathy. Studies have illustrated the benefit of using EBUS-TBNA alone as well as in conjunction with other bronchoscopic techniques for the diagnosis of sarcoidosis. Earlier studies of EBUS-TBNA on sarcoidosis have mainly been retrospective case review analyses; however, several prospective studies as well as randomized controlled trials are available on this topic.

Agarwal et al[73] performed a systematic review and meta-analysis of the efficacy and safety of EBUS-TBNA in the diagnosis of sarcoidosis. The study included 15 studies with a total of 553 patients with sarcoidosis. The diagnostic yield of EBUS-TBNA ranged from 54% to 93%, with the pooled diagnostic accuracy of 79% (95% CI, 71-86). Of interest, there was no statistical difference in the yield in studies using ROSE (80.1%) vs those without ROSE (81.3%). Ten additional studies (including 573 combined patients)[74-83] were identified through updated searches of the systematic review by Agarwal et al.[73] These studies combined with those previously included led to a pooled diagnostic accuracy of 78.2% (95% CI, 75.6-80.4).

Given the high cost and poor availability of EBUS in developing countries, a head-to-head comparison of EBUS-TBNA and conventional TBNA in combination with TBLB and EBB was performed in India by Gupta et al.[78] This randomized controlled trial enrolled 130 patients and randomized them (1:1) to undergo EBUS-TBNA + TBLB and EBB vs conventional TBNA + TBLB and EBB. Although there was no difference in the two arms (92.7% for EBUS-TBNA vs 85.5% for conventional TBNA), EBUS-TBNA had the highest yield of 74.5%, which was better than that of TBNA (48.4%, $P = .004$) and EBB (36.3%, $P < .0001$) but not TBLB (69.9%, $P = .54$). Addition of TBLB significantly enhanced the yield of EBUS-TBNA. However, these results must be viewed with caution because only enlarged right paratracheal and subcarinal lymph nodes typically accessible by conventional TBNA were sampled, and the authors were probably more experienced in conventional TBNA.

Compared with conventional bronchoscopic techniques for obtaining tissue, EBUS-TBNA provides safe and minimally invasive access to the mediastinal and hilar lymph nodes with a pooled diagnostic accuracy of 79.1%. It is therefore recommended that EBUS-TBNA be used for diagnosis in patients with suspected sarcoidosis with mediastinal and/or hilar adenopathy. However, fibrotic lymph nodes may be a challenge to obtain adequate tissue for diagnosis. Conventional bronchoscopic techniques such as TBLB and EBB will enhance the yield of EBUS-TBNA in selected patients.

10. In patients with suspected sarcoidosis with mediastinal and/or hilar adenopathy, we recommend that EBUS-TBNA be used for diagnosis (Grade 1C).

Diagnosis of TB

The increasing use of EBUS-TBNA has led to its application in the diagnosis of nonneoplastic diseases such as TB. This question focuses on the value of incorporating EBUS-TBNA when other modalities are not diagnostic for TB. Three studies met our inclusion criteria and assessed the diagnostic yield of EBUS for the diagnosis of TB, although the diagnostic accuracy of EBUS-TBNA was not always the primary outcome measure. Garcia-Olivé et al[76] and Cetinkaya et al[84] analyzed the role of EBUS-TBNA for the assessment of mediastinal adenopathy with the majority of patients having a final diagnosis of lung cancer. Both studies had a high diagnostic yield (n = 10, 80%; n = 48, 79.2%), but the prevalence of TB was relatively low within the study population. Madan et al[80] reported their initial 1-year experience with EBUS-TBNA in a TB-endemic population. In their study, TB was diagnosed in nearly one-third of the patient population. Despite the fact that it was their early experience in EBUS-TBNA, Madan et al[80] achieved a high yield of 84.8% for the diagnosis of TB. In the first two studies, the diagnosis of TB was reached either by positive acid-fast bacilli smears on the aspirate or the presence of necrotizing granuloma in the setting of positive tuberculin skin test results and appropriate clinical context. Madan et al[80] used the same criteria plus the GeneXpert MTB-RIF test (Cepheid) for the diagnosis of TB.

Although we recommend that EBUS-TBNA be used for diagnosis in patients with suspected TB with mediastinal and/or hilar adenopathy, it must be noted that no single study assessed the role of EBUS-TBNA for the diagnosis of TB as the primary outcome measure. New technology such as EBUS-TBNA may not be readily available in developing countries where the prevalence of the disease is higher. Various diagnostic techniques are available for the diagnosis of TB and should be incorporated during the diagnostic evaluation.

11. In patients with suspected tuberculosis with mediastinal and/or hilar adenopathy who require lymph node sampling, we recommend that EBUS-TBNA be used for diagnosis (Grade 1C).

Diagnosis of Lymphoma

Patients with lymphoma can present with isolated mediastinal adenopathy in which mediastinoscopy, thoracoscopy, or thoracotomy may traditionally have been required to obtain tissue diagnosis. These surgical procedures require general anesthetic, and the

potential complications cannot be ignored. Conversely, EBUS-TBNA can sample mediastinal and/or hilar lymph nodes in a minimally invasive way. Currently available EBUS-TBNA needles can be used to provide only cytologic specimens. There is controversy regarding the role of small-volume specimens for establishing a diagnosis of lymphoma, with reported high discordance between cytologic specimens and histologic specimens. We therefore looked at the role of EBUS-TBNA in establishing the diagnosis of the various subtypes of lymphoma. Five studies with a total of 212 patients met our inclusion criteria and were assessed for diagnostic yield of EBUS for establishing a diagnosis of lymphoma.[85-89] All studies were retrospective case reviews of patients undergoing EBUS-TBNA for suspected lymphoma. Although the pooled diagnostic accuracy was 68.7% (95% CI, 61.9-75.5), there was heterogeneity across studies in the proportion of patients with de novo lymphoma vs relapsed lymphoma. More than one-half of the patients had a history of lymphoma in the studies by Iqbal et al[85] and Kennedy et al.[86] Both studies showed higher diagnostic yield for the diagnosis of relapsed lymphoma compared with de novo lymphoma. Interestingly, the study by Iqbal et al[85] had the lowest overall diagnostic accuracy (ie, 38%).

The definition of diagnosis of lymphoma was also not uniform across the five studies. The two studies demonstrating the highest yield (Kennedy et al[86] [91%] and Moonim et al[87] [89%]) included cases as diagnostic even when additional tissue sampling was necessary to subclassify their lymphoma necessary for clinical management. With the strict criterion of achieving a definitive diagnosis on the basis of a specimen obtained by EBUS-TBNA sufficient for clinical management, the diagnostic yield would drop to 72.7% and 79%, respectively.

Because treatment regimens for both non-Hodgkin's and Hodgkin's lymphoma depend on the specific subtype and histologic grade, a definitive diagnosis of lymphoma requires the evaluation of cell morphology, immunophenotype, and the overall architecture of the tissue. Diagnosis of Hodgkin's lymphoma by using cytologic samples is generally challenging, as Reed-Sternberg cells within the aspirates are usually scarce and evaluation of the overall background architecture is often impossible. This may explain the lower diagnostic yield in some of the studies.[11,15]

In some conditions, minimally invasive EBUS-TBNA may be the preferred modality over surgical intervention. For example, repeat mediastinoscopy or even surgical biopsy posttreatment for relapsed lymphoma can be challenging, with a lower diagnostic yield and higher complication rate. Although the diagnostic yield of EBUS-TBNA for the diagnosis of lymphoma is not as high as that known for lung cancer staging, we suggest that EBUS-TBNA can be used as an initial, minimally invasive diagnostic test.

12. In patients with suspected lymphoma, we suggest that EBUS-TBNA is an acceptable initial, minimally invasive diagnostic test (Ungraded Consensus-Based Statement).

Conclusions

This report provides an evidence-based approach to the technical aspects of EBUS-TBNA performance. Under the guidance of the CHEST methodologists, we applied a rigorous evidence-based process and explored all available literature on the chosen topics. For questions with an acceptable level of evidence, recommendations were developed with an assigned grade based on the strength and quality of the evidence. For questions that lacked sufficient data, a consensus-based statement was generated from the expert knowledge of the panelists who have extensive clinical expertise and considerable investigative research in EBUS-TBNA.

It is worthwhile to highlight a few findings of this report. First, based on our current knowledge, various procedural details surrounding EBUS-TBNA are unlikely to influence the diagnostic yield and are left to institutional practices and operators' preferences. Some aspects of EBUS-TBNA require minimal standards that should be considered by the proceduralists (eg, number of needed passes, training). Second, EBUS-TBNA is not only valuable in the diagnosis and staging of lung cancer but also in the investigation of sarcoidosis, TB, and lymphoma. Third, additional research is needed to address some of the questions we examined and found scant investigation, as well as to answer novel intriguing questions.

Because EBUS technology will inevitably evolve and advance, this report should serve as a starting point for seeking and summarizing knowledge about the optimal performance of EBUS-TBNA and should be updated regularly.

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Author contributions: M. M. W. is the chair of the guideline and drafted text for the Introduction, Conclusion and Balloon Use section, oversaw the drafting of all sections in the manuscript, synthesized all of the sections in the final manuscript, and reviewed and provided feedback on the entire manuscript. F. H. drafted the supporting text for the Rapid On-Site Evaluation section. K. Y. drafted the supporting text for the Diagnosis of Sarcoidosis, Diagnosis of Tuberculosis and Diagnosis of Lymphoma section. R. W. S drafted the supporting text for the Suction and the Assessing EBUS-TBNA Operator Skill sections. L. Y. drafted the supporting text for the Sedation and Molecular Markers sections. M. C. drafted the supporting text for the Artificial Airways and Scope Insertion sections. C. L. drafted the supporting text for the Simulation Training section. K. R. C. served as a liaison to the guideline committee, provided guidance during the development process and provided feedback on the entire manuscript. S. P. conducted systematic reviews for all of the sections, advised the committee on drafting recommendations and supporting text, assisted with manuscript preparation and reviewed and provided feedback on the entire manuscript. G. A. S. drafted the supporting text for the Ultrasonographic Features section. D. J. F. drafted the supporting text for the Needle Size and Number of Needle Passes sections. All authors participated in the systematic review process and in writing the recommendations.

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Additional information: The e-Tables and e-Appendix can be found in the Supplemental Materials section of the online article.

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