Diagnostic Accuracy of Endobronchial Ultrasound-Guided Transbronchial Needle Biopsy in Mediastinal Lymphadenopathy: A Systematic Review and Meta-analysis

Subhash Chandra MD, Mahendra Nehra MD, Dipti Agarwal MD, and Anant Mohan MD

OBJECTIVE: To perform a systematic review and meta-analysis of prospectively conducted studies to define diagnostic performance of endobronchial ultrasound-guided transbronchial needle biopsy (EBUS-TBNB) in mediastinal and hilar lymphadenopathy. METHODS: A comprehensive search was performed using the Embase, Ovid Medline, Ovid Medline In-Process and Other Non-Indexed Citations, All Evidence Based Medicine Reviews—Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CCTR), Health Technology Assessment (HTA), and SCOPUS databases, in the second week of November 2010. Studies were selected in 2 phases by 2 reviewers, independently. Data extraction from each study was performed using a standardized data extraction form. Quality assessment of study methodology was done using a checklist that was developed based on a Quality Assessment of Diagnostic Accuracy Studies tool and the nature of the test. Using the 2 × 2 tables, we computed the sensitivity, specificity, and likelihood ratios. RESULTS: The 14 studies included for quantitative data synthesis had a pooled cohort of 1,658 patients, from 8 different countries. The EBUS-TBNB had excellent pooled specificity of 100% (95% CI 0.90–1.00) and a positive likelihood ratio of 5.1 (95% CI 2.7–9.7). The pooled sensitivity was 0.92 (95% CI 0.91–0.93), and the pooled negative likelihood ratio was 0.13 (95% CI 0.09–0.19). The sensitivity of this intervention was not dependent on rapid on-site evaluation use or size of needle used. The pooled diagnostic odds ratio was 62.7 (95% CI 25.7–153.0). Only one major complication was reported, which resulted in early termination of the procedure. CONCLUSIONS: Evidence of moderate quality confirms the high diagnostic performance of EBUS-TBNB for mediastinal and hilar lymphadenopathy, both in malignant and non-malignant conditions. Available evidence also demonstrates the safety of this procedure. *Key words: endobronchial ultrasound-guided transbronchial needle biopsy; mediastinal lymphadenopathy; diagnostic accuracy.* [Respir Care 2012; 57(3):384–391. © 2012 Daedalus Enterprises]

Introduction

Endobronchial ultrasound-guided transbronchial needle biopsy (EBUS-TBNB) is a relatively new diagnostic procedure gaining popularity worldwide for the purpose of investigating mediastinal lymphadenopathy in both malignant as well as non-malignant etiologies.[1–3] It is also used for staging and classification of lung cancer.[4]

Drs Chandra and Agarwal are affiliated with the Department of Emergency Medicine, College of Medicine, Mayo Clinic, Rochester, Minnesota. Dr Chandra is also affiliated with the Department of Multidisciplinary Epidemiology and Translational Research in Intensive Care, College of Medicine, Mayo Clinic, Rochester, Minnesota. Dr Nehra is affiliated with the Department of Medicine, University of Texas Southwestern Medical Center, Dallas, Texas. Dr Mohan is affiliated with the Division of Pulmonary and Critical Care, Department of Medicine, All India Institute of Medical Sciences, New Delhi, India.

Supplementary material related to this paper is available at http://www.rcjournal.com.

The authors have disclosed no conflicts of interest.

Correspondence: Anant Mohan MD, Associate Professor, Division of Pulmonary and Critical Care, Department of Medicine, All India Institute of Medical Sciences, New Delhi, India. E-mail: anantmohan@yahoo.com.

DOI: 10.4187/respcare.01274

Diagnosis of mediastinal lymphadenopathy can be made by both noninvasive and invasive techniques.[5,6] Noninvasive methods include imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and PET-CT. However, these modalities are devoid of sufficient sensitivity, specificity, and accuracy.[7] For definitive etiological confirmation, a pathological specimen is required.[8] Hence, invasive procedures like bronchoscopy, mediastinoscopy, traditional TBNB and EBUS-TBNB are performed.[9,10]

Several studies have reported the diagnostic performance of EBUS-TBNB in mediastinal lymphadenopathy, but there is no single large multicenter study published to date. In this project, we aimed to perform a systematic review and meta-analysis of prospective studies to define diagnostic performance of EBUS-TBNB in mediastinal and hilar lymphadenopathy, both in malignant and non-malignant etiologies. We calculated pooled sensitivity, specificity, and likelihood ratios to report diagnostic accuracy of EBUS-TBNB.

QUICK LOOK

Current knowledge

Endobronchial ultrasound guided-transbronchial needle biopsy (EBUS-TBNB) is a common diagnostic technique in mediastinal and hilar lymphadenopathy.

What this paper contributes to our knowledge

EBUS-TBNB has an acceptable safety profile and aids in reaching a definitive diagnosis in mediastinal and hilar lymphadenopathy for malignant and non-malignant disorders.

Methods

Eligibility Criteria

We included studies that prospectively defined diagnostic performance of EBUS-TBNB in patients with mediastinal and hilar lymphadenopathy. Studies were eligible if they had a prospective study design, were based on original research, reported diagnostic performance of EBUS-TBNB, and full text was available in English. We excluded retrospective studies, case reports, studies not based on original research, studies based on less than 20 patients, and studies where full text was not available in the English language.

Search Strategy

A comprehensive search strategy was designed and performed by the primary investigator (SC), with input from the clinical content expert (AM). The electronic search included the following electronic databases:

- Embase: 1988 to July 2010 week 2
- Ovid Medline: 1996 to July 2010 week 1
- Ovid Medline In-Process and Other Non-Indexed Citations: July 14, 2010
- All Evidence Based Medicine Reviews—Cochrane Database of Systematic Reviews
- American College of Physicians Journal Club
- Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Central Register of Controlled Trials (CCTR)
- Health Technology Assessment (HTA)
- SCOPUS: 1960 to July 14, 2010

The search was performed in the second week of November 2010 (see the supplementary materials at http://www.rcjournal.com). The following key words were used for search with using different operators (AND, OR, and NOT): "EBUS," "endobronchial ultrasound," "lymph node," and "lymphadenopathy." No language restrictions were applied to the search strategy, but the search was limited to adult human subjects. Conference proceedings from the American Thoracic Society, *Chest*, and the European Respiratory Society from 2007 to 2009, and reference lists of eligible articles were hand searched, and we consulted content experts to identify additional published reports (AM).

Study Selection

Two investigators (SC, MN) independently screened the titles and abstracts of all identified records (phase I) for predefined inclusion and exclusion criterion. Full text of records was obtained on agreement between these 2 investigators on possible inclusion in the review. The same 2 investigators then independently assessed the eligibility of each full text (phase II). Cohen's kappa was used to measure chance-corrected agreement between reviewers for each phase of study selection. All the disagreements were resolved by consensus.

Quality Assessment

A methodology quality assessment checklist for this study was developed considering the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool and the nature of the diagnostic intervention.[11] The QUADAS is a well validated quality assessment tool that covers the majority of bias and variability in methodology quality assessment for studies reporting diagnostic performance of a diagnostic test. Consecutive sampling and prospective study design were included in the methodology quality assessment checklist to address selection bias.[12] Since insuffi-

Table 1. Quality Assessment Criteria*

Was the spectrum of patients representative of the patients who will receive the test in practice?
Were the patients recruited prospectively?
Were patients recruited consecutively?
Was the execution of the index test described in sufficient detail to permit replication of the test?
Were the index test results interpreted without knowledge of the results of the reference standard?
Is the reference standard likely to correctly classify the target condition?
Was the reference test described explicitly?
Was the training level of the physician performing endobronchial ultrasound-guided transbronchial needle biopsy reported?
Was the reference standard independent of the index test?

* Each question was answered either yes or no/unclear.

cient and non-representative tissue sampling are the primary reasons for false negative results of TBNB and depend on physician experience, we included experience or expertise level of physician performed EBUS-TBNB for methodology quality assessment. The experience or expertise level was taken as reported by authors. The quality assessment criteria used are listed in Table 1. We have dropped a few of the items from the QUADAS tool. For example, item 2 in QUADAS (Were selection criteria clearly described?) was perceived as redundant and more of a reporting issue than methodology quality, and the first 3 items in our checklist cover subject selection explicitly. For this systematic review, the reference test was defined as combination of clinical follow-up, positive index test results, video-assisted thoracoscopy (VATS), mediastinoscopy, and open thoracotomy. Since the reference test was a combination of tests and follow-up, QUADAS item 4 (Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the 2 tests?) was also not included in our checklist. Two reviewers (SC, MN), working independently, assessed the quality of included studies, and disagreements were resolved by consensus. We dichotomized answers as "yes" and "no/unclear" for the kappa calculations. Studies scoring less than 50% (arbitrarily defined based on consensus among investigators) on the methodology quality assessment checklist were excluded from quantitative data synthesis.

Outcomes

Primary outcomes of interest of this study were number of true positives, false positives, false negatives, and true negatives on histological confirmation of tissue sample obtained from mediastinal or hilar lymphadenopathy using EBUS-TBNB. These numbers were either reported as is or were calculated from available data on diagnostic performance and number of subjects.

Data Extraction and End Points and Synthesis

Data exaction was done using a standardized data extraction form. The following data were extracted: author, country where study was performed, year of publication, study design, settings, subject selection, details of index (EBUS-TBNB) and reference test, diagnostic performance of index test, complications, feasibility of the index test, and other remarks made. Primary end points for diagnostic performance of EBUS-TBNB were true positive, true negative, false positive, and false negative, on a per-patient basis. If the data were not available in the original report or were unclear, we contacted the corresponding author for clarification. We used the following method for author contact: first, we sent an e-mail requesting primary data. If there was no response within 1 week, a second reminder e-mail was sent.

All the continuous data are presented as either mean with standard deviation or median with interquartile range, as reported in the primary study. Categorical data are presented as percent frequency of occurrence. Using the 2×2 tables, we computed sensitivity (true positive rate), specificity (true negative rate), and the likelihood ratios (the ratio of the probability of the specific test result in people who have the disease to the probability in people who do not) with 95% confidence intervals.[9] The diagnostic performance of the EBUS-TBNB was assessed using Meta-DiSc software (Unit of Clinical Biostatistics, Ramon y Cajal Hospital, Madrid, Spain). Meta-analyses were performed combining the sensitivities, specificities, and likelihood ratios of individual studies. Likelihood ratios were pooled using a random effect model (DerSimonian and Laird). Positive likelihood ratios > 10 and negative likelihood ratios < 0.1 are considered strong diagnostic evidence.[11] The I-square statistic was used to quantify statistical heterogeneity between studies.

Results

Study Selection

The comprehensive multiple database search produced 269 records, after de-duplication, 161 records were screened for study eligibility. Figure 1 demonstrates the flow of study selection. Phase I identified 25 potentially eligible studies (kappa = 0.65, 95% CI 0.50–0.81). For these 25 studies, full texts were obtained from the Mayo Clinic library. In phase II, a total of 14 studies were finalized to be included in this systematic review (kappa = 0.68, 95% CI 0.40–0.96). These 14 studies were included for methodology quality assessment and quantitative data synthesis.

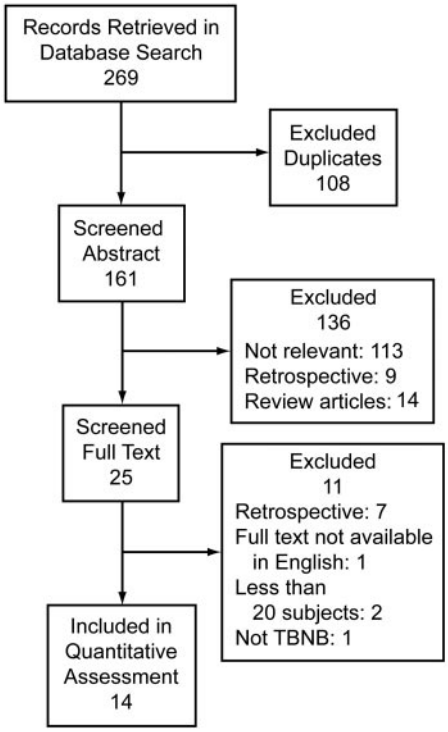

Fig. 1. Schematic presentation of study selection flow.

Characteristics of Included Studies

The 14 studies included for quantitative data synthesis had a pooled cohort of 1,658 patients, from 8 different countries. Table 2 describes important characteristics of the included studies. All the studies were conducted in urban academic settings. The most commonly used needle size was 22; two studies used needle size of 19, one study used 21, and another study did not report the needle size.[15,19,20,21] Study subject selection and reference test varied between studies. Most studies included patients with lymph nodal size > 1 cm on CT scan as one of the inclusion criteria for performing EBUS. In most studies, TBNB was performed under real-time guidance, except in 3 studies where TBNB was performed after initial localization using EBUS.[17,19,20] In included studies, a major complication was reported in one patient. This patient had hyperemia and edema of the airway and developed stridor and hypoxia during the procedure, which warranted early termination of the procedure.[16] Minor complications like self-limiting hemorrhage were reported in 2 patients by Kanoh et al[19] and one patient by Sun et al.[23] The number of passes performed per lymph node was reported in 5 studies.[1,13,21-23] The weighted mean number of passes per lymph node was 2, ranging from 1.2 to 3.8. Rapid on-site evaluation (ROSE) of the biopsy material was performed in only 5 studies.[13–16,22]

Methodology Quality Assessment

The score obtained by each study on the quality assessment checklist is described in Table 1. All the studies prospectively enrolled a consecutive cohort of patients. In all the studies, the results of EBUS-TBNB were interpreted without knowledge of the results of the reference standard. Except for 3 studies where the reference standard was independent of the index test, EBUS-TBNB was part of the reference standard in all the studies.[1,9,23] In one study, the reference standard was unclear.[15]

Diagnostic Performance of EBUS-TBNB

The EBUS-TBNB had pooled specificity of 1.00 (95% CI 0.90–1.00) and the pooled sensitivity was 0.92 (95% CI 0.91–0.93) ranging from 69.0% in the study by Wallace et al[4] to 100% in the study by Garwood et al[16] (Table 3). The pooled positive likelihood ratio was 5.1 (95% CI 2.7–9.7), and the pooled negative likelihood ratio was 0.13 (95% CI 0.09–0.19) (Fig. 2). The pooled diagnostic odds ratio was 62.7 (95% CI 25.7–153.0).

Heterogeneity and Subgroup Analysis

On I-square statistics, specificity (chi-square = 0.00, $P = 1.00$) and positive likelihood ratio (Cochran Q = 12.5, $P = .49$) did not demonstrate significant heterogeneity, and negative likelihood ratio showed marginal inconsistency (Cochran Q = 24.1, $P = .03$) (see Fig. 2), but the sensitivity had shown significant heterogeneity (I-square = 71.4%, chi-square = 50.6, $P = < .001$). To investigate heterogeneity, subgroup analysis was done by grouping studies based on needle size and ROSE. Pooled sensitivity was higher in the studies that used ROSE than those that did not (0.94, 95% CI 0.91–0.96, versus 0.92, 95% CI 0.90–0.94). This difference did not, however, reach statistical significance, $P = .14$. There was no difference in sensitivities obtained by using 19 or 21 versus 22 gauge needles. The study by Wallace et al[4] has reported sensitivity of 0.69. In this study, patients with suspicion of lung cancer on CT were enrolled irrespective of mediastinal lymphadenopathy. The results of this study contributed to the heterogeneity in pooled sensitivity, but exclusion of this study did not eliminate the heterogeneity completely. Another subgroup analysis was performed based on subjects with benign versus predominantly malignant etiologies for lymphadenopathy. Only 2 studies[16,24] have included patients only with benign etiology of lymphadenopathy. The pooled sensitivity in this group was 0.93 (0.86–0.97), with pooled positive likelihood ratio of 7.2 (1.2–43.0) versus 0.92 (0.90–0.93) and 4.9 (2.4–9.9), respectively, for studies including predominantly malignant etiologies. This comparison is not opti-

Table 2. Characteristics of Included Studies

First Author	Year	Country	Quality Assessment Score	Needle Size	*n*	Mean or Median Age (y)	Subject Inclusion	Reference Test
Yasufuku[13]	2004	Japan	6	22	70	64	All patients having mediastinal and/or hilar lymphadenopathy of > 1 cm and with known or suspected malignancy	Combination of EBUS-TBNB, surgical results, and/or clinical follow-up
Ernst[9]	2009	United States	9	22	188	56	All patients with lung masses suspicious for cancer and lymphadenopathy limited to a hilum	Histopathological examination on thoracotomy, thoracoscopy, or during clinical follow-up for 6 months
Fielding[14]	2009	Australia	5	22	68	65	All patients referred with a pulmonary mass and hilar or mediastinal lymph node on CT	Combination of EBUS-TBNB, surgical sampling at thoracotomy, and radiological follow-up
Garcia-Olivé[15]	2009	Spain	5	21	171	63	All patients referred for lung cancer staging who had short axis diameter of > 1 cm on CT in a month prior	Unclear
Garwood[16]	2007	United States	5	22	50	60	Consecutive patients who were suspected to have sarcoidosis, based on chest radiograph or CT, without clinical suspicion of malignancy or infection	Combination of histology samples (obtained by EBUS-TBNB, transbronchial lung biopsy, endobronchial biopsy, and supraclavicular lymph node biopsy) revealing characteristic granulomas or clinical/radiologic follow-up consistent with sarcoidosis
Herth[17]	2003	United States	7	22	242	60	All patients with hilar or mediastinal lymphadenopathy of unknown origin or needing lung cancer staging, especially to exclude N3 nodes	Combination of EBUS-TBNB and surgical biopsy
Herth[18]	2006	Germany	7	22	502	59	All patients with hilar or mediastinal lymphadenopathy who had diagnosis of enlarged lymph nodes of unknown origin or needed lung cancer staging, especially the exclusion of N3 nodes	Combination of EBUS-TBNB and surgical biopsy
Kanoh[19]	2005	Japan	6	19	25	64	All patients who presented with hilar and/or mediastinal lymphadenopathy	Combination of surgical resection and EBUS-TBNB
Plat[20]	2006	Belgium	7	ND	24	65	All patients with fluorodeoxyglucose (FDG)–positron emission tomography (PET) positive lymph nodes	Combination of EBUS-TBNB, surgical sampling through mediastinoscopy, and clinical follow-up
Tremblay[21]	2009	Canada	5	19	24	40	All patients ≥16 y old with CT-confirmed mediastinal or hilar adenopathy (short axis, > 1 cm), clinically suspected sarcoidosis	Combination of EBUS-TBNB and benign clinical course with decisions not to pursue more invasive diagnostic testing
Vilmann[1]	2005	Denmark	6	22	31	61	All patients who were referred for staging of lung cancer or diagnosis of mediastinal lesion based on suspected lung cancer	Thoracotomy and clinical follow-up
Wallace[4]	2008	United States	6	22	138	69	All patients who had known or suspected lung cancer on the basis of lung or mediastinal abnormality on CT and had no proven extra-thoracic metastasis, irrespective of lymph node size	Combination of EBUS-TBNB mediastinoscopy/thoracoscopy, open surgical biopsy, or any mode of histological confirmation
Wong[22]	2007	Japan/Germany	6	22	65	45	All patient with hilar or mediastinal lymph node enlargement (short axis > 1 cm) suggesting sarcoidosis	Combination of mediastinoscopy, clinical follow-up, and video-assisted thoracoscopic surgery
Sun[23]	2010	China	7	22	22	60	All patients whose CT revealed mediastinal/hilar lymph node enlargement (> 1 cm) and/or intrathoracic peritracheal or peribronchial masses	Combination of thoracotomy, mediastinoscopy, or thoracoscopy, or by clinical follow-up

EBUS-TBNB = endobronchial ultrasound-guided transbronchial needle biopsy
CT = computed tomogram
ND = no data

mal, as one group had 2 studies versus 12 in the other group. At the same time, a predominantly malignant etiology group of studies has included benign conditions.

Discussion

We conducted a comprehensive systematic review and meta-analysis of studies that defined diagnostic performance of EBUS-TBNB in mediastinal and hilar lymphadenopathy, prospectively. The studies included in this analysis were ranked medium to high on a quality assessment criteria checklist, indicating that the primary studies were of moderate to good methodological quality. Pooled analysis of diagnostic performance demonstrated that the EBUS-TBNB is 100% specific and 92% sensitive for his-

Table 3. Sensitivity and Specificity of Individual Studies and Pooled

First Author	Sensitivity	95% CI	Specificity	95% CI
Yasufuku[13]	0.971	0.901–0.997	1.000	0.001–1.000
Ernst[9]	0.930	0.884–0.962	1.000	0.025–1.000
Fielding[14]	0.912	0.818–0.967	1.000	0.001–1.000
Garcia-Olivé[15]	0.942	0.895–0.972	1.000	0.001–1.000
Garwood[16]	1.000	0.916–1.000	1.000	0.631–1.000
Herth[17]	0.860	0.804–0.905	1.000	0.590–1.000
Herth[18]	0.936	0.911–0.956	1.000	0.001–1.000
Kanoh[19]	0.870	0.751–0.946	1.000	0.001–1.000
Plat[20]	1.000	0.839–1.000	1.000	0.292–1.000
Tremblay[21]	0.958	0.789–0.999	1.000	0.001–1.000
Vilmann[1]	0.857	0.637–0.970	1.000	0.631–1.000
Wallace[4]	0.690	0.529–0.824	1.000	0.962–1.000
Wong[22]	0.875	0.768–0.944	1.000	0.025–1.000
Sun[23]	0.967	0.885–0.996	1.000	0.001–1.000
Pooled	0.918	0.903–0.931	1.000	0.971–1.000
	Heterogeneity chi-square = 50.65		Heterogeneity chi-square = 0.00	
	Degrees of freedom= 13		Degrees of freedom= 13	
	$P < .001$		$P = 1.00$	
	Inconsistency (I-square) = 74.3%		Inconsistency (I-square) = 0.0%	

tological confirmation of diagnosis in mediastinal and hilar lymphadenopathy. Significant inconsistency existed in the sensitivity of EBUS-TBNB, which was not found to be dependent on ROSE use or size of needle used. The selection of patients based on presence of mediastinal or hilar lymphadenopathy on radiographic examination seemed to be associated with higher sensitivity, but a definitive conclusion could not be made since only one study had an un-selected population. The existence of heterogeneity despite subgroup analysis based on ROSE and needle size indicates the presence of other derivers of inconsistency in the results. These potential derivers could be number of passes per lymph node, location, and lymph nodes. Analysis considering these variables was not possible in this review due to inconsistency in reporting of results.

The diagnostic yield of EBUS-TBNB had shown to increase with number of passes, till 3–5 passes per lymph node, with minimal increase thereafter.[16,25] Hence, 3 passes per lymph node should be an acceptable practice. EBUS-TBNB possesses all the advantages (mortality and morbidity associated with surgery exploration and use of general anesthesia, time, etc) of being minimally invasive when compared to surgical intervention like mediastinoscopy or thoracotomy. Amount of sedation required was marginally higher for EBUS-TBNB than standard TBNB and added a few extra minutes in the procedure.[17,20,21] EBUS-TBNB has extremely high patient satisfaction among bronchoscopic interventions. In a recent study, where patient satisfaction was measured by patient willingness to return for the procedure if required in the future, on a self administered questionnaire, after 3–4 hours of procedure, 98% choose "definitely return" and 2% "probably."[25]

Strength and Limitations

Strengths of this study include a search strategy that involved 5 electronic databases, searching the bibliographies of included articles, and contact with content experts. This minimized the potential for publication bias, but we cannot exclude it completely, and no tests were attempted to quantify publication bias. We also used sound methodology in conducting the review, including assessment of inter-rater reliability for study selection. The study

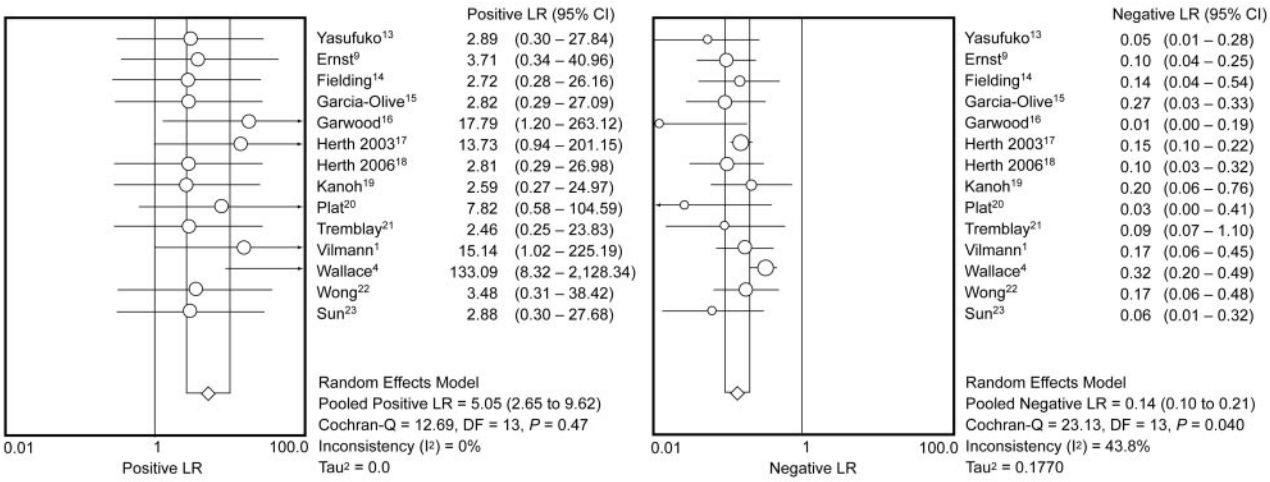

Fig. 2. Positive and negative likelihood ratios for each study and pooled values. LR = likelihood ratio.

is limited by the relatively small number of studies included in the review. We have performed subgroup analysis based on ROSE and needle size, but subgroup analysis based on lymph node size, station, and number of passes was limited by inconsistency in reporting.

External Validity, Clinical Implications, and Future Research

The review included 14 validation studies conducted in 8 different countries, encompassing 1,658 patients. That the statistical estimates were derived from a large sample size including different patient populations suggests a high degree of external validity of the findings in this review. One of the major limitations of existing evidence on diagnostic accuracy of EBUS-TBNB is that most studies have included the results of the index test into the reference standard test. This overestimates the diagnostic performance. In the future, further studies are required in which the diagnostic performance of EBUS-TBNB is compared to the gold standard, histopathological confirmation of diagnosis. Also, a blinded multicenter randomized controlled trial will be helpful in accurate estimation of the diagnostic performance on EBUS-TBNB.

Conclusions

Evidence of moderate quality confirms excellent performance and safety profile of EBUS-TBNB in reaching a definitive diagnosis in mediastinal and hilar lymphadenopathy for other malignant and non-malignant disorders. Diagnostic performance was independent of ROSE by a cytopathologist and needle size used. The presence of inconsistency in sensitivity between different studies mandates a methodologically sound large multicenter randomized controlled trial for more accurate estimation of diagnostic performance.

REFERENCES

1. Vilmann P, Krasnik M, Larsen SS, Jacobsen GK, Clementsen P. Transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy: a combined approach in the evaluation of mediastinal lesions. Endoscopy 2005; 37(9):833-839.
2. Natu S, Hoffman J, Siddiqui M, Hobday C, Shrimankar J, Harrison R. The role of endobronchial ultrasound guided transbronchial needle aspiration cytology in the investigation of mediastinal lymphadenopathy and masses, the North Tees experience. J Clin Pathol 2010;63(5):445-451.
3. Jacob-Ampuero MP, Haas AR, Ciocca V, Bibbo M. Cytologic accuracy of samples obtained by endobronchial ultrasound-guided transbronchial needle aspiration at Thomas Jefferson University Hospital. Acta Cytol 2008;52(6):687-690.
4. Wallace MB, Pascual JMS, Raimondo M, Woodward TA, McComb BL, Crook JE, et al. Minimally invasive endoscopic staging of suspected lung cancer. JAMA 2008;299(5):540-546.
5. Hoerbelt R, Keunecke L, Grimm H, Schwemmle K, Padberg W. The value of a noninvasive diagnostic approach to mediastinal masses. Ann Thorac Surg 2003;75(4):1086-1090.
6. Porte H, Roumilhac D, Eraldi L, Cordonnier C, Puech P, Wurtz A. The role of mediastinoscopy in the diagnosis of mediastinal lymphadenopathy. Eur J Cardiothorac Surg 1998;13(2):196-199.
7. Gould MK, Kuschner WG, Rydzak CE, Maclean CC, Demas AN, Shigemitsu H, et al. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. Ann Intern Med 2003;139(11):879-892.
8. Whitson BA, Groth SS, Maddaus MA. Surgical assessment and intraoperative management of mediastinal lymph nodes in non-small cell lung cancer. Ann Thorac Surg 2007;84(3):1059-1065.
9. Ernst A, Eberhardt R, Krasnik M, Herth FJF. Efficacy of endobronchial ultrasound-guided transbronchial needle aspiration of hilar lymph nodes for diagnosing and staging cancer. J Thorac Oncol 2009;4(8):947-950.
10. Newman LS, Rose CS, Maier LA. Sarcoidosis. N Engl J Med 1997; 336(17):1224-1234.
11. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003;3:25.
12. Meads CA, Davenport CF. Quality assessment of diagnostic before-after studies: development of methodology in the context of a systematic review. BMC Med Res Methodol 2009;9:3.
13. Yasufuku K, Chiyo M, Sekine Y, Chhajed PN, Shibuya K, Iizasa T, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes. Chest 2004; 126(1):122-128.
14. Fielding D, Windsor M. Endobronchial ultrasound convex-probe transbronchial needle aspiration as the first diagnostic test in patients with pulmonary masses and associated hilar or mediastinal nodes. Intern Med J 2009;39(7):435-440.
15. Garcia-Olivé I, Monsó E, Andreo F, Sanz J, Castellà E, Llatjós M, et al. Sensitivity of linear endobronchial ultrasonography and guided transbronchial needle aspiration for the identification of nodal metastasis in lung cancer staging. Ultrasound Med Biol 2009;35(8): 1271-1277.
16. Garwood S, Judson MA, Silvestri G, Hoda R, Fraig M, Doelken P. Endobronchial ultrasound for the diagnosis of pulmonary sarcoidosis. Chest 2007;132(4):1298-1304.
17. Herth FJ, Becker HD, Ernst A. Ultrasound-guided transbronchial needle aspiration: an experience in 242 patients. Chest 2003;123(2): 604-607.
18. Herth FJ, Eberhardt R, Vilmann P, Krasnik M, Ernst A. Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. Thorax 2006;61(9): 795-798.
19. Kanoh K, Miyazawa T, Kurimoto N, Iwamoto Y, Miyazu Y, Kohno N. Endobronchial ultrasonography guidance for transbronchial needle aspiration using a double-channel bronchoscope. Chest 2005; 128(1):388-393.
20. Plat G, Pierard P, Haller A, Hutsebaut J, Faber J, Dusart M, et al. Endobronchial ultrasound and positron emission tomography positive mediastinal lymph nodes. Eur Respir J 2006;27(2):276-281.
21. Tremblay A, Stather DR, MacEachern P, Khalil M, Field SK. A randomized controlled trial of standard vs endobronchial ultra-

sonography-guided transbronchial needle aspiration in patients with suspected sarcoidosis. Chest 2009;136(2):340-346.
22. Wong M, Yasufuku K, Nakajima T, Herth FJ, Sekine Y, Shibuya K, et al. Endobronchial ultrasound: new insight for the diagnosis of sarcoidosis. Eur Respir J 2007;29(6):1182-1186.
23. Sun J, Han B, Zhang J, Zhao H, Qi D, Shen J, et al. Role of endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of bronchogenic carcinoma. Zhongguo Fei Ai Za Zhi 2010;13(5):432-437. *Article in Chinese.*
24. Wong MK, Wong MP, Lam DC, Sihoe A, Cheng LC, Lam B, et al. Endobronchial ultrasound for diagnosis of synchronous primary lung cancers. Lung Cancer 2009;63(1):154-157.
25. Lee HS, Lee GK, Lee HS, Kim MS, Lee JM, Kim HY, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal staging of non-small cell lung cancer: how many aspirations per target lymph node station? Chest 2008;134(2):368-374.
26. Steinfort DP, Irving LB. Patient satisfaction during endobronchial ultrasound-guided transbronchial needle aspiration performed under conscious sedation. Respir Care 2010;55(6):702-706.