# Utility and Safety of Endoscopic Ultrasound With Bronchoscope-Guided Fine-Needle Aspiration in Mediastinal Lymph Node Sampling: Systematic Review and Meta-Analysis

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**BACKGROUND: The use of endoscopic ultrasound with bronchoscope-guided fine-needle aspiration (EUS-B-FNA) has been described in the evaluation of mediastinal lymphadenopathy. Herein, we conduct a meta-analysis to estimate the overall diagnostic yield and safety of EUS-B-FNA combined with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), in the diagnosis of mediastinal lymphadenopathy. METHODS: The PubMed and EmBase databases were searched for studies reporting the outcomes of EUS-B-FNA in diagnosis of mediastinal lymphadenopathy. The study quality was assessed using the QualSyst tool. The yield of EBUS-TBNA alone and the combined procedure (EBUS-TBNA and EUS-B-FNA) were analyzed by calculating the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio for each study, and pooling the study results using a random effects model. Heterogeneity and publication bias were assessed for individual outcomes. The additional diagnostic gain of EUS-B-FNA over EBUS-TBNA was calculated using proportion meta-analysis. RESULTS: Our search yielded 10 studies (1,080 subjects with mediastinal lymphadenopathy). The sensitivity of the combined procedure was significantly higher than EBUS-TBNA alone (91% vs 80%, $P = .004$), in staging of lung cancer (4 studies, 465 subjects). The additional diagnostic gain of EUS-B-FNA over EBUS-TBNA was 7.6% in the diagnosis of mediastinal adenopathy. No serious complication of EUS-B-FNA procedure was reported. Clinical and statistical heterogeneity was present without any evidence of publication bias. CONCLUSIONS: Combining EBUS-TBNA and EUS-B-FNA is an effective and safe method, superior to EBUS-TBNA alone, in the diagnosis of mediastinal lymphadenopathy. Good quality randomized controlled trials are required to confirm the results of this systematic review.** *Key words: EBUS; EUS; tuberculosis; TBNA; sarcoidosis; lung cancer; transbronchial needle aspiration.* [Respir Care 2015;60(7):1040–1050. © 2015 Daedalus Enterprises]

## Introduction

Both endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) enable real-time aspiration of mediastinal lesions under direct vision.[1-5] The 2 procedures have complementary access to the mediastinum.[6-9] Although EBUS-TBNA provides an easy access to pretracheal and right paratracheal lesions, EUS-FNA is useful for accessing the inferior mediastinum, the left paratracheal area, and some areas of the aortopulmonary window. In a meta-analysis, the combination of the 2 procedures was found to provide greater sensitivity than either procedure alone in mediastinal stag-

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The authors have disclosed no conflicts of interest.

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DOI: 10.4187/respcare.03779

ing of lung cancer.[10] EBUS-TBNA and EUS-FNA are conventionally performed using a dedicated echobronchoscope and echoendoscope, respectively. In the former, the access to mediastinal lymph nodes is transtracheal or transbronchial, whereas the latter requires a transesophageal route. While EBUS-TBNA is generally performed by pulmonary physicians or thoracic surgeons, EUS-FNA is largely performed by gastroenterologists. This increases the cost, as well as waiting times, for patients requiring both procedures.

Hwangbo et al[11] have reported the use of the echobronchoscope for carrying out transesophageal needle aspiration, termed as endoscopic ultrasound with bronchoscope-guided fine-needle aspiration (EUS-B-FNA). We have also described our initial experience with this technique recently in unselected subjects with mediastinal lymphadenopathy.[12] In this study, we perform a systematic review and meta-analysis on the utility and safety of EUS-B-FNA in the diagnosis of mediastinal lymph node enlargement.

**QUICK LOOK**

**Current knowledge**

The combination of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) provides greater sensitivity than either procedure alone. The use of the EBUS scope for performing EUS-FNA has been termed endoscopic ultrasound with bronchoscope-guided FNA (EUS-B-FNA).

**What this paper contributes to our knowledge**

The results of this study suggest that combining EUS-B-FNA with EBUS-TBNA is an effective and safe method, superior to EBUS-TBNA alone, in the diagnosis of mediastinal lymphadenopathy.

## Methods

### Search Strategy

We first searched the PubMed and EmBase databases for any systematic review on EUS-B-FNA; no such citation was found. Next, all the authors independently searched the PubMed and EmBase databases for relevant studies published between 2004 and May 2014 describing the diagnostic value of EUS-B-FNA in subjects with mediastinal lymphadenopathy using the following search terms: (ebus OR endobronchial ultrasound OR endobronchial ultrasonography OR eus OR echoendoscope OR endoscopic ultrasonography OR endoscopic ultrasound OR bronchoscopic ultrasound OR esophageal ultrasound OR ultrasound bronchoscope OR ultrasonic bronchoscope) AND (tbna OR tena OR needle aspiration OR fna). From the EmBase database, we included citations under only 2 categories: articles and articles in press. We reviewed the list of references of original studies, editorials, and reviews; and also sifted through our personal files. We excluded the following studies: (1) case reports, abstracts, comments, editorials, and reviews; (2) studies describing the combined use of EUS-FNA and EBUS-TBNA but not performed with the same echobronchoscope; (3) studies describing EUS-B-FNA in $\leq 20$ subjects; (4) studies describing the transesophageal use of echoendoscope for sampling lesions other than those in the mediastinum.

### Initial Review of Studies

The database thus created from the electronic searches was assimilated in the reference manager package Endnote X7 (Thomson Reuters, New York, New York), and all duplicate citations were discarded. Two authors (SD, RA) screened these citations by review of the title and abstract to identify the relevant studies. Any disagreement was resolved by discussion between the authors. This database was then scrutinized again to include only primary articles. The full text of each of these studies was obtained and reviewed in detail.

### Data Abstraction

Data were entered into a standard data extraction form. The following items were extracted: (1) publication details (authors, year of publication, and other citation particulars including the country where the study was conducted); (2) study design (prospective or retrospective); (3) aim of the study, number of subjects, and inclusion criteria; (4) the nature of the operators (whether surgeons, pulmonary physicians, or gastroenterologists), positioning of the patient during the procedure, and the type of sedation used; (5) stations sampled, respective number of subjects and/or lymph nodes assessed by EBUS-TBNA and EUS-B-FNA; (6) size of lymph nodes on chest computed tomogram and/or EBUS and/or endoscopic ultrasound with an echobronchoscope (EUS-B); (7) diameter of EBUS-TBNA needle, number of passes made through EBUS/EUS-B, and availability of rapid on-site cytological examination; (8) the duration of the EBUS-TBNA and EUS-B-FNA procedures; (9) the sensitivity and specificity of EBUS-TBNA, EUS-B-FNA, and the combined procedure; (10) the additional yield of EUS-B-FNA, if reported; (11) reasons for performing EUS-B-FNA; and (12) complications associated with the procedure.

### Assessment of Study Quality

The quality and validity of each study incorporated in this meta-analysis was assessed using the QualSyst tool for qualitative studies.[13] This instrument is comprised of 10 questions each, with scores ranging from 0 to 2 and the highest total score being 20. Each article was independently adjudged by 2 authors (SD, RA) for the stated criteria. Weighted Cohen's kappa co-efficient was used to define the inter-observer agreement for selection of studies.

### Statistical Analysis

The statistical software packages Meta-Disc 1.4 (Ramon Cajal Hospital, Barcelona, Spain) and StatsDirect 2.8.0 (StatsDirect, Cheshire, United Kingdom) were used to perform all the statistical analyses. The analyses performed in this study are on a per patient basis (and not per lymph node), and the test performance characteristics were derived from the raw data of each study.

### Determination of the Pooled Effect

We analyzed the utility of EUS-B-FNA by calculating the sensitivity, specificity, positive likelihood ratio (PLR), negative LR (NLR), and diagnostic odds ratio (DOR; PLR/NLR) of individual studies for EBUS-TBNA alone and the combined procedure (EBUS-TBNA plus EUS-B-FNA). Sensitivity and specificity were pooled using the fixed effects model,[14] whereas the PLR, NLR, and DOR were pooled using the DerSimonian-Laird random effects model to derive a pooled estimate with 95% CI.[15,16]

The additional diagnostic gain with EUS-B-FNA was analyzed by calculating the proportions for the individual studies ($n/N$, where $n$ is the additional gain and $N$ is the total number of subjects evaluated).[17,18] The proportions were pooled using a DerSimonian random effects model, in the presence of significant heterogeneity.

### Assessment of Heterogeneity

Heterogeneity for the individual outcomes was assessed using the $I^2$ test, which measures the extent of inconsistency among the results of the studies. An $I^2$ value $\geq 50\%$ indicates significant heterogeneity.[19] Heterogeneity was also assessed using the Cochran Q statistic, and a $P$ value $< 0.1$ was considered significant.[20]

### Estimation of Publication Bias

The presence of publication bias was evaluated using the funnel plot (log DOR on x-axis against standard error of DOR on y-axis).[21] Publication bias was also investigated using the Egger test[22] and the Begg-Mazumdar test.[23]

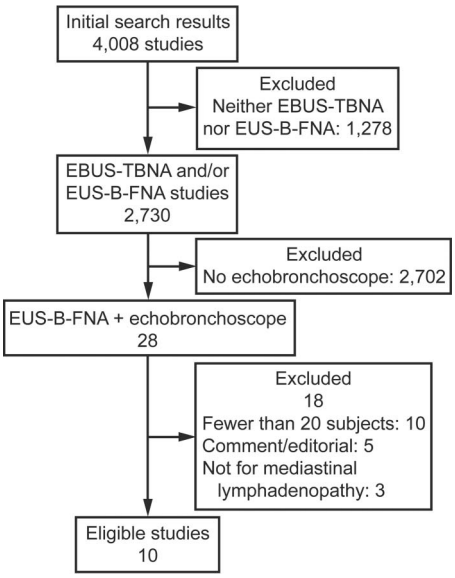


Fig. 1. Systematic review flow chart. EBUS = endobronchial ultrasound; EUS = endoscopic ultrasound; EUS-B-FNA = EUS with bronchoscope-guided fine needle aspiration.

The DOR for the individual studies were calculated using the Meta-Disc software, and then these were entered into the StatsDirect package to construct the funnel plots.

An institutional review board clearance was not required for this study, as this was a meta-analysis of published studies.

## Results

The initial database search retrieved a total of 4,008 citations, of which 10 studies (1,080 subjects) met our inclusion criteria (Fig. 1).[11,24-32] All studies were observational; 6 were prospective,[24,25,27,29,30,32] and 4 had a retrospective design (Table 1).[11,26,28,31] Five studies were aimed at mediastinal staging of lung cancer,[24-26,31,32] using a combination of EBUS-TBNA and EUS-B-FNA (Table 1). One study each was performed for the diagnosis of sarcoidosis, diagnosis of mediastinal lesions, molecular diagnosis of lung cancer, restaging of lung cancer after chemotherapy, and diagnosis of suspected malignant mediastinal lesions in those with non-diagnostic conventional techniques.[11,27-30] The procedure was performed by pulmonologist(s) in 7 studies, a surgeon in one study, and both pulmonologists and surgeons in 2 studies (Table 2). The various nodal stations accessed by EBUS-TBNA or EUS-B-FNA are also listed in Table 2. The demonstration of malignancy by EBUS-TBNA and/or EUS-B-FNA was taken as true positive in all the studies, whereas surgical confirmation and/or follow-up was used in case of benign pathology (Table 3). A 22 gauge TBNA needle was used in most of the studies, a

Table 1. Demographic Characteristics of Subjects in Studies Reporting the Performance of EUS-B-FNA for the Diagnosis of Mediastinal Lymphadenopathy

| First Author | Country | Type of Study | Age (y) | Aim of the Study | Subjects Included |
|---|---|---|---|---|---|
| Hwangbo[11] | Korea | Retrospective | 66 (26–79)* | Feasibility of EUS-B-FNA for diagnosis of mediastinal lesions | Subjects undergoing EUS-B-FNA |
| Hwangbo[24] | Korea | Prospective | 64.5 (34–80)* | Mediastinal staging of lung cancer | Confirmed or suspected NSCLC |
| Herth[25] | United States, Germany, Denmark | Prospective | 57.6† | Mediastinal staging of lung cancer | Confirmed or suspected NSCLC |
| Szulobowski[26] | Poland | Retrospective | 62.7 ± 7.9‡ | Mediastinal staging of lung cancer | Lung cancer with clinical stage Ia-IIIb |
| Bugalho[27] | Portugal | Prospective | 63.1 (38–88)§ | Diagnosis of suspected malignant mediastinal lesions | Mediastinal lesion with suspicion of lung cancer undiagnosed after at least one conventional technique |
| Araya[28] | Japan | Retrospective | 66 (58–85)* | Pathologic and molecular diagnosis of lung cancer | Subjects with lung cancer who underwent EUS-B-FNA |
| Oki[29] | Japan | Prospective | 51.5 ± 18.5‡ | Diagnosis of sarcoidosis | Suspected stage 1/stage 2 sarcoidosis |
| Szlubowski[30] | Poland | Prospective | 61.5 ± 8.1‡ | Restaging of NSCLC after induction therapy | Subjects with stage IIIA/B NSCLC who underwent induction chemotherapy |
| Lee[31] | Korea | Retrospective | 66 (43–86)* | Mediastinal staging of lung cancer | Confirmed or suspected lung cancer |
| Oki[32] | Japan | Prospective | 68.3 ± 8.6‡ | Mediastinal staging of lung cancer | Confirmed or suspected NSCLC |

* Values are median with range in parentheses.
† mean.
‡ mean ± SD.
§ mean with range in parentheses.
EUS-B-FNA = endoscopic ultrasound with bronchoscope-guided fine needle aspiration
NSCLC = non-small cell lung cancer

21 gauge needle was used in a single study,[29] and one study did not report the needle size.[25] Rapid on-site cytological examination was not performed in any study. Of the 10 studies, the procedure was performed under conscious sedation in 8, general anesthesia in one, and either of the 2 modalities in one. The studies were generally of good quality (Table 4) with the median (interquartile range) score being 18 (18–19). The inter-observer agreement for scoring of study quality was good (weighted Cohen's kappa = 0.9).

Four studies (465 subjects) provided data for the true and false positive, as well as the true and false negative, results of both EBUS-TBNA alone and the combined procedure, and were included in the diagnostic accuracy meta-analysis (Table 5).[24,25,31,32] All these studies were aimed at mediastinal staging of lung cancer. The diagnostic sensitivity of EBUS-TBNA alone in these studies ranged from 52% to 92%, with the pooled sensitivity being 80% (95% CI 74–86%) by random effects model (Fig. 2). The diagnostic sensitivity of the combined procedure was 91% (95% CI 86–95%), and was significantly higher than the pooled sensitivity of EBUS-TBNA alone ($P = .004$). The number of combined procedures that need to be performed to achieve one additional diagnosis, as compared with EBUS-TBNA alone, is 10 (95% CI 6–29). The pooled specificity of EBUS-TBNA and the combined procedure was 100% (Fig. 3). The pooled sensitivity, specificity, PLR, NLR, and DOR are provided in Table 6.

Seven studies (653 subjects) reported data on the number of subjects in whom EUS-B-FNA achieved additional diagnostic yield over EBUS-TBNA.[11,24,25,27,30-32] In one study, both EBUS-TBNA and EUS-B-FNA were not performed in all subjects; therefore, it was not included for calculating the additional diagnostic gain.[28] The pooled additional diagnostic gain was 7.6% (95% CI 3.9–12.6%), as depicted in Figure 4. None of the studies reported any serious complication of the EUS-B-FNA procedure. One study reported the development of a lymph node abscess after EBUS-TBNA in one subject.[24]

Table 2. Details of the EBUS-TBNA and EUS-B-FNA Procedures in the Diagnosis of Mediastinal Lymphadenopathy

| First Author | *N* | Operator | Position for EUS-B-FNA | Lesion Size (in mm) Along With Modality* | No. of Lesions/Subjects Accessed by EBUS-TBNA/EUS-B-FNA | Stations | No. of Passes* | Sedation | Duration of Procedure* (min) |
|---|---|---|---|---|---|---|---|---|---|
| Hwangbo[11] | 84 | Pulmonary physician | Supine | CT 9 (5–40) | EBUS-TBNA: 63 subjects | EUS-B-FNA: 1, 3P, 4L, 5, 7, 8, 9, 10L, LUL, LLL, RLL | 1.7 | Conscious sedation | EUS-B-FNA 6.4 (2.1–21) |
| | | | | | EUS-B-FNA: 89 lesions (84 subjects) | EBUS-TBNA: NR | | | |
| | | | | | Both: 31 lesions | | | | |
| Hwangbo[24] | 150 | Pulmonary physician | Supine | EBUS | EBUS-TBNA: 299 lesions (150 subjects) | EUS-B-FNA: 3P, 4L, 5, 7, 8, 9 | EBUS-TBNA 2.3 (1–5) | Conscious sedation | EUS-B-FNA 3.8 (1–25) |
| | | | | 7.8 (3.6–23.6) EUS-B | EUS-B-FNA: 64 lesions (53 subjects) | EBUS-TBNA: 1R, 2R, 2L, 3P, 4R, 4L, 7, 8 | | | |
| | | | | 7.6 (3.6–23.4) | Both: 48 lesions | Both: 3P, 4L, 7, 8 | EUS-B-FNA 1.4 (1–4) | | EBUS-TBNA 18.9 (3–75) |
| Herth[25] | 150 | Pulmonary physician, surgeon | NR | EBUS/EUS-B 17 ± 4.2 | EBUS-TBNA: 390 lesions (139 cases) | EUS-B-FNA: 2R, 2L, 4R, 4L, 7, 8, 9, 10R, 10L | NR | Conscious sedation or general anesthesia | EUS-B-FNA 16; EBUS-TBNA 14 |
| | | | | | EUS-B-FNA: 229 lesions (139 cases) | EBUS-TBNA: 2R, 2L, 4R, 4L, 7, 10R, 10L | | | |
| | | | | | Both: 103 subjects | Both: 2R, 2L, 4R, 4L, 7, 10R, 10L | | | |
| Szulobowski[26] | 214 | Surgeon | Left lateral | EBUS/EUS-B 8.7 ± 3.3 | EBUS-TBNA: NR | EUS-B-FNA: NR | NR | Conscious sedation | EBUS-TBNA/ EUS-B-FNA 14.9 ± 2.3 |
| | | | | | EUS-B-FNA: NR | EBUS-TBNA:NR | | | |
| | | | | | Both: 298 lesions (104 cases) | Either: 2R, 2L, 4R, 4L, 5, 7, 8, 9 | | | |
| Bugalho[27] | 123 | Pulmonary physician | NR | CT 32.2 (17–64), lymph node 17.2 (13–22) | EBUS-TBNA: 67 cases | EUS-B-FNA: NR | EBUS-TBNA/ EUS-B-FNA 5.4 (4–9) | General anesthesia | EBUS-TBNA/ EUS-B-FNA 35.5 (21–65) |
| | | | | | EUS-B-FNA: 8 cases | EBUS-TBNA:NR | | | |
| | | | | | Both: 43 cases | Either: 2R, 2L, 4R, 4L, 7, 8, 10R, 10L, 11R, RUL, RML, RLL, LUL, LLL | | | |

(*continued*)

Table 2. Continued

| First Author | *N* | Operator | Position for EUS-B-FNA | Lesion Size (in mm) Along With Modality* | No. of Lesions/Subjects Accessed by EBUS-TBNA/EUS-B-FNA | Stations | No. of Passes* | Sedation | Duration of Procedure* (min) |
|---|---|---|---|---|---|---|---|---|---|
| Araya[28] | 26 | Pulmonary physician | Supine | EUS-B 28.1 (11–83) | EBUS-TBNA only: 0 cases | EUS-B-FNA: 2L, 4L, 7, 8, 10L, intrapulmonary | EUS-B-FNA 2.6 | Conscious sedation | EUS-B-FNA 16 |
| | | | | | EUS-B-FNA only: 19 cases | EBUS-TBNA:NR | | | |
| | | | | | Both: 7 cases | | | | |
| Oki[29] | 33 | Pulmonary physician | Left lateral | EUS-B 13.6 (6.8–28.7) | EBUS-TBNA: 3 cases | EUS-B-FNA: 2L, 3P, 4L, 4R, 7, 8, 10L | EUS-B-FNA 3.3 (1–7) | Conscious sedation | EUS-B-FNA 22.5 (12.8–40.5) |
| | | | | | Both: 3 cases EUS-B-FNA: 62 lesions (32 cases) | EBUS-TBNA:NR | | | |
| Szlubowski[30] | 106 | Pulmonary physician, surgeon | NR | EBUS/EUS-B 8.7 ± 5.8 | EBUS-TBNA: 127 lesions | EUS-B-FNA: NR | NR | Conscious sedation | EUS-B-FNA 5.1 ± 3.7; |
| | | | | | EUS-B-FNA: 159 lesions | EBUS-TBNA:NR | | | EBUS-TBNA 12.1 ± 3.3 |
| | | | | | Any: 286 lesions | Either: 1, 2R, 2L, 4R, 4L, 7, 8, 9 | | | |
| Lee[31] | 44 | Pulmonary physician | NR | EBUS/EUS-B 10.0 (4–58) | EBUS-TBNA: 79 lesions | EUS-B-FNA: 1R, 2R, 3P, 4L, 5, 7, 8, 10L | EBUS-TBNA/ EUS-B-FNA 2 (1–4) | Conscious sedation | EBUS-TBNA /EUS-B-FNA 40 (15–70) |
| | | | | | EUS-B-FNA 52 lesions | EBUS-TBNA:1R, 2R, 4R, 4L, 7, 11R, 11L | | | |
| Oki[32] | 150 | Pulmonary physician | Left lateral | EBUS/EUS-B 29 (7.5–66.3) | EBUS-TBNA: 257 lesions (121 cases) | EUS-B-FNA: 2L, 3P, 4R, 4L, 5, 7, 8, 10L | EBUS-TBNA/ EUS-B-FNA 2 per node | Conscious sedation | EUS-B-FNA 10.1 (1.3–28.0); EBUS-TBNA 16.5 (4.0–43.8) |
| | | | | | EUS-B-FNA 176 lesions (107 cases) | EBUS-TBNA: 2R, 3P, 4R, 4L, 7, 10L, 11R, 11L | | | |
| | | | | | | Both: NR | | | |

*Values are reported as mean, mean ± SD, or median (range).
EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration
EUS-B = endoscopic ultrasound with echobronchoscope
EUS-B-FNA = endoscopic ultrasound with bronchoscope-guided fine needle aspiration
*N* = total number of subjects enrolled in the study
LUL = left upper lobe
LLL = left lower lobe
RLL = right lower lobe
NR = not reported
RUL = right upper lobe
RML = right middle lobe

Table 3. Criteria Used for Confirmation of Diagnosis in the Included Studies

| First Author | Accepted Standard |
|---|---|
| Hwangbo[11] | Malignancy: pathological confirmation of malignancy by any tissue sampling method (EUS-B-FNA, EBUS-TBNA, surgical biopsy); benign disease: pathological confirmation of a specific benign disease, surgical confirmation of lesions showing no malignant disease or no evidence of lymph node enlargement during follow-up without treatment more than 6 mo |
| Hwangbo[24] | Malignancy: pathologic confirmation of malignancy by any tissue sampling method (EBUS-TBNA, EUS-B-FNA, or surgical biopsy); benign disease: surgical confirmation of lesions showing no malignant disease |
| Herth[25] | Malignancy: positive cytologic result of malignancy accepted as evidence of cancer; benign disease: confirmed by open thoracotomy, thoracoscopy, or clinical follow-up over 6–12 mo |
| Szulobowski[26] | Appropriate pulmonary resection with systemic lymph node dissection of the mediastinal nodes in those with negative results |
| Bugalho[27] | Malignancy: positive result by any method established as evidence; benign disease: confirmed by surgical procedures |
| Araya[28] | Not available |
| Oki[29] | Diagnosis of sarcoidosis: clinicoradiological features compatible with sarcoidosis, pathological findings of noncaseating granulomas, exclusion of other causes of granulomas, clinical follow-up |
| Szlubowski[30] | Malignancy: positive cytologic result of malignancy accepted as evidence of cancer; in subjects with negative results of EUS-B-FNA, transcervical extended mediastinal lymphadenectomy was performed |
| Lee[31] | Malignancy: defined by pathological confirmation via EBUS-TBNA, EUS-B-FNA, mediastinoscopy, or mediastinal lymph node dissection; benign disease: confirmed by surgery |
| Oki[32] | Malignancy: positive findings from the needle aspiration procedure were regarded as true-positive; benign disease: confirmed by lack of lymph node progression on CT over 6 mo |

EUS-B-FNA = endoscopic ultrasound with bronchoscope-guided fine-needle aspiration
EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration
CT = computed tomography

Table 4. QualSyst Tool for Assessment of Quality of the Included Studies

| Criterion | Study | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Hwangbo[11] | Hwangbo[24] | Herth[25] | Szlubowski[26] | Bugalho[27] | Araya[28] | Oki[29] | Szlubowski[30] | Lee[31] | Oki[32] |
| 1 Question/objective sufficiently described? | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 2 Study design evident and appropriate? | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 2 |
| 3 Context for the study clear? | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 4 Connection to a theoretical framework/ wider body of knowledge? | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 2 |
| 5 Sampling strategy described, relevant, and justified? | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 2 |
| 6 Data collection methods clearly described and systematic? | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 |
| 7 Data analysis clearly described and systematic? | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 2 | 2 |
| 8 Use of verification procedure(s) to establish credibility? | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 |
| 9 Conclusions supported by the results? | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 2 |
| 10 Reflexivity of the account? | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Total | 18 | 19 | 19 | 18 | 18 | 15 | 18 | 17 | 19 | 19 |

Clinical heterogeneity was evident in the nature of the studies (prospective vs retrospective), lymph nodes sampled, and number of aspirations per node (Tables 1 and 2). Significant statistical heterogeneity was also observed for the outcome of sensitivity of the combined procedure ($I^2 = 82.4\%$; Cochran Q statistic 17.09, $P = .001$). There was no evidence of publication bias on visual examination of the funnel plot (Fig. 5) or on statistical tests (Begg-Mazumdar: Kendall's tau = 0.3333, $P = .75$; Egger: bias = −0.2799, $P = .91$).

Table 5. Outcomes of the EBUS-TBNA, EUS-B-FNA, and Combined Procedures of the Included Studies

| First Author | *N* | EBUS-TBNA | | | | | | EUS-B-FNA | | | | | | Combined Procedure | | | | | | Additional Diagnostic Gain (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TP | FP | FN | TN | Sensitivity | Specificity | TP | FP | FN | TN | Sensitivity | Specificity | TP | FP | FN | TN | Sensitivity | Specificity | |
| Hwangbo[11] | 61* | NA | NA | NA | NA | NA | NA | 39 | 0 | 2 | 20 | 95.1 | 100 | NA | NA | NA | NA | NA | NA | 19.0 |
| Hwangbo[24] | 143 | 38 | 0 | 7 | 98 | 84.4 | 100 | NA | NA | NA | NA | NA | NA | 41 | 0 | 4 | 98 | 91.1 | 100 | 2.1 |
| Herth[25] | 139 | 65 | 0 | 6 | 68 | 91.5 | 100 | 63 | 0 | 8 | 68 | 88.7 | 100 | 68 | 0 | 3 | 68 | 95.8 | 100 | 2.2 |
| Szulobowski[26] | 104 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 51 | NA | 9 | NA | 85 | 93.2 | NR |
| Bugalho[27] | 121 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 106 | 0 | 12 | 3 | 89.8 | 100 | 6.8 |
| Araya[28] | 26 | NA | NA | NA | NA | NA | NA | 26 | 0 | 0 | 0 | 100 | NA | 26 | 0 | 0 | 0 | 100 | NA | 69.2 |
| Oki[29] | 29 | NA | NA | NA | NA | NA | NA | 25 | 0 | 4 | 4 | 86.2 | 100 | 27 | 0 | 2 | 4 | 93.1 | 100 | NR |
| Szlubowski[30] | 106 | 25 | NA | NA | NA | 48 | 98 | 30 | NA | NA | NA | 61 | 98 | 37 | 2 | 18 | 49 | 67.3 | 96.1 | 11.3 |
| Lee[31] | 37 | 23 | 0 | 6 | 8 | 79.3 | 100 | NA | NA | NA | NA | NA | NA | 29 | 0 | 0 | 8 | 100 | 100 | 13.6 |
| Oki[32] | 146 | 17 | 0 | 16 | 113 | 51.5 | 100 | 15 | 0 | 18 | 113 | 45.5 | 100 | 24 | 0 | 9 | 113 | 72.7 | 100 | 4.8 |

EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration
EUS-B-FNA = endoscopic ultrasound with bronchoscope-guided fine-needle aspiration
*N* = number of evaluable patients (or lesions, where indicated by *)
TP = true positive
FP = false positive
FN = false negative
TN = true negative
NA = not available
NR = not reported

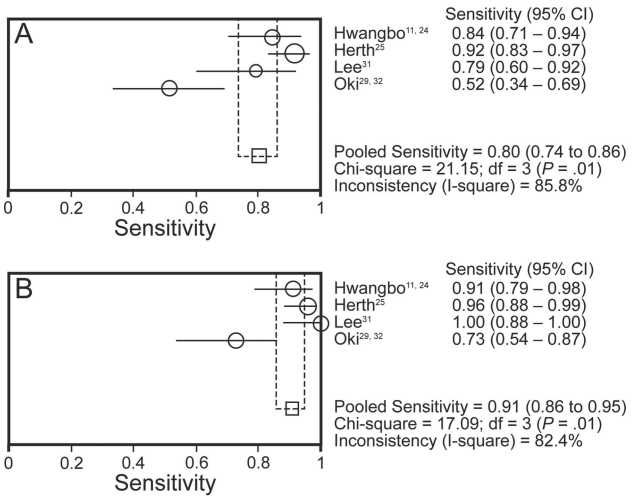


Fig. 2. Forest plot of the summary sensitivity of A: endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and B: the combined procedure in the diagnosis of mediastinal lymphadenopathy; df = degrees of freedom. The sensitivity of individual studies is represented by a circle, through which runs a horizontal line (95% CI). The square at the bottom represent the pooled sensitivity from the studies. There was a significant difference in the pooled sensitivity between the 2 groups ($P = .004$).

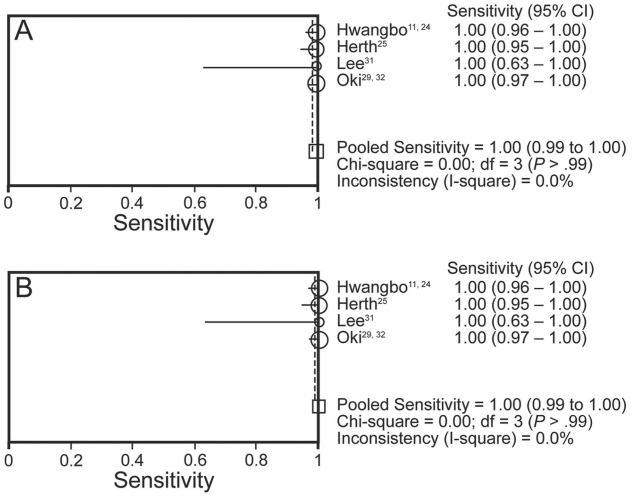


Fig. 3. Forest plots of the summary specificity of A: endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and B: the combined procedure in the diagnosis of mediastinal lymphadenopathy; df = degrees of freedom. The specificity of individual studies is represented by a circle, through which runs a horizontal line (95% CI). The square at the bottom represent the pooled specificity from the studies.

## Discussion

The results of this systematic review suggest that the transesophageal use of the echobronchoscope is a safe and effective method of accessing the mediastinum, and provides incremental diagnostic yield over and above that

Table 6. Summary Characteristics of EBUS-TBNA and the Combined Procedure (EBUS-TBNA and EUS-B-FNA)

| Characteristic | EBUS-TBNA Alone | Combined Procedure |
|---|---|---|
| Sensitivity (%) | 80.3 (73.7–85.9) | 91 (85.8–94.8) |
| Specificity (%) | 100 (98.7–100) | 100 (98.7–100) |
| Positive likelihood ratio | 74.9 (18.9–296.8) | 88.9 (22.5–351.2) |
| Negative likelihood ratio | 0.21 (0.09–0.49) | 0.095 (0.03–0.28) |
| Diagnostic odds ratio | 388.5 (90.9–1659.9) | 1323.5 (278.3–6293.6) |

All values are pooled values with 95% confidence intervals in parentheses.
EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration
EUS-B-FNA = endoscopic ultrasound with bronchoscope-guided fine-needle aspiration

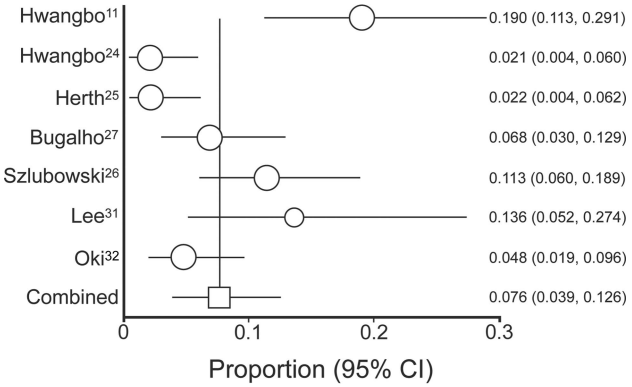


Fig. 4. Additional diagnostic gain of endoscopic ultrasound with bronchoscope-guided fine-needle aspiration (EUS-B-FNA) over endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in subjects with mediastinal lymphadenopathy (random effects model). The gain in individual studies is represented by a circle (percentage) through which runs a horizontal line (95% CI). The square at the bottom represents the pooled additional diagnostic gain from the studies (7.6% [95% CI 3.9–12.6%]).

achieved with EBUS-TBNA alone. Overall, we found a good incremental yield (approximately 8%) of adding EUS-B-FNA to the EBUS-TBNA procedure in the diagnosis of mediastinal lymphadenopathy. The sensitivity of the combined technique was significantly higher than EBUS-TBNA alone (91% vs 80%), in mediastinal staging of lung cancer. In fact, only 10 combined procedures need to be performed to achieve a diagnosis in one additional patient, when compared with EBUS-TBNA alone. The sensitivity of the combined technique is similar to the sensitivity (86%) reported in a meta-analysis of combined EBUS-TBNA plus EUS-FNA by Zhang et al[10] However, our analysis is different from the previous meta-analysis in that we have included only those studies that have utilized the same echobronchoscope for performing both the transbronchial and the transesophageal procedures.

The transesophageal introduction of an echobronchoscope to access mediastinal lymph nodes was first described in 2007.[33] Since then, this unconventional technique has been used not only for mediastinal staging of

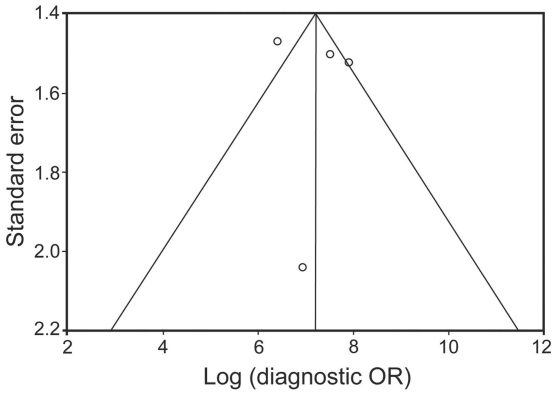


Fig. 5. Funnel plot comparing diagnostic odds ratio (DOR) versus the standard error of DOR. Circles represent individual studies included in the meta-analysis. The vertical line in the center indicates the summary DOR. The other 2 lines represent the 95% CIs.

lung cancer but also for the diagnosis of sarcoidosis, molecular diagnosis of lung cancer, diagnosis of suspected malignant mediastinal lesions in those with non-diagnostic conventional techniques, restaging of lung cancer after chemotherapy, and others. The clinical importance of the combined technique lies in the fact that an additional benefit over EBUS-TBNA can be accomplished utilizing the same instrument in the same setting with the same operator as EBUS-TBNA. There are several other advantages of performing combined transbronchial and transesophageal needle aspiration procedure for mediastinal lymphadenopathy, using a single echobronchoscope (Table 7). It provides a wider access to the mediastinum than either procedure alone (stations 4L, 5, 8, and 9 better accessed with the transesophageal approach; stations 4R, 10, and 11 with the transbronchial approach). It potentially resolves many logistic difficulties by reducing the cost and wait times for patients. It also reduces the dependence of the pulmonary physician/thoracic surgeon on other clinical specialties. Moreover, the procedure is safe; no serious complication resulting from the EUS-B-FNA procedure was reported in any of the studies included in this review.

The diagnostic sensitivity of EBUS-TBNA alone has been found to range from 78% to 92% in previous meta-analyses of studies involving subjects with sarcoidosis, lung cancer, or undiagnosed mediastinal lymphadenopathy.[3,34,35] The pooled sensitivity of EBUS-TBNA alone in our study (80%) falls at the lower end of this range, possibly because rapid on-site cytological examination was not performed in any of the studies included in this review.

Finally, our analysis is not without limitations. The results of this analysis can be considered as hypothesis-generating, as none of the studies included in the analysis was a randomized controlled trial. This is likely to introduce bias in the selection of cases for EUS-B-FNA. There was also significant statistical heterogeneity and considerable clinical heterogeneity in this analysis because of the variations in the study design, inclusion criteria, primary objectives, different operators with varying expertise, the number of aspirations, and lymph node stations among the included studies. However, this clinical heterogeneity can also be considered as useful because it suggests that the combination of EUS-B-FNA and EBUS-TBNA is beneficial in different settings, which would reflect its effectiveness in real world situations. Further, as mentioned, none of the included studies employed rapid on-site cytological examination. The strengths include the inclusion of a large number of subjects and the use of robust statistical methods. The analysis also provides an estimate of the additional diagnostic benefit that an EBUS operator can accomplish by employing this effortless technique in selected patients with mediastinal lymph node enlargement.

Table 7. Individual Studies Reporting the Reasons for Performing EUS-B-FNA

| First Author | Reasons for Performing EUS-B-FNA |
|---|---|
| Hwangbo[11] | Inaccessible by EBUS-TBNA, technical difficulty of EBUS-TBNA, intolerance of bronchoscopy due to cough or dyspnea, brain metastasis with mass effect, medical condition precluding bronchoscopy (ischemic heart disease) |
| Hwangbo[24] | Inaccessible by EBUS-TBNA, well visualized areas by EUS-B-FNA, technical difficulty of EBUS-TBNA |
| Herth[25] | Inaccessible by EBUS-TBNA |
| Szulobowski[26] | Inaccessible by EBUS-TBNA, patient comfort |
| Bugalho[27] | Inaccessible by EBUS-TBNA |
| Araya[28] | Inaccessible by EBUS-TBNA, poor performance status, poor respiratory condition |
| Oki[29] | Not reported |
| Szlubowski[30] | Not reported |
| Lee[31] | Inaccessible by EBUS-TBNA |
| Oki[32] | Inaccessible by EBUS-TBNA, technical difficulty of EBUS-TBNA |

EUS-B-FNA = endoscopic ultrasound with bronchoscope-guided fine-needle aspiration
EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration

## Conclusions

Combining EUS-B-FNA with EBUS-TBNA was found to be a safe and effective method to increase the diagnostic yield in the evaluation of mediastinal lymphadenopathy. With most studies in this systematic review aimed at mediastinal staging of cancer, larger randomized trials from different centers, assessing the utility of this technique for other causes of mediastinal lymphadenopathy, are required to confirm the results of this meta-analysis.

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