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Combined endobronchial and endoscopic ultrasound-guided fine needle aspiration for mediastinal lymph node staging of lung cancer: A meta-analysis

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Abstract ***Study objectives:*** This systematic review and meta-analysis was conducted to evaluate the accuracy of the combined endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) techniques and clarify its current role for the mediastinal lymph node staging of lung cancer.

Methods: Medline, Web of Science, Elsevier and Ovid were searched to identify suitable studies up to 15th July 2012. Two investigators independently reviewed articles and extracted data. All EBUS-TBNA plus EUS-FNA studies for the mediastinal node staging of lung cancer were systematically reviewed. Sensitivity, specificity and other accuracy measures were pooled using random-effect models. Summary receiver operating characteristic curves were used to summarise overall test performance.

Results: Eight studies met our inclusion criteria. The estimated summary measures for quantitative analysis of EBUS-TBNA plus EUS-FNA for mediastinal nodal staging of lung cancer were sensitivity, 0.86 (95% confidence interval [CI], 0.82–0.90); specificity, 1.00 (95% CI, 0.99–1.00); positive likelihood ratio, 51.77 (95% CI, 22.53–118.94); negative likelihood ratio, 0.15 (95% CI, 0.09–0.25); diagnostic odds ratio, 416.83 (95% CI, 140.08–1240.31); and area under the curve (AUC), 0.99.

Conclusions: The current evidence suggests that the combined technique is more sensitive than EBUS-TBNA or EUS-FNA alone. The diagnostic power of this combined technique is accurate. As an almost completely minimally-invasive examination, EUS-FNA plus EBUS-TBNA may replace more invasive methods for evaluating mediastinal node staging of lung cancer.

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1. Introduction

Lung cancer is one of the most common cancers in the world and also the most frequent cause of cancer death. Treatment and prognosis depend on both histological type and stage of disease. Surgery is a promising treatment for curing lung cancer, especially in those patients with disease confined to the lung and hilar lymph nodes. However, mediastinal lymph nodes are involved in 28–38% of non-small cell lung cancers at the time of diagnosis.[1] Therefore, accurate staging (including mediastinal node evaluation) is crucial to guide lung cancer treatment. Current scanning modalities, such as computed tomography (CT) and positron emission tomography (PET), although useful, are not sufficiently sensitive or specific to determine mediastinal nodal involvement.[2] Both mediastinoscopy and thoracoscopy have been recommended as diagnostic standards for staging along with tissue confirmation of suspected metastatic mediastinal lymph nodes.[1] However, due to their invasiveness and significant expense, mediastinoscopy and thoracoscopy are not widely used for mediastinal node staging.

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and, most recently, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)[3–7] are promising invasive imaging tests gaining acceptance as lung cancer staging tools. These methods have been suggested as reasonable alternatives to mediastinoscopy.[3,8–14] Recent studies have found that combining EBUS-TBNA and EUS-FNA into a single procedure has a higher staging accuracy than either procedure alone in patients with confirmed or suspected lung cancer.[3,15–18] Because EBUS-TBNA and EUS-FNA are complementary methods for the diagnosis of mediastinal disease,[6,19–21] they have different accessibilities to the mediastinum.[22–24] This meta-analysis aims to systematically and quantitatively evaluate all published studies assessing the accuracy of the combined approach of EBUS-TBNA and EUS-FNA for the mediastinal node staging of lung cancer.

2. Methods

2.1. Search strategy and study selection

Medline (using PubMed as the search engine), Web of Science, Elsevier and Ovid were searched to identify suitable studies prior to 15th July 2012; no start date limit was applied. The search terms were "EBUS," "TBNA," "EUS," "FNA," "endobronchial ultrasound," "transbronchial needle aspiration," "endoscopic ultrasound," "fine-needle aspiration," "lung cancer," "mediastinal staging," "sensitivity and specificity" and "accuracy." Articles were also identified by use of the related articles' function in PubMed; the references of identified articles were searched manually. If necessary, we contacted the authors for further study details. No language restrictions were imposed. However, conference abstracts to journal editors were excluded because of the limited data they contained.

Studies were included in the meta-analysis if they provided both the sensitivity and specificity of the combined approach of EBUS-TBNA and EUS-FNA for mediastinal node staging of lung cancer. This meta-analysis only selected studies that included at least 10 lung cancer patients, since very small studies may be vulnerable to selection bias. Two reviewers (R.F.Z. and K.J.Y.) independently determined study eligibility, and differing decisions were resolved by consensus. Publications possibly based on the same study (e.g. same authors, institutions, period of study) were discussed by our reviewers (R.F.Z., L.Z. and K.J.Y); only the best-quality study was used.

2.2. Data extraction and quality assessment

The final set of articles was assessed independently by two reviewers (R.F.Z. and L.Z.). The reviewers were blinded to publication details, and disagreements between them were resolved by consensus. Data retrieved from the reports included author, publication year, participant characteristics, test methods, sensitivity and specificity data and methodological quality.

The STARD (Standards for Reporting Diagnostic Accuracy) scoring guidelines[25] assessed the methodological quality of diagnostic study reporting. The QUADAS (Quality Assessment for Studies of Diagnostic Accuracy) scoring guidelines[26] assessed the quality of diagnostic accuracy in primary studies by appraising use of empirical evidence, expert opinion and formal consensus. In addition, the following study design characteristics were retrieved: (1) random sampling of patients; (2) blinded interpretation of determination and reference standard results; (3) prospective data collection; and (4) reference standards.

2.3. Statistical analysis

We used standard methods recommended for meta-analysis of diagnostic test evaluations.[27] Analyses were performed using the following statistical software programs: STATA, version 10.0 (STATA Corporation; College Station, TX, United States) and Meta-DiSc (XI Cochrane Colloquium; Barcelona, Spain). For each study, we computed the following measures of test accuracy: sensitivity; specificity; positive likelihood ratio (PLR); negative likelihood ratio (NLR); and diagnostic odds ratio (DOR). The analysis was based on a summary receiver-operator characteristic (SROC) curve.[27,28] A random-effect model was used to calculate the average

sensitivity, specificity and other accuracy measures across studies.[29]

Sensitivity was calculated by the formula: true positive (n)/(true positive (n) + false negative (n)) × 100%. Specificity was calculated by the formula: true negative (n)/(true negative (n) + false positive (n)) × 100%. Patients positive to either of the two tests were defined as positive and only patients negative to both tests were defined as negative.

The term heterogeneity, when used in relation to meta-analysis, refers to the degree of variability in results across studies. We used the χ^2 and Fisher exact tests to detect statistically significant heterogeneity. In order to assess the effects of STARD and QUADAS scores on the diagnostic ability of EBUS-TBNA and EUS-FNA, we included the scores as covariates of univariate meta-regression analysis (weighted inverse variance). We also analysed the effects of other covariates on DOR (i.e. random sampling of patients, blinded interpretation of determination and reference standard results, prospective data collection). The relative DOR (RDOR) was calculated according to standard methods to analyse the change in diagnostic precision in the study per covariate unit.[30] Since publication bias is a concern in meta-analysis of diagnostic studies, we tested the potential presence of this bias using both funnel plots and the Egger test.[31]

3. Results

We conducted an independent full-text review and considered eight 3, 15–18, 22–24 quantitative analysis studies of 822 lung cancer patients using a combined EBUS-TBNA and EUS-FNA approach for mediastinal node staging of lung cancer (Fig. 1, Table 1). As shown in Table 2, six of the eight studies (75%) had a prospective design; in one study (12.5%), the samples were collected from randomised patients; two studies (25%) reported a blind design. The mediastinal node staging of lung cancer was confirmed both by surgery and patient follow-up. The STARD and QUADAS scores of these studies are outlined in Table 2.

3.1. Diagnostic accuracy

Fig. 2 shows the Forest plot of sensitivity and specificity for eight assays in evaluating the mediastinal node staging of lung cancer. The sensitivity ranged from 0.68 to 1.00 (mean, 0.86; 95% confidence interval [CI], 0.82–0.90), while specificity ranged from 0.98 to 1.00 (mean, 1.00; 95% CI, 0.99–1.00). The PLR was 51.77 (95% CI, 22.53–118.94), NLR was 0.15 (95% CI, 0.09–0.25) and DOR was 416.83 (95% CI, 140.08–1240.31). The sensitivity, specificity, PLR, NLR and DOR χ^2 values were 28.79 ($p < 0.001$), 6.75 ($p = 0.455$), 5.30 ($p = 0.623$), 24.11 ($p = 0.001$) and 8.75 ($p = 0.271$), respectively, indicating a statistically significant heterogeneity between studies.

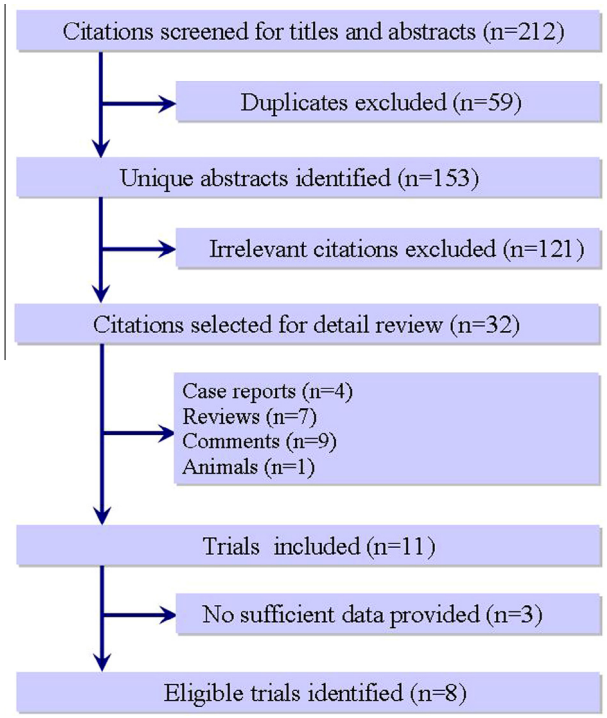

Fig. 1. Study identification, inclusion and exclusion for meta-analysis.

The SROC curve and its respective area under the curve (AUC) present an overall best performance summary and display the tradeoff between sensitivity and specificity. Unlike the traditional receiver-operator characteristic (ROC) plot that explores the effect of variable thresholds on sensitivity and specificity in a single study, each data point in the SROC plot represents a separate study. A graph of the SROC curve for the combined approach of EBUS-TBNA and EUS-FNA showing true-positive rates versus false-positive rates from individual studies is seen in Fig. 3. In our study, the AUC was 0.99 (weighted AUC, 0.99), indicating a very high level of overall accuracy.

3.2. Complications

Only two serious complications were reported. Pneumothorax was directly related to endosonography after lung biopsy in one patient.[3] In another patient, a lymph node abscess developed following EBUS-TBNA; however, EBUS-FNA was not used for this patient. The lymph node abscess resolved after antibiotic treatment.[16] Most of the procedures were well-tolerated by the patients.

3.3. Multiple regression analysis and publication bias

The STARD guidelines[25] provided a quality score (maximum score: 25) compiled for every study on the

Table 1
Summary of included studies.*

Study/year	Country	Patients no.	EBUS-TBNA					EUS-FNA					EBUS-TBNA + EUS-FNA					
			TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Rintoul et al.[22]/2005	United Kingdom	18	11	0	2	5	84.6	100	3	0	1	2	75	100	11	0	2	5	84.6	100
Vilmann et al.[23]/2005	Denmark	31	–	–	–	–	85	100	–	–	–	–	80	100	20	0	0	11	100	100
Wallace et al.[24]/2008	United States	138	29	0	13	96	69.0	100	29	0	13	96	69.0	100	39	0	3	96	92.9	100
Herth et al.[17]/2010	Germany	139	65	0	6	68	91.5	100	63	0	8	68	88.7	100	68	0	3	68	95.8	100
Hwangbo et al.[16]/2010	Korea	143	38	0	7	98	84.4	100	–	–	–	–	–	–	41	0	4	98	91.1	100
Annema et al.[3]/2010	Netherlands	123	–	–	–	–	–	–	–	–	–	–	–	–	58	0	13	52	81.7	100
Szlubowski et al.[18]/2010	Poland	120	13	1	15	99	46.4	99	14	1	14	99	50	99	19	2	9	90	67.9	97.8
Ohnishi et al.[15]/2011	Japan	110	25	0	14	71	64.1	100	19	0	20	71	48.7	100	28	0	11	71	71.8	100

* EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; TP: true positive; FP: false positive; FN: false negative; TN: true negative.

basis of title and introduction, methods, results and discussion (Table 2). Quality scoring was also done by QUADAS (maximum score, 14)[26] (Table 2). These scores were used in the meta-regression analysis to assess study quality effect on the RDOR for the combined approach in the mediastinal node staging of lung cancer. As shown in Table 3, studies with higher quality (STARD score, $\geqslant 18$; QUADAS score, $\geqslant 11$) produced RDOR values that were not significantly higher than studies with lower quality. We also noted that differences for studies with or without blind, random and prospective designs did not reach statistical significance. This finding indicated that the study design did not substantially affect diagnostic accuracy.

Publication bias was detected by using the Egger test. The Egger test result was not significant ($p = 0.104$). The funnel plots for publication bias (Fig. 4) also showed symmetry. These results did not show publication bias.

4. Discussion

Histologic evaluation of mediastinal lymph nodes in lung cancer is essential to both stage the disease accurately and to plan treatment. Mediastinoscopy, a surgical procedure requiring general anaesthesia, is the current diagnostic standard for staging mediastinal lymph nodes; even with a negative predictive value of 89% and a positive predictive value of 100%, it has limitations.[32] Mediastinoscopy is best suited for sampling lymph nodes in the pretracheal and paratracheal regions, but it is limited in accessing the inferior and posterior mediastinum and the aortopulmonary regions. Although generally safe, mediastinoscopy has a 2% risk of major morbidity and a 0.08% risk of mortality; it also has a substantially greater cost than either EUS-FNA or EBUS-TBNA.[14,32–35] Hence, EBUS-TBNA and EUS-FNA have emerged as alternatives for primary mediastinal staging because of their high diagnostic accuracy, access to nodes beyond the reach of the mediastinoscope and low morbidity.[4,5,11,14] Previous studies have shown that both endoscopic technologies are individually superior to mediastinoscopy.[10,36] The advantages of EBUS-TBNA combined with EUS-FNA have been reported by several studies.[3,16,17]

In the present systematic review, eight trials used the combined technique to evaluate the mediastinal lymph node staging of lung cancer (table 2). In addition, the individual diagnostic power of EBUS-TBNA or EUS-FNA was also provided among seven trials.[15–18,22–24] The combined technique had more diagnostic accuracy than EBUS-TBNA or EUS-FNA alone. Annema and colleagues also showed that EBUS-TBNA combined with EUS-FNA had greater test power than mediastinoscopy alone.[3] Both EBUS-TBNA and EUS-FNA have shown excellent sensitivity and positive predictive value in lung cancer staging. In addition to mediastinal

Table 2
Characteristics of included studies.

Study/year	Blind design	Random	Prospective	Reference standard	Quality score	
					Standards for Reporting Diagnostic Accuracy (STARD)	Quality Assessment for Studies of Diagnostic Accuracy (QUADAS)
Rintoul et al.[22]/2005	No	No	Yes	Surgery and follow-up	16	10
Vilmann et al.[23]/2005	Unknown	No	Yes	Surgery and follow-up	16	11
Wallace et al.[24]/2008	Yes	No	Unknown	Surgery and follow-up	23	11
Herth et al.[17]/2010	Unknown	No	Unknown	Surgery and follow-up	15	9
Hwangbo et al.[16]/2010	Unknown	No	Yes	Surgery	18	9
Annema et al.[3]/2010	Unknown	Yes	Yes	Surgery	20	12
Szlubowski et al.[18]/2010	Unknown	No	Yes	Surgery	15	7
Ohnishi et al.[15]/2011	Yes	No	Yes	Surgery	18	12

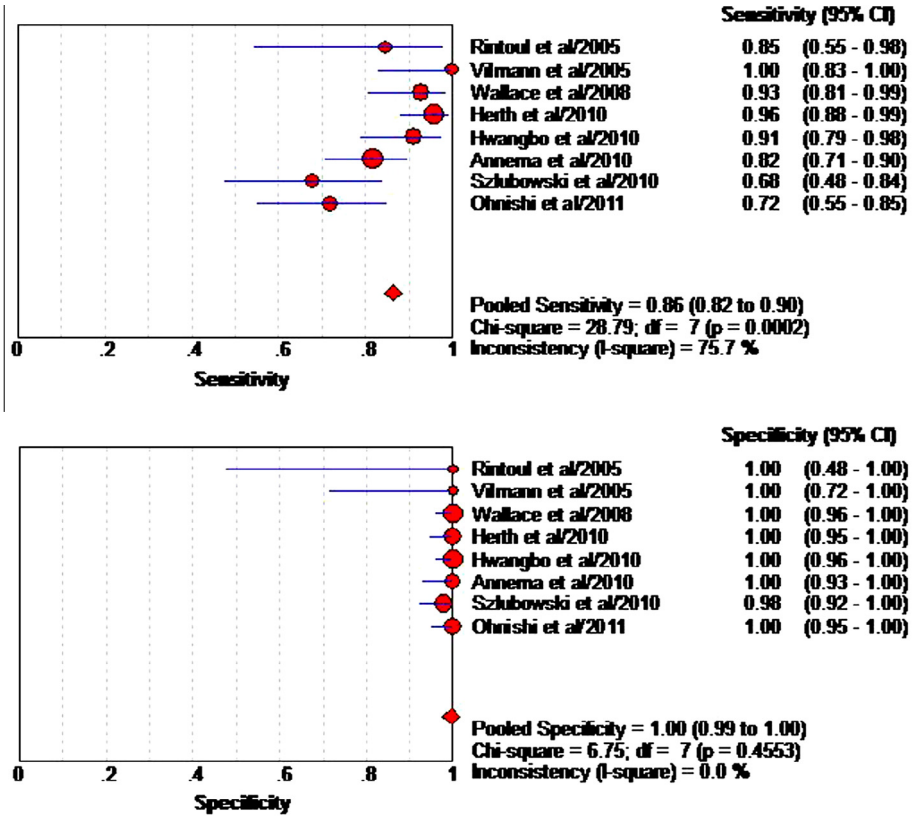

Fig. 2. Forest plot of estimates of sensitivity and specificity for quantitative analysis of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) plus endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) for mediastinal lymph node staging. ● = point estimates of sensitivity and specificity from each study; error bars = 95% confidence interval (CI). Pooled estimates for the combined approach were as follows: sensitivity, 0.86 (95% CI, 0.82–0.90); specificity, 1.00 (95% CI, 0.99–1.00).

stations, EBUS-TBNA can also access hilar lymph nodes in the same setting, and EUS-FNA can access periesophageal disease sites.[17] The major advantage of the combined EBUS-TBNA and EUS-FNA technique is the increased accessibility to the mediastinal lymph nodes. Thus, EBUS-TBNA and EUS-FNA are complementary techniques, and their combined use theoretically enables complete evaluation of the mediastinum. Consequently, this complementary approach may be the reason that this combined technique has a greater diagnostic accuracy than EBUS-TBNA or EUS-FNA alone. The present meta-analysis has shown that the mean sensitivity of EBUS-TBNA plus EUS-FNA assay is 0.86, the mean specificity is 1.00 and the AUC is 0.99, indicating a very high level of accuracy.

The DOR is a single indicator of test accuracy[37] that combines sensitivity and specificity data into a single number. The DOR is the ratio of the positive test result odds in the patient with disease relative to the positive test result odds in the patient without disease. The

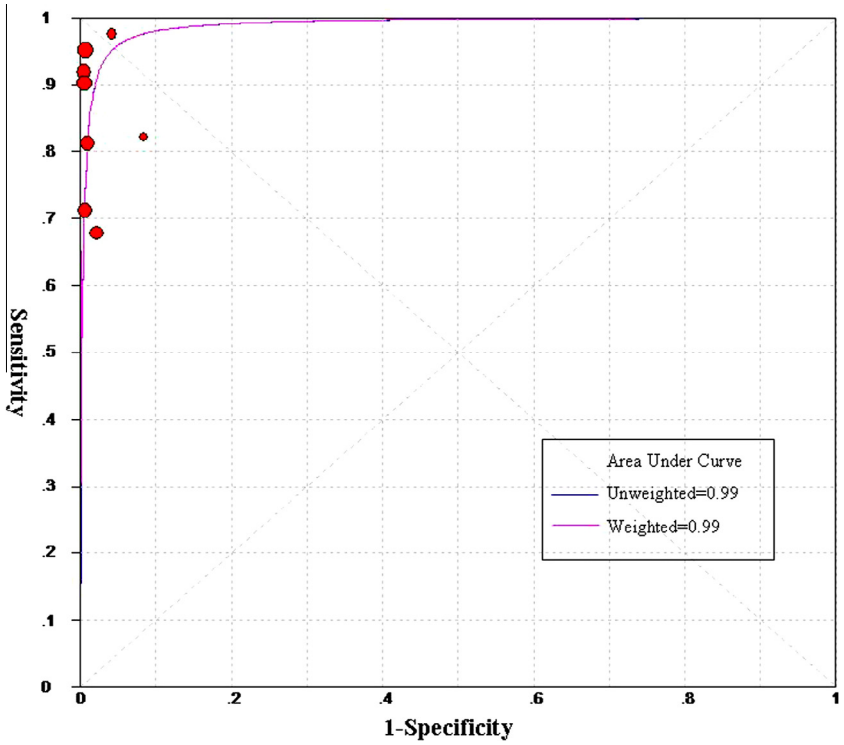

Fig. 3. Summary receiver-operator characteristic (SROC) curves for endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) plus endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) assays. ● = each study in the meta-analysis (size of each study is indicated by size of the solid circle); red line = weighted regression; and blue line = unweighted regression. SROC curves summarise the overall diagnostic accuracy.

DOR value ranges from 0 to infinity, with higher values indicating better discriminatory test performance. A DOR of 1.0 indicates that a test does not discriminate between patients with the disorder and those without it. In the present meta-analysis, we found that the mean DOR was 416.83, indicating a very high level of overall accuracy.

The SROC curve and the DOR are not easy to interpret and use in clinical practice.[38] Thus, we also presented both PLR and NLR as diagnostic accuracy measures because likelihood ratios are considered more meaningful clinically.[39] The likelihood ratio incorporates both the sensitivity and specificity of the test and provides a direct estimate of how much a test result will change the odds of having a disease. The PLR indicates how much the odds of the disease increase when a test is positive. And the NLR indicates how much the odds of the disease decrease when a test is negative. Likelihood ratios of >10 or <0.1 generate large and often conclusive shifts from pretest to posttest probability (indicating high accuracy).In the present study, a PLR value of 51.77 suggested that lung cancer patients with mediastinal lymph node involvement have an approximately 52-fold greater chance of having a positive combined endosonography assay as compared with controls. This probability is high enough to confirm the presence of lung cancer in the mediastinal lymph nodes. On the other hand, the present meta-analysis found a NLR value to be 0.15. Thus, if the combined endosonography assay result is negative for any individual, the probability of this individual having mediastinal lymph node involvement is 15%; this probability is not low enough to rule out mediastinal lymph node metastases. In some trials[16,17] of the present meta-analysis, the combined transbronchial and transesophageal approach used a much less invasive single ultrasound bronchoscope. This may be a more practical and convenient approach because it is simpler, less costly and less time-consuming. However, a bronchoscope cannot access some lymph node stations. Also, conventional EUS-FNA can reach otherwise inaccessible extrathoracic disease sites such as the left adrenal area; a bronchoscope is not long enough to reach that region. However, EUS has better image

Table 3
Weighted meta-regression of the effects of methodological characteristics and study design on diagnostic accuracy of EBUS-TBNA + EUS-FNA*.

Covariates	Studies, no.	Coefficient	RDOR	*p*-Value
STARD ⩾ 18	4	1.785	5.96	0.190
QUADAS ⩾ 11	4	3.477	32.37	0.496
Blind	2	−1.127	0.32	0.543
Random	1	−1.348	0.26	0.585
Prospective	6	−2.338	0.10	0.122

* EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration.

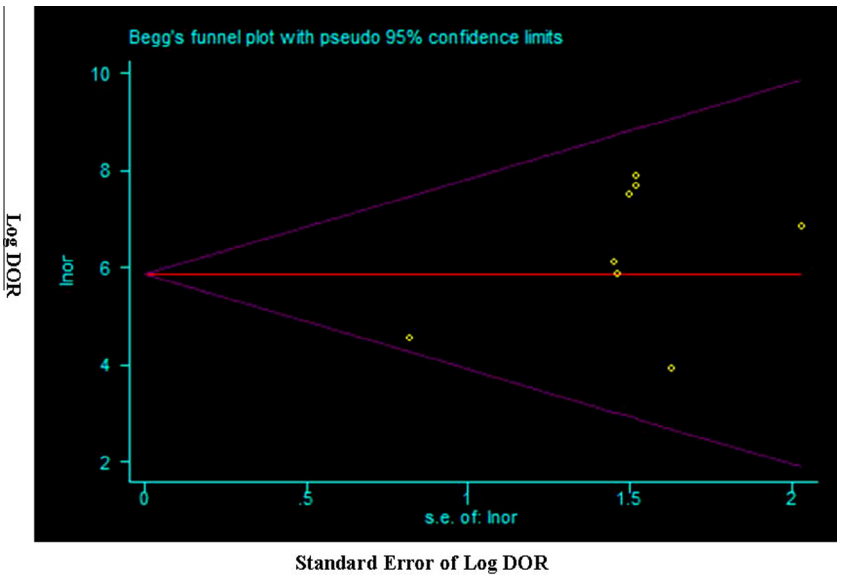

Fig. 4. Funnel graph for the assessment of potential publication bias in endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) plus endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) assays. The funnel graph plots the log of the DOR against the statistical error (SE) of the log of the DOR (an indicator of sample size). ● = each study in the meta-analysis; centre line = SDOR. The result of the Egger test for publication bias was not significant ($p = 0.104$).

quality and a wider scanning plane than the EBUS. The EUS needle also has an elevator function, whereas the EBUS needle does not. These issues may influence the pooled diagnostic accuracy of this combined approach. Thus, the value of NLR may be overestimated when using a single ultrasound bronchoscope.

An exploration of the reasons for heterogeneity rather than a single summary measure computation is an important goal of meta-analysis.[40] In our meta-analysis, both STARD and QUADAS scores were used in the meta-regression analysis to assess the effect of RDOR study quality. Studies with higher quality (i.e. STARD score of $\geqslant 18$ or QUADAS score of $\geqslant 11$) were not observed to have better test performances than those with lower quality. However, we found a statistically significant heterogeneity for sensitivity and NLR among the studies analysed.

Some limitations of this meta-analysis should be acknowledged. First, some of the individual studies analysed have a small number of cases, which may affect statistical power. A second limitation was that EBUS-TBNA and EUS-FNA were performed in different orders at multiple institutions and with different patients. No sufficient details were provided in the included trials. Consequently, it is hard to confirm whether performing EBUS-TBNA and EUS-FNA in different orders could lead to multiple levels of diagnostic power. In addition, various inclusion criteria were used for the patients, such as confirmation or suspicion of lung cancer and radiologically normal or abnormal mediastinal diagnostic imaging. All of these various criteria may cause heterogeneity in the trials.

5. Conclusions

This is the first meta-analysis assessing the combined approach of EBUS-TBNA and EUS-FNA for mediastinal node staging of lung cancer. The current evidence suggests that the combined technique is more sensitive than EBUS-TBNA or EUS-FNA alone. The diagnostic power of this combined technique is accurate. As an almost completely minimally-invasive examination, EBUS-TBNA plus EUS-FNA may replace more invasive methods for evaluating mediastinal node staging of lung cancer. This combined endoscopic approach is strongly recommended before surgery or invasive surgical staging to avoid futile thoracotomies.

Conflict of interest statement

None declared.

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References

1. Silvestri GA, Gould MK, Margolis ML, et al. Noninvasive staging of non-small cell lung cancer: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest* 2007;**132**:178S–201S.
2. Toloza EM, Harpole L, McCrory DC. Noninvasive staging of non-small cell lung cancer: a review of the current evidence. *Chest* 2003;**123**:137S–46S.

3. Annema JT, van Meerbeeck JP, Rintoul RC, et al. Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. *JAMA* 2010;**304**:2245–52.
4. Adams K, Shah PL, Edmonds L, Lim E. Test performance of endobronchial ultrasound and transbronchial needle aspiration biopsy for mediastinal staging in patients with lung cancer: systematic review and meta-analysis. *Thorax* 2009;**64**:757–62.
5. Gu P, Zhao YZ, Jiang LY, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. *Eur J Cancer* 2009;**45**:1389–96.
6. Herth FJ, Rabe KF, Gasparini S, Annema JT. Transbronchial and transoesophageal (ultrasound-guided) needle aspirations for the analysis of mediastinal lesions. *Eur Respir J* 2006;**28**:1264–75.
7. Micames CG, McCrory DC, Pavey DA, Jowell PS, Gress FG. Endoscopic ultrasound-guided fine-needle aspiration for non-small cell lung cancer staging: a systematic review and metaanalysis. *Chest* 2007;**131**:539–48.
8. Kunst PW. Mediastinoscopy is complementary to EBUS-EUS. *Ann Thorac Surg* 2011;**91**:989–90 [author reply 990–981].
9. Witte B, Neumeister W, Huertgen M. Does endoesophageal ultrasound-guided fine-needle aspiration replace mediastinoscopy in mediastinal staging of thoracic malignancies? *Eur J Cardiothorac Surg* 2008;**33**:1124–8.
10. Tournoy KG, De Ryck F, Vanwalleghem LR, et al. Endoscopic ultrasound reduces surgical mediastinal staging in lung cancer: a randomized trial. *Am J Respir Crit Care Med* 2008;**177**:531–5.
11. Sawhney MS, Bakman Y, Holmstrom AM, et al. Impact of preoperative endoscopic ultrasound on non-small cell lung cancer staging. *Chest* 2007;**132**:916–21.
12. Cerfolio RJ, Bryant AS, Eloubeidi MA. Routine mediastinoscopy and esophageal ultrasound fine-needle aspiration in patients with non-small cell lung cancer who are clinically N2 negative: a prospective study. *Chest* 2006;**130**:1791–5.
13. Khoo KL, Ho KY, Nilsson B, Lim TK. EUS-guided FNA immediately after unrevealing transbronchial needle aspiration in the evaluation of mediastinal lymphadenopathy: a prospective study. *Gastrointest Endosc* 2006;**63**:215–20.
14. Navani N, Lawrence DR, Kolvekar S, et al. EBUS-TBNA prevents mediastinocopies in the diagnosis of isolated mediastinal lymphadenopathy: a prospective trial. *Am J Respir Crit Care Med* 2012;**186**:255–60.
15. Ohnishi R, Yasuda I, Kato T, et al. Combined endobronchial and endoscopic ultrasound-guided fine needle aspiration for mediastinal nodal staging of lung cancer. *Endoscopy* 2011;**43**:1082–9.
16. Hwangbo B, Lee GK, Lee HS, et al. Transbronchial and transesophageal fine-needle aspiration using an ultrasound bronchoscope in mediastinal staging of potentially operable lung cancer. *Chest* 2010;**138**:795–802.
17. Herth FJ, Krasnik M, Kahn N, Eberhardt R, Ernst A. Combined endoscopic-endobronchial ultrasound-guided fine-needle aspiration of mediastinal lymph nodes through a single bronchoscope in 150 patients with suspected lung cancer. *Chest* 2010;**138**:790–4.
18. Szlubowski A, Zielinski M, Soja J, et al. A combined approach of endobronchial and endoscopic ultrasound-guided needle aspiration in the radiologically normal mediastinum in non-small-cell lung cancer staging – a prospective trial. *Eur J Cardiothorac Surg* 2010;**37**:1175–9.
19. Yasufuku K, Nakajima T, Chiyo M, et al. Endobronchial ultrasonography: current status and future directions. *J Thorac Oncol* 2007;**2**:970–9.
20. Annema JT, Rabe KF. State of the art lecture: EUS and EBUS in pulmonary medicine. *Endoscopy* 2006;**38**(Suppl. 1):S118–22.
21. Bhutani MS, Hofstetter W. Transesophageal EUS and EUS-FNA for lung cancer: where do we go from here? *J Clin Gastroenterol* 2007;**41**:644–6.
22. Rintoul RC, Skwarski KM, Murchison JT, et al. Endobronchial and endoscopic ultrasound-guided real-time fine-needle aspiration for mediastinal staging. *Eur Respir J* 2005;**25**:416–21.
23. 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**:833–9.
24. Wallace MB, Pascual JM, Raimondo M, et al. Minimally invasive endoscopic staging of suspected lung cancer. *JAMA* 2008;**299**:540–6.
25. Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ* 2003;**326**:41–4.
26. 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.
27. Deville WL, Buntinx F, Bouter LM, et al. Conducting systematic reviews of diagnostic studies: didactic guidelines. *BMC Med Res Methodol* 2002;**2**:9.
28. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. *Stat Med* 1993;**12**:1293–316.
29. Vamvakas EC. Meta-analyses of studies of the diagnostic accuracy of laboratory tests: a review of the concepts and methods. *Arch Pathol Lab Med* 1998;**122**:675–86.
30. Suzuki S, Moro-oka T, Choudhry NK. The conditional relative odds ratio provided less biased results for comparing diagnostic test accuracy in meta-analyses. *J Clin Epidemiol* 2004;**57**:461–9.
31. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clin. Res. Ed.)* 1997;**315**:629–34.
32. Detterbeck FC, Jantz MA, Wallace M, Vansteenkiste J, Silvestri GA. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;**132**:202S–20S.
33. Harewood GC, Wiersema MJ, Edell ES, Liebow M. Cost-minimization analysis of alternative diagnostic approaches in a modeled patient with non-small cell lung cancer and subcarinal lymphadenopathy. *Mayo Clin Proc* 2002;**77**:155–64.
34. Aabakken L, Silvestri GA, Hawes R, et al. Cost-efficacy of endoscopic ultrasonography with fine-needle aspiration vs. mediastinotomy in patients with lung cancer and suspected mediastinal adenopathy. *Endoscopy* 1999;**31**:707–11.
35. Sharples LD, Jackson C, Wheaton E, et al. Clinical effectiveness and cost-effectiveness of endobronchial and endoscopic ultrasound relative to surgical staging in potentially resectable lung cancer: results from the ASTER randomised controlled trial. Health Technol Assess (Winchester, England) 2012;**16**:1–75 (iii–iv).
36. Ernst A, Anantham D, Eberhardt R, Krasnik M, Herth FJ. Diagnosis of mediastinal adenopathy-real-time endobronchial ultrasound guided needle aspiration versus mediastinoscopy. *J Thorac Oncol* 2008;**3**:577–82.
37. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol* 2003;**56**:1129–35.
38. Deeks JJ. Systematic reviews in health care: systematic reviews of evaluations of diagnostic and screening tests. *BMJ* 2001;**323**:157–62.
39. Gallagher EJ. Clinical utility of likelihood ratios. *Ann Emerg Med* 1998;**31**:391–7.
40. Petitti DB. Approaches to heterogeneity in meta-analysis. *Stat Med* 2001;**20**:3625–33.