Endosonography with lymph node sampling for restaging the mediastinum in lung cancer: A systematic review and pooled data analysis

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ABSTRACT

Background: Mediastinal restaging after induction treatment is still a difficult and controversial issue. We aimed to investigate the diagnostic accuracy of endobronchial ultrasound-guided transbronchial needle aspiration and endoscopic ultrasound-guided fine-needle aspiration for restaging the mediastinum after induction treatment in patients with lung cancer.

Methods: Embase and PubMed databases were searched from conception to March 2019. Data from relevant studies were analyzed to assess sensitivity and specificity of endobronchial ultrasound-guided transbronchial needle aspiration and endoscopic ultrasound-guided fine-needle aspiration, and to fit the hierarchical summary receiver operating characteristic curves.

Results: A total of 10 studies consisting of 558 patients fulfilled the inclusion criteria. All patients were restaged by endobronchial ultrasound-guided transbronchial needle aspiration, endoscopic ultrasound-guided fine-needle aspiration, or both. Negative results were confirmed by subsequent surgical approaches. There were no complications reported during any endosonography approaches reviewed. The pooled sensitivities of endobronchial ultrasound-guided transbronchial needle aspiration and endoscopic ultrasound-guided fine-needle aspiration were 65% (95% confidence interval [CI], 52-76) and 73% (95% CI, 52-87), respectively, and specificities were 99% (95% CI, 78-100) and 99% (95% CI, 90-100), respectively. The area under the hierarchical summary receiver operating characteristic curves were 0.85 (95% CI, 0.81-0.88) for endobronchial ultrasound-guided transbronchial needle aspiration and 0.99 (95% CI, 0.98-1) for endoscopic ultrasound-guided fine-needle aspiration. Moreover, for patients who received chemotherapy alone, the pooled sensitivity of endosonography with lymph node sampling for restaging was 66% (95% CI, 56-75), and specificity was 100% (95% CI, 34-100); for patients who received chemoradiotherapy, the results seemed similar with a sensitivity of 77% (95% CI, 47-92) and specificity of 99% (95% CI, 48-100).

Conclusions: Endosonography with lymph node sampling is an accurate and safe technique for mediastinal restaging of lung cancer. (J Thorac Cardiovasc Surg 2020;159:1099-108)

The diagram that summarizes the findings and describes a clinically reasonable pathway for NSCLC restaging.

Central Message

Endosonography with lymph node sampling is an accurate and safe technique for mediastinal restaging of lung cancer.

Perspective

Accurate mediastinal restaging of lung cancer is crucial because the stage of disease directly determines the prognosis and guides treatment options. Endosonography with lymph node sampling has been confirmed as an accurate and safe technique for mediastinal staging and restaging of lung cancer.

See Commentary on page 1109.

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Received for publication Jan 19, 2019; revisions received July 17, 2019; accepted for publication July 17, 2019; available ahead of print Oct 5, 2019.

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0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2019.07.095>

Abbreviations and Acronyms

CI	= confidence interval
CT	= computed tomography
EBUS-TBNA	= endobronchial ultrasound-guided transbronchial needle aspiration
EUS-FNA	= endoscopic ultrasound-guided fine-needle aspiration
LR	= likelihood ratio
NSCLC	= non-small cell lung cancer
PET	= positron emission tomography

Scanning this QR code will take you to the article title page to access supplementary information.

At present, the treatment for stage IIIA-N2 non-small cell lung cancer (NSCLC) is chemoradiotherapy.¹ However, surgical resection may be appropriate for select patients with N2 disease, particularly for those whose disease responds to induction chemotherapy or chemoradiotherapy. Accurate restaging of the mediastinum in these patients will be of increasing importance to identify patients who have been successfully down-staged and who may benefit from subsequent surgical resection.

The effective approach for restaging is controversial and the subject of much debate. Mediastinoscopy is well established as an invasive mediastinal staging procedure for patients with potentially operable NSCLC and allows histologic confirmation or exclusion of N2 or N3 disease in most patients.^{2,3} Performing re-mediastinoscopy is recognized as technically difficult because of adhesions and fibrotic changes induced by the initial procedure and induction treatment.^{4,5} As a result, it has lower accuracy^{6,7} compared with primary mediastinoscopy.⁸ Other surgical approaches, such as thoracoscopy, are invasive and costly. The accuracies of imaging techniques such as computed tomography (CT) and positron emission tomography (PET)/CT for restaging varies largely.^{5,9,10} The low sensitivity and specificity of imaging techniques for mediastinal restaging necessitate tissue sampling for the accurate determination of mediastinal lymph node status.

Minimally invasive procedures such as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) are used for detecting mediastinal nodal metastases. Both techniques are confirmed with reliably accurate results for the initial staging of lung cancer.¹¹⁻¹³ There

have been an increasing number of reports that analyze the accuracy in the restaging of the mediastinum, whereas the numbers recruited within each study are relatively small and the precision on the derived estimates in each is wide.^{10,14,15} Thus, we aimed to carry out a systematic review and pooled data analysis with valuable data to understand the diagnostic operating characteristics EBUS-TBNA and EUS-FNA for the restaging of mediastinal lymph nodes after induction treatment for lung cancer.

MATERIALS AND METHODS

The present study was performed as a systematic review, in accordance to the meta-analysis of observational studies in epidemiology guidelines for systematic reviews of observational studies (Table E1). In addition, we also conducted in line with the preferred reporting items for systematic reviews and meta-analysis statement for reporting systematic reviews and meta-analysis (Table E2).

Search Strategy and Selection Criteria

A systematic literature search was performed on Embase and PubMed databases from conception to March 2019. We used a combination of index terms and free text words related to mediastinal restaging in lung cancer (eg, “lung cancer,” “mediastinal restaging”) and endosonography (eg, “endobronchial ultrasound,” “endoscopic ultrasound,” “endosonography,” “ultrasound bronchoscope,” “fine-needle aspiration”). Our search had no language restrictions. In addition, the reference lists of relevant publications were searched as a supplement.

Study Eligibility

Two independent investigators examined titles and abstracts of all search results. The included studies met the following criteria: (1) Patients with lung cancer with mediastinal lymph node metastases that were previously pathologically diagnosed; (2) patients who received induction treatment, such as platinum-based chemotherapy, radiotherapy, or both; (3) patients who had stable disease or partial response after induction treatment defined by radiologists; (4) negative results for lymph node metastases by EBUS-TBNA/EUS-FNA were verified by surgical approaches, such as mediastinoscopy or thoracotomy. Reviews, case reports, editorials, and expert opinions were excluded.

Data Extraction

Data extraction was performed by 1 investigator and verified by a second investigator. Disagreements were resolved by consensus. For each included study, we extracted relevant data about tumor stage at first staging, details of the endoscopic testing protocol, type and duration of induction treatment, complications occurring during the endoscopic procedures, and confirmatory tests for negative results of endoscopic procedures.

We constructed 2×2 tables for each study, based on the numbers of true- and false-positives and true- and false-negatives for EBUS-TBNA and EUS-FNA. Patients with mediastinal nodal metastases (N2/N3 disease) were deemed positives; patients without mediastinal nodal metastases (N0/N1 disease) were deemed negatives.

We evaluated the diagnostic accuracy of EBUS-TBNA or EUS-FNA alone in detecting mediastinal nodal metastases. Only 1 included study assessed the diagnostic results of the combined use of these 2 approaches.¹⁶ Furthermore, in a sensitivity analysis, we assess the impact of different modalities of induction treatment (chemotherapy alone and chemoradiotherapy).

Study Quality Assessment

We used the Quality Assessment of Diagnostic Accuracy Studies-2 tool to assess study quality and the potential for bias.¹⁷ Two investigators

FIGURE 1. Search process of the present meta-analysis. *EBUS-TBNA*, Endobronchial ultrasound-guided transbronchial needle aspiration; *EUS-FNA*, endoscopic ultrasound-guided fine-needle aspiration.

(L.J. and W.S.) independently applied the tool to each included study. Disagreements were resolved by consensus.

Statistical Methods

We performed a bivariate meta-analysis using a linear mixed model approach to calculate summary estimates of sensitivity, specificity, and positive and negative likelihood ratios (LRs) to fit a hierarchical summary receiver-operating characteristic curve.^{18,19} The correlation between sensitivity and specificity makes tests for heterogeneity difficult; most variation in sensitivity is explained by variation in specificity and vice versa.^{20,21} Therefore, statistical tests such as those used in meta-analyses of interventions are not helpful. Because of this, we assumed that heterogeneity was present in our data and planned to address it using a random effects model. We did not assess publication bias, because no proven statistical method exists for this type of meta-analysis.²⁰ We used Stata (version 12; StataCorp, College Station, Tex) and Meta-DiSc (Version 1.4; Madrid, Spain) to perform all calculations.

RESULTS

Characteristics of Eligible Studies

Ten studies consisting of 558 patients fulfilled the study inclusion criteria and were analyzed. The flowchart of systematic search is presented in Figure 1. The chance-

corrected agreement (ie, kappa) between independent reviewers was 0.79.²² All included patients were diagnosed pathologically in the initial staging. Five studies included stage IIIA-N2 patients²³⁻²⁷ and 5 studies included stage IIIA/B(N2/N3) patients.^{16,28-31} The induction treatments of included studies contained chemotherapy and chemoradiation. The patients who had stable disease or partial response after induction treatment were defined by radiologists through CT or PET/CT. Five studies^{25-27,29,31} performed EBUS-TBNA alone, and 4 studies^{23,24,28,30} performed EUS-FNA alone. One study used a combined approach to assess mediastinal lymph node metastases.¹⁶ All negative results of EBUS-TBNA or EUS-FNA were confirmed by subsequent surgical approaches. No complications were observed. The mean age, gender, pathological diagnose, initial staging, induction treatment, restaging examinations, and confirmatory tests are shown in Table 1. The quality assessment of diagnostic accuracy studies-2 tool for quality assessment of the included studies is shown in Table E3.

TABLE 1. The characteristics of the included studies

Author (y)	Period	Total patients	Mean age (range) or $\pm$ SD	Female (%)	Pathologic diagnosis (%)	Initial staging	Induction treatment	Re-evaluation test	Restaging test	Confirmatory test	Sensitivity and specificity of EBUS/EUS for restaging after neoadjuvant
Annema (2003)	2001.2-2003.3	19	58 (34-73)	6 (31.6)	SCC: 9 (47.4) AdC: 7 (36.8) LCC: 2 (10.5) ASC: 1 (5.3)	IIIA-N2	Three cycles of cisplatin-based chemotherapy	CT	EUS	Thoracotomy	Sensitivity: 75%; Specificity: 100%
Varadarajulu (2006)	2000.7-2004.6	14	62.8 (51-78)	5 (35.7)	NR	IIIA-N2	Two cycles of carboplatin plus paclitaxel and radiotherapy	CT/PET	EUS	Thoracotomy	Sensitivity: 87.5%; Specificity: 100%
Herth (2008)	2003.2-2006.3	124	58 (19-82)	73 (58.9)	SCC: 24 (19) AdC: 79 (64) ASC: 15 (12) LCC: 6 (5)	IIIA-N2	Two or 3 cycles of cisplatin-based chemotherapy	CT	EBUS	Thoracotomy	Sensitivity: 76%, Specificity: 100%
Stigt (2009)	2006.2-2008.5	28	60 (47-78)	6 (21.4)	AdC: 6 (21.4) SCC: 15 (53.6) NS-NSCLC: 7 (25)	IIIA-N2	chemoradiation: 22; chemotherapy: 6	PET-CT	EUS	Thoracotomy	Sensitivity: 76%, Specificity: 100%
Szlubowski (2010)	2007.6-2008.12	61	59.3 $\pm$ 7.5	12 (19.7)	NR	IIIA-N2	Three to 5 cycles of cisplatin plus vinorelbine	CT	EBUS	TEMLA	Sensitivity: 67%, Specificity: 86%
Bartheld (2011)	2003.3-2009.3	58	NR	25 (43.1)	AdC: 26 (45) SCC: 21 (36) NS: 8 (14) ASC: 1 (2) ACC: 1 (2) NC: 1 (2)	IIIA/B-N2/3	Two or 3 cycles of platinum-based chemotherapy: 55; chemoradiation: 3	CT	EUS	Thoracotomy/ mediastinoscopy	Sensitivity: 44%, Specificity: 100%
Zielinski (2013)	2007.1-2010.12	88	NR	NR	NR	IIIA/B-N2/3	Chemoradiation	CT	EBUS	TEMLA	Sensitivity: 64.3%, Specificity: 100%
Szlubowski (2014)	2009.1-2012.12	106	61.5 $\pm$ 8.1	28 (26.4)	NR	IIIA/B-N2/3	Three to 5 cycles of cisplatin plus vinorelbine	NR	EBUS/EUS	TEMLA	Combine: 67.3%, 96%; EBUS: 48%, 98%; EUS: 61%, 98%
Erdogan (2017)	2011.1-2013.12	44	58.3 $\pm$ 8.6	5 (11.4)	NS: 11 (25) SCC: 22 (50) AdC: 10 (22.7) Mix NSCLC and SCLC: 1 (2.3)	IIIA-N2	Three cycles of platinum-based chemotherapy, or radiotherapy, or both	CT/PET	EBUS	Thoracotomy/ mediastinoscopy	Sensitivity: 82.1%, Specificity: 100%
Yoon (2018)	2012.10-2015.7	16	58 (39-73)	6 (37.5)	NSCLC	IIIA-N2	Chemoradiation	CT/PET	EBUS	surgery	Sensitivity: 33.3%, specificity: 75%

SD, Standard deviation; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; SCC, squamous carcinoma; AdC, adenocarcinoma; CT, computed tomography; NR, not reported; PET, positron emission tomography; NC, neuroendocrine carcinoma; NSCLC, non-small cell lung cancer; NS-NSCLC, not specified; TEMLA, transcervical extended mediastinal lymphadenectomy; SCLC, small cell lung cancer.

Diagnostic Accuracy of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

The pooled sensitivity of EBUS-TBNA was 65% (95% confidence interval [CI], 52-76), and specificity was 99% (95% CI, 78-100) (Figure 2, A). The area under the hierarchical summary receiver-operating characteristic curve was 0.85 (95% CI, 0.81-0.88) (Figure 2, B). The LR- was 0.35 (95% CI, 0.25-0.50) (Table 2).

Diagnostic Accuracy of Endoscopic Ultrasound-Guided Fine-Needle Aspiration

The pooled sensitivity of EUS-FNA was 73% (95% CI, 52-87), and specificity was 99% (95% CI, 90-100) (Figure 3, A). The area under the curve was 0.99 (95% CI, 0.98-1) (Figure 3, B), and LR- was 0.27 (95% CI, 0.14-0.53) (Table 2).

Subgroup Analysis

Moreover, we evaluated the impact of different modalities of induction treatment (chemotherapy alone and chemoradiotherapy). For patients who received chemotherapy alone, the pooled sensitivity of endosonography with lymph node sampling for the restaging was 66% (95% CI, 56-75), and specificity was 100% (95% CI, 34-100) (Figure 4, A). For patients who received chemoradiotherapy, the results seemed similar with sensitivity of 77% (95% CI, 47%-92%) and specificity of 99% (95% CI, 48-100) (Figure 4, B) (Table 2).

DISCUSSION

Accurate mediastinal restaging of lung cancer is crucial because the stage of disease directly determines the

FIGURE 2. The sensitivity, specificity, and hierarchical summary receiver operating characteristic of EBUS-TBNA. A, The pooled sensitivity of EBUS-TBNA was 65% (95% CI, 52-76), and specificity was 99% (95% CI, 78-100). B, The area under the hierarchical summary receiver operating characteristic curve was 0.85 (95% CI, 0.81-0.88). *CI*, Confidence interval; *HSROC*, hierarchical summary receiver-operating characteristic.

prognosis and guides treatment options. Endosonography with lymph node sampling has been confirmed with more favorable results than all other commonly used techniques for mediastinal staging of lung cancer. Although widely

accepted in NSCLC staging, little is known about the role of EBUS-TBNA and EUS-FNA in lung cancer restaging after induction treatment. To our knowledge, this is the first state-of-the-art pooled data analysis on the diagnostic

TABLE 2. The diagnostic accuracy of the included studies

Variables	No. of patients	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Negative likelihood ratio	AUC
In all mediastinal stations					
Overall	558	0.70 (0.60-0.79)	1.00 (0.87-1.00)	0.30 (0.22-0.41)	0.91 (0.88-0.93)
EBUS-TBNA	440	0.65 (0.52-0.76)	0.99 (0.78-1.00)	0.35 (0.25-0.50)	0.85 (0.81-0.88)
EUS-FNA	226	0.73 (0.52-0.87)	0.99 (0.90-1.00)	0.27 (0.14-0.53)	0.99 (0.90-1.00)
Combine	106	0.67 (0.53-0.79)	0.96 (0.86-0.99)	N/A	0.81 (0.73-0.87)
Subgroup analysis					
Chemotherapy alone	365	0.66 (0.56-0.75)	1.00 (0.34-1.00)	0.35 (0.26-0.48)	0.80 (0.77-0.84)
Chemotherapy radiotherapy	146	0.77 (0.47-0.92)	0.99 (0.48-1.00)	0.24 (0.09-0.64)	0.96 (0.94-0.98)

If negative likelihood ratio (LR-) is smaller: essentially a definite diagnosis when negative result. 95% CI, 95% Confidence interval; AUC, area under the curve; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; N/A, not applicable.

operating characteristics of endosonography with lymph node sampling for lung cancer restaging. In the present study, we found that EBUS-TBNA and EUS-FNA were accurate methods for restaging mediastinal lymph nodes after induction treatment for lung cancer using chemotherapy or chemoradiation therapy.

The staging of lymph nodes in patients with lung cancer is typically performed using an invasive or noninvasive approach. Chest CT and PET scans are the most used noninvasive methods and are reported to be safe but have limited sensitivity and specificity. CT has low accuracy in the restaging of the mediastinum with a diagnostic accuracy of 0.58 to 0.60.^{5,6} In the previous reports, PET/CT had high sensitivity rates of 73% to 92%. However, because of false-positive results, its specificity ranged between 62% and 89%.^{5,10} Deppen and colleagues³² performed a meta-analysis and reported that the use of PET/CT was less specific in diagnosing malignancy in populations with endemic infectious lung diseases compared with nonendemic regions. The pooled specificity was only 61% in areas with endemic infectious lung diseases. According to these results, reliance on imaging techniques alone is not sufficient to confirm metastasis; thus, histopathologic diagnosis should be considered.

Mediastinoscopy has been the gold standard in staging mediastinal lymph nodes. The average sensitivity of mediastinoscopy is 80%; however, it has a 2% risk of major morbidity and 0.08% risk of mortality, and is substantially costly.^{33,34} Repeat mediastinoscopy, although possible, is technically difficult and has a lower accuracy compared with primary mediastinoscopy.³⁵ EBUS-TBNA and EUS-FNA are both minimally invasive procedures for detecting mediastinal nodal metastases and have become the standard of care for staging patients with lung cancers. The American College of Chest guidelines recommended EBUS-TBNA as the invasive method of choice for the staging of lung cancer.¹³ More recently, the European Society of Gastrointestinal Endoscopy in collaboration with the European Respiratory and Thoracic Surgeons Societies issued new guidelines recommending endosonography over

surgery for staging of NSCLC. When EUS-FNA is available, they also recommended the combination of EBUS-TBNA and EUS-FNA over either test alone.³⁶ These guidelines gave a grade C recommendation for the use of EBUS-TBNA and EUS-FNA for restaging the mediastinum after neoadjuvant therapy (Video 1).

EBUS-TBNA has been shown to have a high yield for diagnosing and staging lung cancer ranging from 89% to 98%.³⁷⁻⁴⁰ Additionally, the sensitivities of EUS-FNA ranged from 45% to 80% for initial staging of lung cancer.⁴¹⁻⁴³ In the present study, we found that for lung cancer restaging, the pooled sensitivities of EBUS-TBNA and EUS-FNA were 65% and 73%, respectively, which were lower compared with reported sensitivity for the initial staging of lung cancer.

The main limitations of EBUS-TBNA or EUS-FNA were that some lymph node stations such as level 5 and 6 are not accessible using either strategy. However, combined EBUS-TBNA and EUS-FNA could achieve near-complete minimally invasive mediastinal staging.^{44,45} Multiple studies demonstrated a higher diagnostic yield for EBUS-TBNA compared with cervical mediastinoscopy.^{46,47} Zhang and colleagues⁴⁸ conducted a meta-analysis with the aim to assess the diagnostic yield of the combined EBUS-TBNA and EUS-FNA approaches in NSCLC staging. The sensitivity and specificity were 86% and 100%, respectively, and the NLR was 0.15. The sensitivity of the combined approach was significantly better than that of either strategy alone.⁴⁸ Only 1 study used the combined endosonography approach for restaging NSCLC and the reported sensitivity, specificity, and accuracy were 70%, 96%, and 83%, respectively.

Our analysis of the pooled data showed that the specificity of EBUS-TBNA and or EUS-FNA is perfect, but the sensitivity is defective. This may be attributed to the fact that induction treatment with chemotherapy or chemoradiation led to the formation of necrosis and fibrosis in the metastatic lymph nodes. Sampling of these lymph nodes may be more difficult with less cellular material for histologic analysis. In these treated metastatic lymph nodes, the malignant cells may be focal within the node or located within areas of

FIGURE 3. The sensitivity, specificity, and hierarchical summary receiver-operating characteristic of EUS-FNA. A, The pooled sensitivity of EUS-FNA was 73% (95% CI, 52-87), and specificity was 99% (95% CI, 90-100). B, The area under the curve was 0.99 (95% CI, 0.98-1). CI, Confidence interval; HSROC, hierarchical summary receiver-operating characteristic.

dense extracellular matrix. This may partially explain why, in many of the false-negative results, lymph node tissue was aspirated successfully but no malignant cells were seen. Likewise, pathologic interpretation is often more difficult when necrosis is present within the aspirated sample.

In centers where EBUS-TBNA is not available, EUS-FNA and mediastinoscopy are acceptable alternatives for the diagnosis and staging of lung cancer. The American College of Physicians Executive Summary recommended the use EBUS-TBNA or EUS-FNA or combined EBUS/

FIGURE 4. The sensitivity, specificity, and hierarchical summary receiver-operating characteristic of endosonography for patients who received chemotherapy alone and chemoradiotherapy. A, For patients who received chemotherapy alone, the pooled sensitivity of endosonography with lymph node sampling for the restaging was 66% (95% CI, 56-75) and specificity was 100% (95% CI, 34-100). B, For patients who received chemoradiotherapy, the results seemed similar with sensitivity of 77% (95% CI, 47-92) and specificity of 99% (95% CI, 48-100). CI, Confidence interval.

EUS-FNA for lung cancer staging over surgical staging. They based the recommendation on the availability of the technology and the appropriate skills of the proceduralist.¹³ The combined EBUS-TBNA and EUS-FNA is the preferred procedure over either one alone. This was also recommended in the guidelines by the European Society of Gastrointestinal Endoscopy Guideline, in cooperation with the European Respiratory Society and the European Society

of Thoracic Surgeons.⁴⁹ The EUS-FNA may be performed in the same setting with EBUS-TBNA and using the same EBUS bronchoscope and by the pulmonologists. It is usually referred to as endoscopic ultrasound-bronchoscope fine-needle aspiration: (EUS-B-FNA). This technique does not significantly increase the cost of the procedure. The EBUS scope is usually retracted from the airways and positioned into the esophagus to perform the EUS-

VIDEO 1. The process of EBUS operation. Video available at: [https://www.jtcvs.org/article/S0022-5223\(19\)31649-6/fulltext](https://www.jtcvs.org/article/S0022-5223(19)31649-6/fulltext).

FNA. More recently, the EBUS scope was used to perform EUS-B-FNA of the left adrenal nodules in patients with lung cancer as part of staging. The EBUS scope is advanced to the stomach, and the left adrenal nodule is then identified and sampled under real-time EUS-B-FNA. In a recent article by Crombag and colleagues,⁵⁰ the mediastinal and left adrenal gland were appropriately sampled using the same EBUS scope. This was suggested to lower the cost in selected patients. However, no cost-effective data are available about this topic, and more studies are warranted.

Study Limitations

Some limitations need to be acknowledged. There was a lack of standardization of diagnostic testing, and PET/CT was not used routinely. Also, the strategies used for primary pathologic staging and induction treatment varied. Different chemotherapy agents and various numbers of treatment cycles were used, and some patients received radiation in addition of chemotherapy. This has the potential of influencing the outcome of restaging lung cancer. As the lung cancer management continues to advance, more neoadjuvant agents such as nivolumab to block the programmed death 1 protein or agents that target its ligand will be more widely used, and this will surely affect the outcome of lung cancer restaging.⁵¹ More studies are needed to further investigate the ideal restaging procedures. In the included studies, there were no description of the lymph node histopathologic structure. Such description may help the endoscopists when sampling lymph nodes for restaging lung cancers. The distribution of malignant cells in the treated lymph nodes could be a crucial information and warrants further investigation. Having the malignant cells distributed centrally versus peripherally or scattered focally inside the lymph node may guide the endoscopists in choosing the location the needle insertion during EBUS-TBNA or EUS-FNA. This may have an impact on choosing

the size of the sampling needle used and how many locations inside the lymph node should the endoscopists sample and the number of passes needed to increase the yield. Moreover, the sensitivity and specificity of EBUS or EUS apply to only the locations that are possible to assess with either modality. For example, EUS may have limited access to certain mediastinal nodes (4R), and EBUS has limitations to lower mediastinal nodes (stations 8 and 9). There is no comparability between the 2 approaches because they are stand-alone staging techniques. Prospective studies are warranted to clarify all these questions and help to increase the yield of endosonography for lymph node sampling for restaging lung cancers.

CONCLUSIONS

Endosonography with lymph node sampling is an accurate and safe technique in mediastinal restaging in lung cancer patients after induction treatment.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: EBUS, EUS, fine-needle aspiration, lung cancer, mediastinal restaging

TABLE E1. Meta-analysis of observational studies in epidemiology checklist.

Criteria	Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include <ul style="list-style-type: none">✓ Problem definition✓ Hypothesis statement✓ Description of study outcomes✓ Type of exposure or intervention used✓ Type of study designs used✓ Study population	Mediastinal restaging after induction treatment is still a difficult and controversial issue. The diagnostic accuracy of EBUS-TBNA and EUS-FNA for restaging the mediastinum after induction treatment in patients with lung cancer is reliable. Diagnostic accuracy of EBUS-TBNA and EUS-FNA Endosonography with lymph node sampling for restaging the mediastinum We included observation studies. We placed no restriction.
Reporting of search strategy should include <ul style="list-style-type: none">✓ Qualifications of searchers✓ Search strategy, including time period included in the synthesis and keywords✓ Databases and registries searched✓ Search software used, name and version, including special features✓ Use of hand searching✓ List of citations located and those excluded, including justifications✓ Method of addressing articles published in languages other than English✓ Method of handling abstracts and unpublished studies✓ Description of any contact with authors	The credentials of the 2 investigators, Jun Liu and Wenhua Liang, are indicated in the author list. PubMed from conception to July 2017 EMBASE from conception to July 2017 See “Material and Methods” section in the article PubMed and EMBASE We did not use a search software. EndNote was used to merge retrieved citations and eliminate duplications We hand-searched bibliographies of retrieved papers for additional references Details of the literature search process are outlined in the flow chart. We placed no restrictions on language; all included studies have English abstract. We had contacted a few authors by sending emails for unpublished studies. We contacted authors who did not reported the types of introduction therapy.
Reporting of methods should include <ul style="list-style-type: none">✓ Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested✓ Rationale for the selection and coding of data✓ Assessment of confounding✓ Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results✓ Assessment of heterogeneity✓ Description of statistical methods in sufficient detail to be replicated✓ Provision of appropriate tables and graphics	Detailed inclusion and exclusion criteria were described in the “ Materials and Methods ” section. Data extracted from each of the studies were relevant to tumor stage at first staging, details of the endoscopic testing protocol, type and duration of induction treatment, complications occurring during the endoscopic procedures, and confirmatory tests for negative results of endoscopic procedures. Restricted the analysis to introduction therapy adjusted estimates. We used the Quality Assessment of Diagnostic Accuracy Studies-2 tool to assess study quality and the potential for bias. Sensitivity analyses were performed subgroup analysis. We assumed that heterogeneity was present in our data and planned to address it using a random effects model. Description of methods of meta-analyses, sensitivity analyses and assessment of publication bias are detailed in the methods. We included 1 box detailing the terms used for database search, 1 flow chart, 1 summary table, and 1 table of outcome analyses.
Reporting of results should include <ul style="list-style-type: none">✓ Graph summarizing individual study estimates and overall estimate✓ Table giving descriptive information for each study included✓ Results of sensitivity testing✓ Indication of statistical uncertainty of findings	Figure 1 Table 1 Table 2 95% CIs were presented with all summary estimates

(Continued)

TABLE E1. Continued

Criteria	Brief description of how the criteria were handled in the meta-analysis
Reporting of discussion should include ✓ Quantitative assessment of bias ✓ Justification for exclusion ✓ Assessment of quality of included studies	Sensitivity analyses were discussed according to subgroup analysis. We excluded studies that had not meet the eligible criteria. We discussed the results of the sensitivity analyses, and potential reasons for the observed heterogeneity.
Reporting of conclusions should include ✓ Consideration of alternative explanations for observed results ✓ Generalization of the conclusions ✓ Guidelines for future research ✓ Disclosure of funding source	Different chemotherapy agents and various numbers of treatment cycles were used and some patients received radiation in addition of chemotherapy. This has the potential of influencing the outcome of restaging lung cancer. Endosonography with lymph node sampling is an accurate and safe technique in mediastinal restaging in patients with lung cancer after induction treatment. For nondiagnostic results, a further more invasive approach should be thoroughly considered. We recommend future prospective studies on the association between these variables. No funding.

EBUS-TBNA, Endobronchial ultrasound-guided transbronchial needle aspiration; *EUS-FNA*, endoscopic ultrasound-guided fine-needle aspiration; *CI*, confidence interval.

TABLE E2. Preferred reporting items for systematic reviews and meta-analysis statement checklist

Section/topic	No.	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	8-9
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9-10
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	10-11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and CIs, ideally with a forest plot.	10-11
Synthesis of results	21	Present results of each meta-analysis done, including CIs and measures of consistency.	10-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-11
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11

(Continued)

TABLE E2. Continued

Section/topic	No.	Checklist item	Reported on page #
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, health care providers, users, and policy makers).	11-14
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review level (eg, incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-15
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	15

PICOS, Patient, intervention, comparison, outcome, study design.

TABLE E3. Quality assessment of Diagnostic Accuracy Studies-2 tool for quality assessment of the included studies

Study (Year)	DOM 1A1	DOM 1A2	DOM 1A3	DOM 1A4	DOM 1B	DOM 2A1	DOM 2A2	DOM 2A3	DOM 2B	DOM 3A1	DOM 3A2	DOM 3A3	DOM 3B	DOM 4A1	DOM 4A2	DOM 4A3	DOM 4A4	DOM 4A5
Annema (2003)	U	Y	Y	H	L	Y	Y	L	L	Y	Y	L	L	Y	Y	Y	Y	L
Varadarajulu (2006)	Y	Y	Y	L	L	Y	Y	L	L	Y	Y	L	L	Y	Y	Y	Y	L
Herth (2008)	U	Y	Y	H	L	Y	Y	L	L	Y	Y	L	L	Y	Y	Y	Y	L
Stigt (2009)	U	Y	Y	H	L	Y	Y	L	L	Y	Y	L	L	Y	Y	Y	Y	L
Szlubowski (2010)	U	Y	Y	U	L	Y	Y	L	L	Y	Y	L	L	Y	Y	Y	Y	L
von Bartheld (2011)	Y	Y	Y	L	L	Y	Y	L	L	Y	Y	L	L	Y	Y	Y	N	L
Zielinski (2013)	Y	Y	Y	L	L	Y	Y	L	L	Y	Y	L	L	Y	Y	Y	N	L
Szlubowski (2014)	U	Y	Y	U	L	Y	Y	L	L	Y	Y	L	L	Y	Y	Y	N	L
Cetinkaya (2017)	U	Y	Y	U	L	Y	Y	L	L	Y	Y	L	L	Y	Y	Y	N	L
Yoon (2018)	U	Y	Y	U	L	Y	Y	L	L	Y	Y	L	L	Y	Y	Y	Y	L

DOM1A1, Consecutive or random sample of patients enrolled; *DOM1A2*, case-control design avoided; *DOM1A3*, study avoided inappropriate exclusions; *DOM1A4*, selection of patients introduced bias; *DOM1B*, concern that included patients do not match the review question; *DOM2A1*, index test results interpreted without knowledge of results of reference standard; *DOM2A2*, prespecified threshold used; *DOM2A3*, could the conduct of index test have introduced bias; *DOM2B*, concern that index test conduct or interpretation differ from review question; *DOM3A1*, reference standard correctly classifies condition; *DOM3A2*, reference standard results interpreted independently from index test results; *DOM3A3*, could the reference standard, its conduct, or its interpretation have introduced bias; *DOM3B*, concern that target condition defined by reference standard does not match review question; *DOM4A1*, appropriate interval between index test and reference standard; *DOM4A2*, all included specimens received the reference standard; *DOM4A3*, all included specimens received the same reference standard; *DOM4A4*, all patients included in the analysis; *DOM4A5*, could the patient flow have introduced bias; *U*, unclear; *Y*, yes; *H*, high; *L*, low; *N*, no.